IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and INTERMUNE, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. _____
SANDOZ, INC., SANDOZ INTERNATIONAL GMBH and SANDOZ AG,	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Genentech, Inc. ("Genentech") and InterMune, Inc. ("InterMune") (Genentech and InterMune, collectively, "Plaintiffs"), by their attorneys, for their Complaint against Defendants, Sandoz, Inc., Sandoz International GmbH and Sandoz AG (collectively, "Sandoz" or "Defendants"), allege as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the Food and Drug Laws and Patent Laws of the United States, Titles 21 and 35 of the United States Code, respectively, concerning Defendants' submission of Abbreviated New Drug Application No. 212560, which seeks approval from the U.S. Food and Drug Administration ("FDA") to market a generic copy of Plaintiffs' drug Esbriet® (pirfenidone) 267 and 801 mg tablets, in violation of Plaintiffs' exclusive rights held under numerous patents that Plaintiffs have listed with the FDA for Esbriet®.

2. Plaintiffs seek a judgment of patent infringement under 35 U.S.C. § 271(e)(2)(A), and the remedies provided under the Hatch-Waxman Act specified in 35 U.S.C. § 271(e)(4),

including, but not limited to, the specific remedy provided in 35 U.S.C. § 271(e)(4)(A), which provides that the Court "shall order the effective date of any approval of the drug … involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed."

PARTIES

3. Plaintiff Genentech is a corporation organized and existing under the laws of Delaware, having its principal place of business at 1 DNA Way, South San Francisco, CA 94080. Genentech develops and commercializes pharmaceutical products throughout the United States, including within this judicial district, on its own behalf and on behalf of its affiliates within the Roche group of companies, including InterMune. Genentech holds New Drug Applications ("NDAs") in the United States for (i) Esbriet® capsules, 267 mg and (ii) Esbriet® tablets, 267, 534, and 801 mg. Genentech is also exclusively licensed by InterMune under the below-listed Asserted Patents, which cover Esbriet® FDA-approved formulations and its FDA-approved uses for safely and effectively treating Idiopathic Pulmonary Fibrosis.

4. Plaintiff InterMune is a corporation organized and existing under the laws of Delaware, having its principal place of business at 1 DNA Way, South San Francisco, CA 94080. InterMune owns the United States patents that have been listed with the FDA in connection with the NDAs held by Genentech for Esbriet®, including, but not limited to, all the Asserted Patents listed below.

5. On information and belief, Defendant Sandoz, Inc. is a corporation organized and existing under the laws of Colorado, having a principal place of business at 100 College Road West, Princeton, New Jersey 08540.

6. On information and belief, Sandoz, Inc. is a wholly owned subsidiary in the United States of Sandoz International GmbH ("Sandoz International"). On further information and belief, Sandoz International is a corporation organized and existing under the laws of the Federal Republic of Germany having a principal place of business at Industriestrasse 25, 83607 Holzkirchen, Germany.

7. On information and belief, Sandoz AG is a wholly owned subsidiary of Sandoz International. On further information and belief, Sandoz AG is a corporation organized and existing under the laws of the Switzerland having a principal place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

8. On information and belief, Sandoz International, acting in concert with the other Defendants, is in the business of, among other things, developing, preparing, manufacturing, selling, marketing, and distributing generic drugs, including distributing, selling, and marketing generic drugs throughout the United States, including within the State of Delaware, through its own actions and through the actions of its agents and subsidiaries, including Sandoz, Inc. and Sandoz AG, from which Sandoz International derives a substantial portion of its revenue.

9. On information and belief, Sandoz, Inc. acted in concert with Sandoz International and Sandoz AG to prepare and submit ANDA No. 212560 (the "Sandoz ANDA") for Sandoz, Inc.'s 267 AND 801 mg pirfenidone tablets (the "Sandoz ANDA Product"), which was done at the direction of, under the control of, and for the direct benefit of Sandoz International and Sandoz AG. Following FDA approval of the Sandoz ANDA, Sandoz, Inc. will manufacture and supply the approved generic product, which it will then market and sell the product throughout the United States at the direction, under the control, and for the direct benefit of Sandoz International and Sandoz AG.

JURISDICTION AND VENUE

10. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 101, *et seq.,* seeking a finding and declaratory judgment of patent infringement under 35 U.S.C. § 271(e)(2)(A) and the remedies provided under the Hatch-Waxman Act specified in 35 U.S.C. § 271(e)(4). Jurisdiction exists under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202, and venue is proper in this Court under 28 U.S.C. §§ 1391(c) and 1400(b).

11. Venue is proper in this Court because, among other things, Sandoz, Inc. consented to jurisdiction and venue in the United States District Court for the District of Delaware in this matter, through its counsel, by e-mail dated January 28, 2019. Sandoz International and Sandoz AG are foreign corporations not residing in any United States district and may be sued in any judicial district. 28 U.S.C. § 1391(c).

PERSONAL JURISDICTION OVER SANDOZ, INC.

12. Plaintiffs reallege paragraphs 1-11 as if fully set forth herein.

13. On information and belief, Sandoz, Inc. develops, manufactures, and/or distributes generic drugs for sale and use throughout the United States, including in this judicial district.

14. This Court has personal jurisdiction over Sandoz, Inc. because, Sandoz, Inc. consented to jurisdiction and venue in the United States District Court for the District of Delaware in this matter, through its counsel, by e-mail dated January 28, 2019.

PERSONAL JURISDICTION OVER SANDOZ INTERNATIONAL

15. Plaintiffs reallege paragraphs 1-14 as if fully set forth herein.

16. On information and belief, Sandoz International develops, manufactures, and/or distributes generic drugs for sale and use throughout the United States, including in this judicial district.

17. This Court has personal jurisdiction over Sandoz International because, *inter alia*, Sandoz International, on information and belief: (1) has substantial, continuous, and systematic contacts with this State, either directly or through at least one of its wholly-owned subsidiaries or agents; (2) intends to market, sell, and/or distribute the Sandoz ANDA Products to residents of this State upon approval of ANDA No. 212560, either directly or through at least one of its wholly-owned subsidiaries or agents; (3) enjoys substantial income from sales of its generic pharmaceutical products in this State on its own and through Sandoz, Inc.; and (4) controls and directs Sandoz, Inc.

18. Alternatively, to the extent the above facts do not establish personal jurisdiction over Sandoz International, this Court may exercise jurisdiction over Sandoz International pursuant to Fed. R. Civ. P. 4(k)(2) because: (a) Plaintiffs' claims arise under federal law; (b) Sandoz International would be a foreign defendant not subject to personal jurisdiction in the courts of any State; and (c) Sandoz International has sufficient contacts with the United States as a whole, including, but not limited to, filing ANDAs with the FDA and manufacturing and selling generic pharmaceutical products through its U.S. subsidiaries that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sandoz International satisfies due process.

PERSONAL JURISDICTION OVER SANDOZ AG

19. Plaintiffs reallege paragraphs 1-18 as if fully set forth herein.

20. On information and belief, Sandoz AG develops, manufactures, and/or distributes generic drugs for sale and use throughout the United States, including in this judicial district.

21. This Court has personal jurisdiction over Sandoz AG because, *inter alia*, Sandoz AG, on information and belief: (1) has substantial, continuous, and systematic contacts with this State, either directly or through at least one of its wholly-owned subsidiaries or agents; (2) intends to market, sell, and/or distribute the Sandoz ANDA Products to residents of this State upon approval of ANDA No. 212560, either directly or through at least one of its wholly-owned subsidiaries or agents; (3) enjoys substantial income from sales of its generic pharmaceutical products in this State on its own and through Sandoz, Inc.; and (4) controls and directs Sandoz, Inc.

22. Alternatively, to the extent the above facts do not establish personal jurisdiction over Sandoz AG, this Court may exercise jurisdiction over Sandoz AG pursuant to Fed. R. Civ. P. 4(k)(2) because: (a) Plaintiffs' claims arise under federal law; (b) Sandoz AG would be a foreign defendant not subject to personal jurisdiction in the courts of any State; and (c) Sandoz AG has sufficient contacts with the United States as a whole, including, but not limited to, filing ANDAs with the FDA and manufacturing and selling generic pharmaceutical products through its U.S. subsidiaries that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sandoz AG satisfies due process.

BACKGROUND FACTS

23. Esbriet®, which contains pirfenidone as its active ingredient, is a drug used for treating patients afflicted with a rare, fatal lung disease called Idiopathic Pulmonary Fibrosis ("IPF").

24. IPF results in scarring of the lungs, which makes breathing difficult and prevents the heart, muscles, and vital organs from receiving enough oxygen to work properly. The disease can advance quickly or slowly, but eventually the lungs will harden and stop working altogether. The prognosis for IPF patients is extremely poor, with patients experiencing significant progressive worsening of disease, and median survival of 2-5 years after diagnosis. IPF is irreversible and fatal. The cause is unknown, and there is no cure.

25. Prior to Esbriet®, no drug had been approved in the United States as safe and effective for treating IPF. Approval in the United States came only after extensive clinical research by Plaintiff InterMune, which demonstrated that Esbriet® slows progression of the disease. The FDA's approval of Esbriet® would not have been possible without the twelve years of effort by InterMune, a biopharmaceutical company that dedicated itself to developing medicines for treating IPF.

26. The FDA approved the first NDA for Esbriet® on October 15, 2014, shortly after Plaintiff InterMune was acquired by Plaintiff Genentech. This approval did not come easily. The FDA initially denied approval in 2010 following many years of research & development and multiple clinical trials. This necessitated further large-scale clinical trials and resubmission of the NDA in 2014. The clinical experimentation spanned over a decade and these combined results ultimately convinced the FDA that Esbriet® could be used safely and effectively to treat IPF patients.

27. When it first approved Esbriet®, the FDA accorded it status as a Breakthrough Therapy, and awarded Esbriet® Orphan Drug Exclusivity for treating IPF, which runs until October 15, 2021.

28. Sandoz now seeks to piggy-back on Plaintiffs' hard work by seeking FDA approval of the Sandoz ANDA that cross-references and relies upon Plaintiffs' clinical trial data. In so doing, Sandoz has not conducted any of the clinical trials needed to demonstrate effectiveness and safe conditions of use for its proposed Sandoz ANDA Product. Rather, Sandoz asks that the FDA permit the Sandoz ANDA to rely on proprietary clinical data submitted by Plaintiffs InterMune and Genentech.

29. This action arose when Sandoz sent a letter notifying Plaintiffs that (i) it had filed the Sandoz ANDA seeking to rely on Plaintiffs' safety and efficacy data without consent, and (ii) it is seeking FDA approval to commercially launch the Sandoz ANDA Product before Plaintiffs' exclusive patent rights to Esbriet® have expired.

THE ASSERTED PATENTS

- U.S. Patent No. 7,566,729

30. U.S. Patent No. 7,566,729 ("the '729 patent"), entitled "Modifying Pirfenidone Treatment for Patients with Atypical Liver Function," was duly and legally issued by the United States Patent & Trademark Office ("Patent Office") on July 28, 2009, and has not expired.

31. Plaintiffs have maintained the entire right, title, and interest in the '729 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '729 patent is attached as Exhibit 1.

- U.S. Patent No. 7,635,707

32. U.S. Patent No. 7,635,707 ("the '707 patent"), entitled "Pirfenidone Treatment for Patients with Atypical Liver Function," was duly and legally issued by the Patent Office on December 22, 2009, and has not expired.

33. Plaintiffs have maintained the entire right, title, and interest in the '707 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '707 patent is attached as Exhibit 2.

- U.S. Patent No. 7,767,700

34. U.S. Patent No. 7,767,700 ("the '700 patent"), entitled "Method of Providing Pirfenidone Therapy to a Patient," was duly and legally issued by the Patent Office on August 3, 2010, and has not expired.

35. Plaintiffs have maintained the entire right, title, and interest in the '700 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '700 patent is attached as Exhibit 3.

- U.S. Patent No. 7,816,383

36. U.S. Patent No. 7,816,383 ("the '383 patent"), entitled "Methods of Administering Pirfenidone Therapy," was duly and legally issued by the Patent Office on October 19, 2010, and has not expired.

37. Plaintiffs have maintained the entire right, title, and interest in the '383 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '383 patent is attached as Exhibit 4.

- U.S. Patent No. 7,910,610

38. U.S. Patent No. 7,910,610 ("the '610 patent"), entitled "Methods of Administering Pirfenidone Therapy," was duly and legally issued by the Patent Office on March 22, 2011, and has not expired.

39. Plaintiffs have maintained the entire right, title, and interest in the '610 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '610 patent is attached as Exhibit 5.

- U.S. Patent No. 8,013,002

40. U.S. Patent No. 8,013,002 ("the '002 patent"), entitled "Methods of Administering Pirfenidone Therapy," was duly and legally issued by the Patent Office on September 6, 2011, and has not expired.

41. Plaintiffs have maintained the entire right, title, and interest in the '002 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '002 patent is attached as Exhibit 6.

- U.S. Patent No. 8,084,475

42. U.S. Patent No. 8,084,475 ("the '475 patent"), entitled "Pirfenidone Therapy and Inducers of Cytochrome P450," was duly and legally issued by the Patent Office on December 27, 2011, and has not expired.

43. Plaintiffs have maintained the entire right, title, and interest in the '475 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '475 patent is attached as Exhibit 7.

- U.S. Patent No. 8,318,780

44. U.S. Patent No. 8,318,780 ("the '780 patent"), entitled "Methods of Administering Pirfenidone Therapy," was duly and legally issued by the Patent Office on November 27, 2012, and has not expired.

45. Plaintiffs have maintained the entire right, title, and interest in the '780 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '780 patent is attached as Exhibit 8.

- U.S. Patent No. 8,383,150

46. U.S. Patent No. 8,383,150 ("the '150 patent"), entitled "Granulate Formulation of Pirfenidone and Pharmaceutically Acceptable Excipients," was duly and legally issued by the Patent Office on February 26, 2013, and has not expired.

47. Plaintiffs have maintained the entire right, title, and interest in the '150 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '150 patent is attached as Exhibit 9.

- U.S. Patent No. 8,420,674

48. U.S. Patent No. 8,420,674 ("the '674 patent"), entitled "Method of Providing Pirfenidone Therapy to a Patient," was duly and legally issued by the Patent Office on April 16, 2013, and has not expired.

49. Plaintiffs have maintained the entire right, title, and interest in the '674 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '674 patent is attached as Exhibit 10.

- U.S. Patent No. 8,592,462

50. U.S. Patent No. 8,592,462 ("the '462 patent"), entitled "Pirfenidone Treatment for Patients with Atypical Liver Function," was duly and legally issued by the Patent Office on November 26, 2013, and has not expired.

51. Plaintiffs have maintained the entire right, title, and interest in the '462 patent throughout the period of Defendants' infringement. A copy of the '462 patent is attached as Exhibit 11.

- U.S. Patent No. 8,609,701

52. U.S. Patent No. 8,609,701 ("the '701 patent"), entitled "Pirfenidone Treatment for Patients with Atypical Liver Function," was duly and legally issued by the Patent Office on December 17, 2013, and has not expired.

53. Plaintiffs have maintained the entire right, title, and interest in the '701 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '701 patent is attached as Exhibit 12.

- U.S. Patent No. 8,648,098

54. U.S. Patent No. 8,648,098 ("the '098 patent"), entitled "Pirfenidone Therapy and Inducers of Cytochrome P450," was duly and legally issued by the Patent Office on February 11, 2014, and has not expired.

55. Plaintiffs have maintained the entire right, title, and interest in the '098 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '098 patent is attached as Exhibit 13.

- U.S. Patent No. 8,754,109

56. U.S. Patent No. 8,754,109 ("the '109 patent"), entitled "Pirfenidone Therapy and Inducers of Cytochrome P450," was duly and legally issued by the Patent Office on June 17, 2014, and has not expired.

57. Plaintiffs have maintained the entire right, title, and interest in the '109 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '109 patent is attached as Exhibit 14.

- U.S. Patent No. 8,778,947

58. U.S. Patent No. 8,778,947 ("the '947 patent"), entitled "Methods of Administering Pirfenidone Therapy," was duly and legally issued by the Patent Office on July 15, 2014, and has not expired.

59. Plaintiffs have maintained the entire right, title, and interest in the '947 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '947 patent is attached as Exhibit 15.

- U.S. Patent No. 9,561,217

60. U.S. Patent No. 9,561,217 ("the '217 patent"), entitled "Pharmaceutical Composition Containing as an Active Ingredient 5-methyl-1-phenyl-2-(1H)-Pyridone," was duly and legally issued by the Patent Office on February 7, 2017, and has not expired.

61. Plaintiffs have maintained the entire right, title, and interest in the '217 patent throughout the period of Defendants' infringement and have the exclusive right to sue for infringement. A copy of the '217 patent is attached as Exhibit 16.

62. The '729, '707, '700, '383, '610, '002, '475, '780, '150, '674, '462, '701, '098, '109, '947 and '217 patents are referred to collectively herein as the "Asserted Patents."

ACTS GIVING RISE TO THIS ACTION

63. Plaintiff Genentech is the holder of NDA No. 208780 (the "Genentech NDA") by which the FDA granted approval for 267, 534, and 801 mg pirfenidone tablets for treating IPF. Genentech holds the exclusive right to market these tablets in the United States under the trademark Esbriet®.

64. Esbriet® tablets and the use of Esbriet® tablets in accordance with its FDA-approved label are covered by one or more claims of the Asserted Patents.

65. The FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") lists the Asserted Patents in connection with Esbriet® tablets.

66. By letter dated December 20, 2018 (the "Notice Letter") Sandoz notified Plaintiffs that it had submitted the Sandoz ANDA to the FDA, seeking approval for commercial manufacture, use, and sale of the Sandoz ANDA Product in the United States prior to the expiration of the Asserted Patents.

67. In the Notice Letter, Sandoz notified Plaintiffs that, as a part of its ANDA, it had filed a certification under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) with respect to the Asserted Patents (the "Paragraph IV Certification"), that those patents are allegedly invalid, unenforceable and/or will not be infringed by the commercial manufacture, use, and sale of the Sandoz ANDA Product in the United States.

68. By filing the Sandoz ANDA, Sandoz has necessarily represented to the FDA that the Sandoz ANDA Product will have the same pirfenidone active ingredient, route of administration, dosage form, and dosage strengths as Plaintiffs' FDA-approved Esbriet® tablets, and will be bioequivalent.

69. Sandoz's Notice Letter contained an offer of confidential access ("OCA"), the terms of which the parties attempted to negotiate in good faith in an effort to reach a mutually acceptable agreement, and under which the Sandoz ANDA would be provided to Plaintiffs. The parties were unable to reach an agreement on the OCA terms because Sandoz's proposed OCA contained unreasonable restrictions well beyond those that would apply under a protective order on who could view the ANDA. For example, the proposed Sandoz OCA contained a broad regulatory work bar (including but not limited to an FDA bar), which, among other things, does not have a carve-out for adversarial proceedings. The proposed Sandoz OCA unreasonably restricted the ability of counsel to seek the opinions of scientific consultants without written permission from Sandoz's designated counsel; and Sandoz had broad authority to reject any request by Plaintiffs to seek outside expert access to the Sandoz ANDA. The restrictions Sandoz placed on access to the Sandoz ANDA contravene 21 U.S.C. § 355(j)(5)(C)(i)(III), which states that an offer of confidential access "shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, **as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information**" (emphasis added). Plaintiffs have not been able to evaluate the Sandoz ANDA. Plaintiffs require discovery from Sandoz in this action.

70. This Complaint is being filed before the expiration of forty-five days from the date Plaintiffs received the Notice Letter.

COUNT I

INFRINGEMENT OF THE '729 PATENT

71. Plaintiffs reallege paragraphs 1 to 70 as if fully set forth herein.

72. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '729 patent.

73. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '729 patent.

74. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '729 patent infringed at least one of the claims of the '729 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

75. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '729 patent would further infringe at least one claim of the '729 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

76. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '729 patent either literally or under the doctrine of equivalents.

77. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '729 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '729 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA

Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

78. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '729 patent, either literally or under the doctrine of equivalents.

79. On information and belief, Sandoz had knowledge of the '729 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '729 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '729 patent.

80. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '729 patent, either literally or under the doctrine of equivalents.

81. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '729 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT II

INFRINGEMENT OF THE '707 PATENT

82. Plaintiffs reallege paragraphs 1 to 81 as if fully set forth herein.

83. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '707 patent.

84. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '707 patent.

85. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '707 patent infringed at least one of the claims of the '707 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

86. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '707 patent would further infringe at least one claim of the '707 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

87. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '707 patent either literally or under the doctrine of equivalents.

88. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '707 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '707 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

89. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '707 patent, either literally or under the doctrine of equivalents.

90. On information and belief, Sandoz had knowledge of the '707 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know

that it will aid and abet others' direct infringement of at least one of the claims of the '707 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '707 patent.

91. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '707 patent, either literally or under the doctrine of equivalents.

92. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '707 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT III

INFRINGEMENT OF THE '700 PATENT

93. Plaintiffs reallege paragraphs 1 to 92 as if fully set forth herein.

94. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe claims 1-4, 7-10, 13-16 and 19 of the '700 patent.

95. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '700 patent.

96. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '700 patent infringed at least one of the claims of the '700 patent, including but not limited to claims 1-4, 7-10, 13-16 and 19, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

97. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during

the term of the '700 patent would further infringe at least one claim of the '700 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

98. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '700 patent either literally or under the doctrine of equivalents.

99. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '700 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '700 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

100. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '700 patent, either literally or under the doctrine of equivalents.

101. On information and belief, Sandoz had knowledge of the '700 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '700 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '700 patent.

102. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '700 patent, either literally or under the doctrine of equivalents.

103. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '700 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT IV

INFRINGEMENT OF THE '383 PATENT

104. Plaintiffs reallege paragraphs 1 to 103 as if fully set forth herein.

105. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '383 patent.

106. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '383 patent.

107. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '383 patent infringed at least one of the claims of the '383 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

108. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '383 patent would further infringe at least one claim of the '383 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

109. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '383 patent either literally or under the doctrine of equivalents.

110. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '383 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '383 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

111. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '383 patent, either literally or under the doctrine of equivalents.

112. On information and belief, Sandoz had knowledge of the '383 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '383 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '383 patent.

113. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '383 patent, either literally or under the doctrine of equivalents.

114. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '383 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT V

INFRINGEMENT OF THE '610 PATENT

115. Plaintiffs reallege paragraphs 1 to 114 as if fully set forth herein.

116. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '610 patent.

117. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '610 patent.

118. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '610 patent infringed at least one of the claims of the '610 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

119. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '610 patent would further infringe at least one claim of the '610 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

120. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '610 patent either literally or under the doctrine of equivalents.

121. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '610 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '610 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA

Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

122. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '610 patent, either literally or under the doctrine of equivalents.

123. On information and belief, Sandoz had knowledge of the '610 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '610 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '610 patent.

124. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '610 patent, either literally or under the doctrine of equivalents.

125. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '610 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT VI

INFRINGEMENT OF THE '002 PATENT

126. Plaintiffs reallege paragraphs 1 to 125 as if fully set forth herein.

127. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '002 patent.

128. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '002 patent.

129. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '002 patent infringed at least one of the claims of the '002 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

130. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '002 patent would further infringe at least one claim of the '002 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

131. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '002 patent either literally or under the doctrine of equivalents.

132. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '002 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '002 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

133. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '002 patent, either literally or under the doctrine of equivalents.

134. On information and belief, Sandoz had knowledge of the '002 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know

that it will aid and abet others' direct infringement of at least one of the claims of the '002 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '002 patent.

135. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '002 patent, either literally or under the doctrine of equivalents.

136. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '002 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT VII

INFRINGEMENT OF THE '475 PATENT

137. Plaintiffs reallege paragraphs 1 to 136 as if fully set forth herein.

138. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '475 patent.

139. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '475 patent.

140. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '475 patent infringed at least one of the claims of the '475 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

141. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during

the term of the ‘475 patent would further infringe at least one claim of the ‘475 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

142. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the ‘475 patent either literally or under the doctrine of equivalents.

143. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the ‘475 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the ‘475 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

144. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the ‘475 patent, either literally or under the doctrine of equivalents.

145. On information and belief, Sandoz had knowledge of the ‘475 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others’ direct infringement of at least one of the claims of the ‘475 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the ‘475 patent.

146. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the ‘475 patent, either literally or under the doctrine of equivalents.

147. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '475 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT VIII

INFRINGEMENT OF THE '780 PATENT

148. Plaintiffs reallege paragraphs 1 to 147 as if fully set forth herein.

149. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '780 patent.

150. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '780 patent.

151. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '780 patent infringed at least one of the claims of the '780 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

152. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '780 patent would further infringe at least one claim of the '780 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

153. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '780 patent either literally or under the doctrine of equivalents.

154. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '780 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '780 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

155. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '780 patent, either literally or under the doctrine of equivalents.

156. On information and belief, Sandoz had knowledge of the '780 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '780 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '780 patent.

157. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '780 patent, either literally or under the doctrine of equivalents.

158. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '780 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT IX

INFRINGEMENT OF THE '150 PATENT

159. Plaintiffs reallege paragraphs 1 to 158 as if fully set forth herein.

160. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe claims 1-7, 11-14, 16-19 and 23-27 of the '150 patent.

161. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '150 patent.

162. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '150 patent infringed at least one of the claims of the '150 patent, including but not limited to claims 1-7, 11-14, 16-19 and 23-27, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

163. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '150 patent would further infringe at least one claim of the '150 patent, including but not limited to claims 1 and 27, under 35 U.S.C. §§ 271 (a), (b), and/or (c).

164. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '150 patent either literally or under the doctrine of equivalents.

165. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '150 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of

the '150 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

166. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '150 patent, either literally or under the doctrine of equivalents.

167. On information and belief, Sandoz had knowledge of the '150 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '150 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '150 patent.

168. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '150 patent, either literally or under the doctrine of equivalents.

169. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '150 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT X

INFRINGEMENT OF THE '674 PATENT

170. Plaintiffs reallege paragraphs 1 to 169 as if fully set forth herein.

171. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe claims 6-10 the '674 patent.

172. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '674 patent.

173. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '674 patent infringed at least one of the claims of the '674 patent, including but not limited to claims 6-10, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

174. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '674 patent would further infringe at least one claim of the '674 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

175. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '674 patent either literally or under the doctrine of equivalents.

176. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '674 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '674 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

177. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '674 patent, either literally or under the doctrine of equivalents.

178. On information and belief, Sandoz had knowledge of the '674 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '674 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '674 patent.

179. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '674 patent, either literally or under the doctrine of equivalents.

180. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '674 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XI

INFRINGEMENT OF THE '462 PATENT

181. Plaintiffs reallege paragraphs 1 to 180 as if fully set forth herein.

182. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '462 patent.

183. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '462 patent.

184. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United

States prior to the expiration of the '462 patent infringed at least one of the claims of the '462 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

185. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '462 patent would further infringe at least one claim of the '462 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

186. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '462 patent either literally or under the doctrine of equivalents.

187. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '462 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '462 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

188. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '462 patent, either literally or under the doctrine of equivalents.

189. On information and belief, Sandoz had knowledge of the '462 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '462 patent,

either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '462 patent.

190. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '462 patent, either literally or under the doctrine of equivalents.

191. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '462 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XII

INFRINGEMENT OF THE '701 PATENT

192. Plaintiffs reallege paragraphs 1 to 191 as if fully set forth herein.

193. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe claims 1-17 and 19 of the '701 patent.

194. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '701 patent.

195. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '701 patent infringed at least one of the claims of the '701 patent, including but not limited to claims 1-17 and 19, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

196. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during

the term of the '701 patent would further infringe at least one claim of the '701 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

197. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '701 patent either literally or under the doctrine of equivalents.

198. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '701 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '701 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

199. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '701 patent, either literally or under the doctrine of equivalents.

200. On information and belief, Sandoz had knowledge of the '701 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '701 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '701 patent.

201. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '701 patent, either literally or under the doctrine of equivalents.

202. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '701 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XIII

INFRINGEMENT OF THE '098 PATENT

203. Plaintiffs reallege paragraphs 1 to 202 as if fully set forth herein.

204. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '098 patent.

205. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '098 patent.

206. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '098 patent infringed at least one of the claims of the '098 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

207. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '098 patent would further infringe at least one claim of the '098 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

208. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '098 patent either literally or under the doctrine of equivalents.

209. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '098 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '098 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

210. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '098 patent, either literally or under the doctrine of equivalents.

211. On information and belief, Sandoz had knowledge of the '098 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '098 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '098 patent.

212. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '098 patent, either literally or under the doctrine of equivalents.

213. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '098 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XIV

INFRINGEMENT OF THE '109 PATENT

214. Plaintiffs reallege paragraphs 1 to 213 as if fully set forth herein.

215. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '109 patent.

216. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '109 patent.

217. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '109 patent infringed at least one of the claims of the '109 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

218. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '109 patent would further infringe at least one claim of the '109 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

219. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '109 patent either literally or under the doctrine of equivalents.

220. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '109 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '109 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA

Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

221. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '109 patent, either literally or under the doctrine of equivalents.

222. On information and belief, Sandoz had knowledge of the '109 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '109 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '109 patent.

223. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '109 patent, either literally or under the doctrine of equivalents.

224. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '109 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XV

INFRINGEMENT OF THE '947 PATENT

225. Plaintiffs reallege paragraphs 1 to 224 as if fully set forth herein.

226. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '947 patent.

227. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '947 patent.

228. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '947 patent infringed at least one of the claims of the '947 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

229. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during the term of the '947 patent would further infringe at least one claim of the '947 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

230. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '947 patent either literally or under the doctrine of equivalents.

231. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '947 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '947 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

232. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '947 patent, either literally or under the doctrine of equivalents.

233. On information and belief, Sandoz had knowledge of the '947 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know

that it will aid and abet others' direct infringement of at least one of the claims of the '947 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '947 patent.

234. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '947 patent, either literally or under the doctrine of equivalents.

235. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '947 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

COUNT XVI

INFRINGEMENT OF THE '217 PATENT

236. Plaintiffs reallege paragraphs 1 to 235 as if fully set forth herein.

237. Sandoz's Notice Letter regarding its Paragraph IV Certification does not deny that the Sandoz ANDA Product will infringe the '217 patent.

238. On information and belief, Sandoz does not deny that the Sandoz ANDA Product will infringe at least certain claims of the '217 patent.

239. Defendants' submission of the Sandoz ANDA to obtain approval to engage in the commercial manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States prior to the expiration of the '217 patent infringed at least one of the claims of the '217 patent, either literally or under the doctrine of equivalents under 35 U.S.C. § 271(e)(2)(A).

240. Defendants' manufacture, use, offer to sell, or sale of the Sandoz ANDA Product in the United States or importation of the Sandoz ANDA Product into the United States during

the term of the '217 patent would further infringe at least one claim of the '217 patent under 35 U.S.C. §§ 271 (a), (b), and/or (c).

241. On information and belief, the Sandoz ANDA Product, when offered for sale, sold, and/or imported, and when used as directed, would be used in a manner that would directly infringe at least one of the claims of the '217 patent either literally or under the doctrine of equivalents.

242. On information and belief, the use of the Sandoz ANDA Product constitutes a material part of at least one of the claims of the '217 patent; Defendants know that the Sandoz ANDA Product is especially made or adapted for use in infringing at least one of the claims of the '217 patent, either literally or under the doctrine of equivalents; and the Sandoz ANDA Product is not a staple article of commerce or commodity of commerce suitable for substantial noninfringing use.

243. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product would contributorily infringe at least one of the claims of the '217 patent, either literally or under the doctrine of equivalents.

244. On information and belief, Sandoz had knowledge of the '217 patent and, by its promotional activities and package inserts for the Sandoz ANDA Product, knows or should know that it will aid and abet others' direct infringement of at least one of the claims of the '217 patent, either literally or under the doctrine of equivalents, and specifically intends that those activities will infringe the '217 patent.

245. On information and belief, the offering to sell, sale, and/or importation of the Sandoz ANDA Product by Defendant would actively induce infringement of at least one of the claims of the '217 patent, either literally or under the doctrine of equivalents.

246. If Defendants' marketing and sale of the Sandoz ANDA Product prior to expiration of the '217 patent and all other relevant exclusivities are not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no remedy at law.

* * *

247. Defendants' activities, as alleged herein, were undertaken with knowledge of the Asserted Patents and without a good faith belief that they are not infringing those patents. This is an exceptional case.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray that this Court grant the following relief:

1. A judgment that the claims of the Asserted Patents were infringed by Defendants' submission of the Sandoz ANDA, either literally or under the doctrine of equivalents, and are not invalid or unenforceable, and that Defendants' making, using, offering to sell, or selling in the United States, or importing into the United States the Sandoz ANDA Product will infringe the claims of the Asserted Patents, either literally or under the doctrine of equivalents.

2. An Order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of the Sandoz ANDA shall be a date which is not earlier than the latest expiration date of the Asserted Patents, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled.

3. An Order permanently enjoining Defendants, their affiliates, subsidiaries, and each of their officers, agents, servants and employees and those acting in privity or concert with them, from making, using, offering to sell, or selling in the United States, or importing into the United States the Sandoz ANDA Product until after the latest expiration date of the Asserted

Patents, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled.

4. Damages or other monetary relief, including costs, fees, pre- and post-judgment interest, to Plaintiffs if Defendants engage in commercial manufacture, use, offers to sell, sale, or importation in or into the United States of the Sandoz ANDA Product prior to the latest expiration date of the Asserted Patents, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled.

5. Such further and other relief as this Court deems proper and just, including any appropriate relief under 35 U.S.C. § 285.

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January 31, 2019

EXHIBIT 1

US007566729B1

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 7,566,729 B1**
(45) **Date of Patent: Jul. 28, 2009**

(54) **MODIFYING PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION**

(75) Inventors: **Williamson Ziegler Bradford**, Ross, CA (US); **Javier Szwarcberg**, San Francisco, CA (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/428,393**

(22) Filed: **Apr. 22, 2009**

Related U.S. Application Data

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(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/327**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Methods are provided for administering pirfenidone to a patient that has exhibited abnormal biomarkers of liver function in response to pirfenidone administration. The methods include administering to a patient pirfenidone at doses lower than the full target dosage for a time period, followed by administering to the patient pirfenidone at the full target dosage.

9 Claims, No Drawings

MODIFYING PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 61/113,107, filed Nov. 10, 2008, the disclosure of which is incorporated by reference in its entirety.

BACKGROUND

1. Field of the Disclosure

The disclosure relates generally to methods for reducing adverse effects associated with the treatment of diseases and disorders. More particularly, the disclosure relates to methods for reducing abnormal liver function associated with 5-methyl-1-phenyl-2-(1H)-pyridone ("pirfenidone") therapy.

2. Brief Description of Related Technology

U.S. Pat. Nos. 3,974,281, 4,042,699, and 4,052,509 generally relate to pirfenidone administration. U.S. Pat. Nos. 5,310,562, 5,518,729, and 5,716,632, all to Margolin and incorporated by reference herein, relate to pirfenidone administration.

Pulmonary fibrosis can be caused by a number of different conditions, including sarcoidosis, hypersensitivity pneumonitis, collagen vascular disease, and inhalant exposure. Idiopathic pulmonary fibrosis (IPF) is a distinct entity, characterized by breathing difficulty, radiographic abnormalities, and progressive loss of lung function. It is invariably progressive, and carries a grave prognosis with a median life expectancy of 2-3 years.

Pirfenidone has been administered to IPF patients. In a compassionate-use study, Raghu et al. ("Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study." Am J Respir Crit Care Med 159:1061-1069, 1999) reported administration of pirfenidone. No adverse events in hematology or blood chemistry were noted.

Nagai et al. conducted an uncontrolled, open-label study of pirfenidone in patients ("Open label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis." Internal Medicine 41:1118-1123, 2002). During treatment, no liver dysfunctions, hematologic abnormalities, or allergic or shock reactions were reported.

Moises et al. "A double-blind, multicenter study comparing pirfenidone and prednisone for moderate-to-severe pulmonary fibrosis." Chest 124:116S, 2003 reported administration of pirfenidone.

Azuma et al. "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." Am J Respir Crit Care Med 171:1040-1047, 2005) describes administration of pirfenidone to a maximum of 1800 mg/day of pirfenidone, and reports a protocol for stepwise reduction and rechallenge with drug after an adverse event.

Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See *FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, October 2007.

SUMMARY

One aspect of the invention provides methods for administering a therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal biomarkers of liver function after pirfenidone administration for the treatment of fibrosis, e.g. idiopathic pulmonary fibrosis (IPF). In some embodiments, a patient is identified who exhibits a significantly abnormal level of one, two, three or more biomarkers of liver function, e.g. the level of a grade 2 abnormality, after administration of an original full target dose of pirfenidone, e.g. about 2400 mg/day or 2403 mg/day. In such patients, the dose of pirfenidone is reduced or discontinued until levels of the abnormal biomarkers approach or are within normal range, after which patients are administered increasing doses of pirfenidone, up to the original full target dose. Alternatively, the dose of pirfenidone is not reduced at all, but liver biomarkers continue to be monitored. As used herein, "original full target dose" means the therapeutically effective dose approved by the U.S. Food and Drug Administration or a similar agency in a foreign country, optionally other than Japan. In some embodiments, the original full target dose is about 2400 mg/day or 2403 mg/day pirfenidone, or about 34 mg/kg/day (e.g. 33-35 mg/kg/day), or from 2200 to 2600 mg/day pirfenidone, or from 31 mg/kg/day to 37 mg/kg/day. The total daily dose is administered one, two or three times per day.

Thus, the invention provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has a liver function grade 2 abnormality. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until the liver function biomarkers return to grade 0 or grade 1, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until the liver function biomarkers return to grade 0 or grade 1, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return

to grade 0 or grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In any of the embodiments described herein, any of the reduced doses of pirfenidone may be administered for a time period of 2 days, 3 days, 4 days, 5 days, 6 days, one week, about two weeks, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits.

In any of the embodiments described herein, the patient can have fibrotic lesional tissue. In one embodiment, the patient is suffering from pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions. In one embodiment, the patient is suffering from pulmonary fibrosis, or idiopathic pulmonary fibrosis.

In some embodiments, the biomarker of liver function is alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase. Elevated gamma-glutamyl transferase has been observed in some patients receiving pirfenidone, without clinical liver impairment, and thus elevated gamma-glutamyl transferase alone is not necessarily a sign of liver impairment. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase. In another embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5-fold increased compared to the upper limit of normal (ULN). In a related embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5- to about 5-fold increased compared to the upper limit of normal (ULN), i.e. a "liver function grade 2 abnormality". In some embodiments, the abnormal level of bilirubin is greater than about 1.5- to about 3-fold increased compared to the upper limit of normal (ULN), i.e., a "liver function grade 2 abnormality".

In some embodiments the abnormal biomarkers of liver function, e.g. elevated alanine transaminase and/or aspartate transaminase and/or elevated bilirubin, are accompanied by clinical signs of impaired liver function such as jaundice.

Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the examples. While the method is susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

The invention provides methods for administering a full therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal levels of biomarkers of liver function after the patient has been treated with pirfenidone. Because liver function abnormalities can be indicative of drug-induced liver injury (hepatotoxicity), it is important to determine whether the abnormalities reflect liver injury or merely indicate limited toxicity that will resolve over time while continuing to take the drug. According to the present invention, even patients that exhibit abnormal liver function may continue taking pirfenidone at the original full target dose, optionally after a short time period of discontinuing pifenidone or taking the pirfenidone at reduced doses. This administration regimen has the advantage of maximizing the time on the full target dose of drug and therefore the potential for a beneficial therapeutic effect.

The patient may be suffering from any disease for which pirfenidone therapy may be useful in ameliorating symptoms. These diseases include, but are not limited to: chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis (IPF), rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and autoimmune diseases, such as Multiple Sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myclogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

The methods of the invention optionally include identifying abnormal liver function in a patient receiving pirfenidone, and monitoring biomarkers of liver function in a patient

receiving a reduced dose of pirfenidone. In any of the methods described herein, AST and ALT may be elevated, e.g. to a grade 2 or grade 3 level. Alternatively, AST and bilirubin may be elevated, or AST or ALP may be elevated, or AST and GGT may be elevated, or ALT and bilirubin may be elevated, or ALT and ALP may be elevated, or ALT and GGT may be elevated, or bilirubin and ALP may be elevated, or bilirubin and GGT may be elevated, e.g. to a grade 2 or grade 3 level. Alternatively, three biomarkers of liver function may be elevated, e.g., ALT and AST and bilirubin, or ALT and AST and ALP, to a grade 2 or grade 3 level. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (b) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to grade 1, or until all biomarkers or liver function has returned to within normal limits, or to grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to grade 1, or until all biomarkers or liver function has returned to within normal limits, or to grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function grade 2 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to grade 1, or until all biomarkers or liver function has returned to within normal limits, or to grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to grade 1, or until all biomarkers or liver function has returned to within normal limits, or to grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to grade 1, or until all biomarkers or liver function has returned to within normal limits, or to grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

Pirfenidone can be provided in tablet or capsule forms or any other oral dosage form, and typically is formulated for oral administration. Exemplary capsule formulations are described in WO 2007/038315 (Int'l Appl. No. PCT/US2006/037057).

Pirfenidone therapy can be associated with adverse effects including photosensitivity rash, anorexia (decreased appetite), stomach discomfort, nausea, heartburn, drowsiness (somnolence), fatigue, upper respiratory tract infection, fever, positive urinary occult blood, elevation of C-reactive protein (CRP), decreased weight, headache, constipation, and malaise. Abnormal liver function also can occur as an adverse effect (AE) in patients receiving pirfenidone. Prior to receiving pirfenidone, the baseline liver function of the patient can be, and typically is, normal. Liver function can be assessed by various means known in the art, such as blood chemistry tests measuring biomarkers of liver function. Examples of biomarkers of liver function include, but are not limited to, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Alanine transaminase (ALT), also called serum glutamic pyruvate transaminase (SGPT) or alanine aminotransferase (ALAT), catalyzes the transfer of an amino group from alanine to α-ketoglutarate to produce pyruvate and glutamate. When the liver is damaged, levels of ALT in the blood can rise due to the leaking of ALT into the blood from damaged or necrosed hepatocytes.

Aspartate transaminase (AST) also called serum glutamic oxaloacetic transaminase (SGOT or GOT) or aspartate aminotransferase (ASAT), catalyzes the transfer of an amino group from aspartate to α-ketoglutarate to produce oxaloacetate and glutamate. AST can increase in response to liver

damage. Elevated AST also can result from damage to other sources, including red blood cells, cardiac muscle, skeletal muscle, kidney tissue, and brain tissue. The ratio of AST to ALT can be used as a biomarker of liver damage.

Bilirubin is a catabolite of heme that is cleared from the body by the liver. Conjugation of bilirubin to glucuronic acid by hepatocytes produces direct bilirubin, a water-soluble product that is readily cleared from the body. Indirect bilirubin is unconjugated, and the sum of direct and indirect bilirubin constitutes total bilirubin. Elevated total bilirubin can be indicative of liver impairment.

Alkaline phosphatase (ALP) hydrolyzes phosphate groups from various molecules and is present in the cells lining the biliary ducts of the liver. ALP levels in plasma can rise in response to liver damage, and are higher in growing children and elderly patients with Paget's disease. However, elevated ALP levels usually reflect biliary tree disease.

Adverse effect grades for abnormal liver function are defined herein by the modified Common Toxicity Criteria (CTC) provided in Table 1. See the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published Aug. 9, 2006 by the National Cancer Institute, incorporated herein by reference in its entirety.

TABLE 1

Modified Common Toxicity Criteria

	Grade				
Toxicity	0	1	2	3	4
ALT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
AST	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
Bilirubin	WNL	>ULN-1.5 × ULN	>1.5-3 × ULN	>3-10 × ULN	>10 × ULN
ALP	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
GGT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN

(WNL = within normal limits; ULN = upper limit of normal)

The ULN for various indicators of liver function depends on the assay used, the patient population, and each laboratory's normal range of values for the specified biomarker, but can readily be determined by the skilled practitioner. Exemplary values for normal ranges for a healthy adult population are set forth in Table 2 below. See Cecil Textbook of Medicine, pp. 2317-2341, W.B. Saunders & Co. (1985).

TABLE 2

ALT	8-20 U/L
AST	8-20 U/L
Bilirubin	0.2-1.0 mg/dL
	3.4-17.1 μmol/L
ALP	20-70 U/L
GGT	Men: 9-50 U/L
	Women: 8-40 U/L

Grade 0 levels are characterized by biomarker levels within normal limits (WNL). "Normal" liver function, as used herein, refers to Grade 0 adverse effects. "Abnormal" liver function, as used herein, refers to Grade 1 and above adverse effects.

"Grade 1 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than the ULN and less than or equal to 2.5-times the ULN. Grade 1 liver function abnormalities also include elevations of bilirubin levels greater than the ULN and less than or equal to 1.5-times the ULN.

"Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver function abnormalities also include elevations of bilirubin levels greater than 1.5-times and less than or equal to 3-times the ULN.

"Grade 3 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 5-times and less than or equal to 20-times the ULN. Grade 3 liver function abnormalities also include elevations of bilirubin levels greater than 3-times and less than or equal to 10-times the ULN.

"Grade 4 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 20-times the ULN. Grade 4 liver function abnormalities also include elevations of bilirubin levels greater than 10 the ULN.

The present disclosure provides methods for treating a patient having idiopathic pulmonary fibrosis and receiving a full target dose of pirfenidone, wherein the full target dose is 2400 or 2403 mg pirfenidone per day. In accordance with the methods, a patient with abnormal liver function is administered a second dose of pirfenidone, wherein the second dose is 1600 or 1602 mg pirfenidone per day until liver function is within normal limits, followed by administering the patient the full target dose of 2400 or 2403 mg pirfenidone per day.

The methods disclosed herein are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described herein (including those described in the examples), unless stated otherwise.

Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

EXAMPLES

The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1

Pirfenidone Dosing Regimen

Patients begin pirfenidone treatment by receiving escalating doses of pirfenidone over a period of 15 days until the full maintenance dose is reached. Specifically, from days 1 to 7, patients are administered one capsule of 267 mg pirfenidone

three times per day. During days 8 to 14, patients receive two capsules of 267 mg pirfenidone three times per day. From day 15 onward, patients are treated with three capsules of 267 mg pirfenidone three times per day. Pirfenidone is administered orally, and each dose should be taken with food. If the patient is unable to eat, then the pirfenidone dose should be taken with milk or juice (excluding grapefruit juice).

Pirfenidone is known to cause photosensitivity reactions; therefore, throughout the treatment period, patients should use sun block that protects against at least UV-A with a sun protective factor (SPF) of 50. In addition, patients should wear appropriate clothing to minimize sun exposure, and if possible, avoid other medications known to cause photosensitivity reactions.

Once the full maintenance dose is reached, pirfenidone is administered orally to patients three times per day to provide a daily dose of 2403 mg pirfenidone. Each of the three doses of 801 mg pirfenidone includes three capsules of 267 mg pirfenidone each. The contents of the pirfenidone 267 mg capsules are pirfenidone (82.15%); croscarmellose sodium (8.15%); microcrystalline cellulose (7.39%); povidine, USP, EP (1.85%); and magnesium stearate (0.46%).

Patients are treated with pirfenidone for up to 72 weeks. Some patients are treated longer than 72 weeks. At weeks 2, 4, 6, 12, and every 12 weeks (±2 weeks) thereafter during the treatment period, with the exception of week 72 and the treatment completion visit, patients are examined and histories are collected as detailed in the steps below.

1. Patient history is collected to include review of adverse effects (AEs) and severe adverse effects (SAEs), use of concomitant medications, use of oxygen, hospitalizations, IPF exacerbations or acute respiratory decompensation, and dosing.

2. Patients receive a physical examination, and vital signs and weight are measured.

3. Pulmonary function is assessed by spirometry before and after administration of bronchodilators. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) are measured.

4. Clinical laboratory tests are performed, including hematology, serum chemistries, pregnancy tests for women of childbearing capacity, and urinalysis with microscopic examination.

5. Questionnaires are administered, including the University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ), St. George's Hospital Respiratory Questionnaire (SGRQ), and the World Health Organization Quality of Life (WHO QOL) questionnaire. After week 72, only the UCSD SOBQ and SGRQ are obtained at the scheduled 12 week visits.

Additionally, every 24 weeks starting with Week 12 (for example, weeks 12, 36, and 60), electrocardiogram (ECG) measurements are obtained. ECG data is obtained before administering bronchodilators for the pulmonary function test (PFT) measurements. At the week 36 visit, pharmacokinetic (PK) data is obtained for selected patients.

If a patient experiences a Grade 1 or greater elevation in alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin at baseline or after the start of pirfenidone dosing up to and including week 6, an additional safety chemistry blood test must be obtained between weeks 8 and 10.

Example 2

Modification of Pirfenidone Dosing Regimen in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to one capsule of 267 mg pirfenidone three times per day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

At any time after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 capsules per day. After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose also can be re-escalated in a manner consistent with the initial dose escalation, up to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly or every 2 weeks, or every 3 weeks, or every month to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 3

Temporary Discontinuation of Pirfenidone Dosing in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is discontinued. Following discontinuation of the pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. Pirfenidone dosing is discontinued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade

0). The pirfenidone dose can be discontinued for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, if the patient has been off drug for 14 days or more, the pirfenidone dose is re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 or 9 capsules per day, i.e. 1602 mg/day or 2403 mg/day. Alternatively, after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose is re-instituted at a dose of 6 capsules per day, i.e. 1602 mg/day, and re-escalated after 1 week to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly, or every 2 weeks, or every month, to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 4

Modification of Pirfenidone Dosing Regimen to 2 Capsules Three Times Per Day in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to two capsules of 267 mg pirfenidone three times per day, i.e. 1602 mg/day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After 1 week of treatment at 1602 mg/day, if AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated to the maximum of 9 capsules per day, i.e. 2403 mg.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art. Although methods have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used.

All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

What is claimed is:

1. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising

(a) administering to said patient pirfenidone at doses lower than 2400 mg/day for a time period, followed by

(b) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day.

2. The method of claim **1** wherein prior to step (a) pirfenidone is discontinued until biomarkers of liver function are within normal limits.

3. The method of claim **1** wherein step (a) comprises administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

4. The method of claim **1** wherein step (a) comprises administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits, followed by administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week.

5. The method of claim **1** wherein step (a) comprises discontinuing pirfenidone for about one week, or until biomarkers of liver function are within normal limits, followed by administering about 800 mg/day or 801 mg/day pirfenidone for about one week, followed by administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week.

6. The method of claim **1**, wherein the pirfenidone is administered three times per day with food.

7. The method of claim **1**, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase, aspartate transaminase, bilirubin, and alkaline phosphatase.

8. The method of claim **1** further comprising the step of measuring one or more biomarkers of liver function during step (a).

9. The method of claim **1**, wherein said one or more biomarkers of liver function comprise alanine transaminase and aspartate transaminase.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,566,729 B1
APPLICATION NO. : 12/428393
DATED : July 28, 2009
INVENTOR(S) : Williamson Z. Bradford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page:

At field (73), "Intermune" should be -- InterMune --.

At Column 4, lines 35-36, "synoviitis" should be -- synovitis --.

At Column 4, lines 36-37, "tenosynoviitis" should be -- tenosynovitis --.

Signed and Sealed this

Sixteenth Day of February, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT 2

US007635707B1

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 7,635,707 B1**
(45) **Date of Patent: *Dec. 22, 2009**

(54) **PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/553,292**

(22) Filed: **Sep. 3, 2009**

Related U.S. Application Data

(63) Continuation-in-part of application No. 12/488,228, filed on Jun. 19, 2009, now abandoned, which is a continuation of application No. 12/428,393, filed on Apr. 22, 2009, now Pat. No. 7,566,729.

(60) Provisional application No. 61/113,107, filed on Nov. 10, 2008, provisional application No. 61/228,943, filed on Jul. 27, 2009.

(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/327**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Methods are provided for administering pirfenidone to a patient that has exhibited abnormal biomarkers of liver function in response to pirfenidone administration. The methods include administering to a patient pirfenidone at doses lower than the full target dosage for a time period, followed by administering to the patient pirfenidone at the full target dosage. The methods also include administering pirfenidone at the full target dose with no reduction and administering permanently reduced doses of pirfenidone.

14 Claims, No Drawings

PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 61/228,943, filed Jul. 27, 2009, the disclosure of which is incorporated by reference in its entirety. This application is a continuation-in-part of U.S. application Ser. No. 12/488,228, filed Jun. 19, 2009, which claims priority to U.S. Pat. No. 7,566,729, dated Jul. 28, 2009, which claims priority to U.S. Provisional Application Ser. No. 61/113,107, filed on Nov. 10, 2008, the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

1. Field of the Disclosure

The disclosure relates generally to methods for reducing adverse effects associated with the treatment of diseases and disorders. More particularly, the disclosure relates to methods for reducing abnormal liver function associated with 5-methyl-1-phenyl-2-(1H)-pyridone ("pirfenidone") therapy.

2. Brief Description of Related Technology

U.S. Pat. Nos. 3,974,281, 4,042,699, and 4,052,509 generally relate to pirfenidone administration. U.S. Pat. Nos. 5,310,562, 5,518,729, and 5,716,632, all to Margolin and incorporated by reference herein, relate to pirfenidone administration.

Pulmonary fibrosis can be caused by a number of different conditions, including sarcoidosis, hypersensitivity pneumonitis, collagen vascular disease, and inhalant exposure. Idiopathic pulmonary fibrosis (IPF) is a distinct entity, characterized by breathing difficulty, radiographic abnormalities, and progressive loss of lung function. It is invariably progressive, and carries a grave prognosis with a median life expectancy of 2-3 years.

Pirfenidone has been administered to IPF patients. In a compassionate-use study, Raghu et al. ("Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study." Am J Respir Crit Care Med 159:1061-1069, 1999) reported administration of pirfenidone. No adverse events in hematology or blood chemistry were noted.

Nagai et al. conducted an uncontrolled, open-label study of pirfenidone in patients ("Open label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis." Internal Medicine 41:1118-1123, 2002). During treatment, no liver dysfunctions, hematologic abnormalities, or allergic or shock reactions were reported.

Moises et al. "A double-blind, multicenter study comparing pirfenidone and prednisone for moderate-to-severe pulmonary fibrosis." Chest 124:116S, 2003 reported administration of pirfenidone.

Azuma et al. "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." Am J Respir Crit Care Med 171:1040-1047, 2005) describes administration of pirfenidone to a maximum of 1800 mg/day of pirfenidone, and reports a protocol for stepwise reduction and rechallenge with drug after an adverse event.

Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See *FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, October 2007.

SUMMARY

One aspect of the invention provides methods for administering a therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal biomarkers of liver function after pirfenidone administration for the treatment of fibrosis, e.g. idiopathic pulmonary fibrosis (IPF). In some embodiments, a patient is identified who exhibits a significantly abnormal level of one, two, three or more biomarkers of liver function, e.g. the level of a Grade 2 abnormality, after administration of an original full target dose of pirfenidone, e.g. about 2400 mg/day or 2403 mg/day. In such patients, the dose of pirfenidone is reduced or discontinued until levels of the abnormal biomarkers approach or are within normal range, after which patients are administered increasing doses of pirfenidone, up to the original full target dose. Alternatively, the dose of pirfenidone is not reduced at all, but liver biomarkers continue to be monitored. In another embodiment, after an optional temporary dose reduction or discontinuation, patients are administered pirfenidone at a permanently reduced dose of 1602 mg/day. As used herein, "original full target dose" means the therapeutically effective dose approved by the U.S. Food and Drug Administration or a similar agency in a foreign country, optionally other than Japan. In some embodiments, the original full target dose is about 2400 mg/day or 2403 mg/day pirfenidone, or about 34 mg/kg/day (e.g. 33-35 mg/kg/day), or from 2200 to 2600 mg/day pirfenidone, or from 31 mg/kg/day to 37 mg/kg/day. The total daily dose is administered one, two or three times per day.

Thus, the invention provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 2 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (c) administering the original

full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

The invention also provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 1 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as

follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In any of the embodiments described herein, any of the reduced doses of pirfenidone may be administered for a time period of 2 days, 3 days, 4 days, 5 days, 6 days, one week, about two weeks, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits.

In any of the embodiments described herein, the patient can have fibrotic lesional tissue. Such a patient is a patient who would benefit from pirfenidone administration. In one embodiment, the patient is suffering from pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions. In one embodiment, the patient is suffering from lymph node fibrosis associated with HIV. In one embodiment, the patient is suffering from pulmonary fibrosis, or idiopathic pulmonary fibrosis. In another embodiment, the patient is a person who would benefit from pirfenidone administration, optionally with the proviso that the patient is not suffering from idiopathic pulmonary fibrosis.

In some embodiments, the biomarker of liver function is alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase. Elevated gamma-glutamyl transferase has been observed in some patients receiving pirfenidone, without clinical liver impairment, and thus elevated gamma-glutamyl transferase alone is not necessarily a sign of liver impairment. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase. In another embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5-fold increased compared to the upper limit of normal (ULN). In a related embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5- to about 5-fold increased compared to the upper limit of normal (ULN), i.e. a "liver function Grade 2 abnormality". In some embodiments, the abnormal level of bilirubin is greater than about 1.5- to about 3-fold increased compared to the upper limit of normal (ULN), i.e., a "liver function Grade 2 abnormality".

In some embodiments the abnormal biomarkers of liver function, e.g. elevated alanine transaminase and/or aspartate transaminase and/or elevated bilirubin, are accompanied by clinical signs of impaired liver function such as jaundice.

Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the examples. While the method is susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

The invention provides methods for administering a full therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal levels of biomarkers of liver function after the patient has been treated with pirfenidone. Because liver function abnormalities can be indicative of drug-induced liver injury (hepatotoxicity), it is important to determine whether the abnormalities reflect liver injury or merely indicate limited toxicity that will resolve over time while continuing to take the drug. According to the present invention, even patients that exhibit abnormal liver function may continue taking pirfenidone at the original full target dose, optionally after a short time period of discontinuing pirfenidone or taking the pirfenidone at reduced doses. This administration regimen has the advantage of maximizing the time on the full target dose of drug and therefore the potential for a beneficial therapeutic effect.

The patient may be suffering from any disease for which pirfenidone therapy may be useful in ameliorating symptoms. Such a patient is a patient who would benefit from pirfenidone administration. These diseases include, but are not limited to: chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis (IPF), rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as Multiple Sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (in-

cluding both benign and malignant hyperplasias), including acute myclogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal, carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

The methods of the invention optionally include identifying abnormal liver function in a patient receiving pirfenidone, and monitoring biomarkers of liver function in a patient receiving a reduced dose of pirfenidone. In any of the methods described herein, AST and/or ALT may be elevated, e.g. to a Grade 2 or Grade 3 level. In some embodiments, the elevation is to a Grade 1 level. Alternatively, AST and bilirubin may be elevated, or AST or ALP may be elevated, or AST and GGT may be elevated, or ALT and bilirubin may be elevated, or ALT and ALP may be elevated, or ALT and GGT may be elevated, or bilirubin and ALP may be elevated, or bilirubin and GGT may be elevated, e.g., to a Grade 1, Grade 2, or Grade 3 level. Alternatively, three biomarkers of liver function may be elevated, e.g., ALT and AST and bilirubin, or ALT and AST and ALP, to a Grade 1, Grade 2, or Grade 3 level. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality after pirfenidone administration as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period. In some embodiments, step (a) is followed by (b) administering the original full target dose. In other embodiments, the original full target dose is continued without a temporary reduction or discontinuation of the dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (b) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month,

or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

Pirfenidone can be provided in tablet or capsule forms or any other oral dosage form, and typically is formulated for oral administration. Exemplary capsule formulations are described in WO 2007/038315 (Int'l Appl. No. PCT/US2006/037057).

Pirfenidone therapy can be associated with adverse effects including photosensitivity rash, anorexia (decreased appetite), stomach discomfort, nausea, heartburn, drowsiness (somnolence), fatigue, upper respiratory tract infection, fever, positive urinary occult blood, elevation of C-reactive protein (CRP), decreased weight, headache, constipation, and malaise. Abnormal liver function also can occur as an adverse effect (AE) in patients receiving pirfenidone. Prior to receiving pirfenidone, the baseline liver function of the patient can be, and typically is, normal. Liver function can be assessed by various means known in the art, such as blood chemistry tests measuring biomarkers of liver function. Examples of biomarkers of liver function include, but are not limited to, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Alanine transaminase (ALT), also called serum glutamic pyruvate transaminase (SGPT) or alanine aminotransferase (ALAT), catalyzes the transfer of an amino group from alanine to α-ketoglutarate to produce pyruvate and glutamate. When the liver is damaged, levels of ALT in the blood can rise due to the leaking of ALT into the blood from damaged or necrosed hepatocytes.

Aspartate transaminase (AST) also called serum glutamic oxaloacetic transaminase (SGOT or GOT) or aspartate aminotransferase (ASAT), catalyzes the transfer of an amino group from aspartate to α-ketoglutarate to produce oxaloacetate and glutamate. AST can increase in response to liver damage. Elevated AST also can result from damage to other sources, including red blood cells, cardiac muscle, skeletal muscle, kidney tissue, and brain tissue. The ratio of AST to ALT can be used as a biomarker of liver damage.

Bilirubin is a catabolite of heme that is cleared from the body by the liver. Conjugation of bilirubin to glucuronic acid by hepatocytes produces direct bilirubin, a water-soluble product that is readily cleared from the body. Indirect bilirubin is unconjugated, and the sum of direct and indirect bilirubin constitutes total bilirubin. Elevated total bilirubin can be indicative of liver impairment.

Alkaline phosphatase (ALP) hydrolyzes phosphate groups from various molecules and is present in the cells lining the biliary ducts of the liver. ALP levels in plasma can rise in response to liver damage, and are higher in growing children and elderly patients with Paget's disease. However, elevated ALP levels usually reflect biliary tree disease.

Adverse effect Grades for abnormal liver function are defined herein by the modified Common Toxicity Criteria (CTC) provided in Table 1. See the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published Aug. 9, 2006 by the National Cancer Institute, incorporated herein by reference in its entirety.

TABLE 1

Modified Common Toxicity Criteria

	Grade				
Toxicity	0	1	2	3	4
ALT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
AST	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
Bilirubin	WNL	>ULN-1.5 × ULN	>1.5-3 × ULN	>3-10 × ULN	>10 × ULN
ALP	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
GGT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN

(WNL = within normal limits; ULN = upper limit of normal)

The ULN for various indicators of liver function depends on the assay used, the patient population, and each laboratory's normal range of values for the specified biomarker, but can readily be determined by the skilled practitioner. Exemplary values for normal ranges for a healthy adult population are set forth in Table 2 below. See Cecil Textbook of Medicine, pp. 2317-2341, W.B. Saunders & Co. (1985).

TABLE 2

ALT	8-20 U/L
AST	8-20 U/L
Bilirubin	0.2-1.0 mg/dL 3.4-17.1 μmol/L
ALP	20-70 U/L
GGT	Men: 9-50 U/L Women: 8-40 U/L

Grade 0 levels are characterized by biomarker levels within normal limits (WNL). "Normal" liver function, as used herein, refers to Grade 0 adverse effects. "Abnormal" liver function, as used herein, refers to Grade 1 and above adverse effects.

"Grade 1 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than the ULN and less than or equal to 2.5-times the ULN. Grade 1 liver function abnormalities also include elevations of bilirubin levels greater than the ULN and less than or equal to 1.5-times the ULN.

"Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver function abnormalities also include elevations of bilirubin levels greater than 1.5-times and less than or equal to 3-times the ULN.

"Grade 3 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 5-times and less than or equal to 20-times the ULN. Grade 3 liver function abnormalities also include elevations of bilirubin levels greater than 3-times and less than or equal to 10-times the ULN.

"Grade 4 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 20-times the ULN. Grade 4 liver function abnormalities also include elevations of bilirubin levels greater than 10 the ULN.

The present disclosure provides methods for treating a patient having idiopathic pulmonary fibrosis and receiving a full target dose of pirfenidone, wherein the full target dose is 2400 or 2403 mg pirfenidone per day. In accordance with the methods, a patient with abnormal liver function is administered a second dose of pirfenidone, wherein the second dose is 1600 or 1602 mg pirfenidone per day until liver function is within normal limits, followed by administering the patient the full target dose of 2400 or 2403 mg pirfenidone per day.

The present disclosure also provides methods for treatment of patients that exhibit Grade 1 abnormality in one or more biomarkers of liver function after pirfenidone administration. The method includes administering to the patient pirfenidone at doses of 2400 mg/day or 2403 mg/day or administering to the patient pirfenidone at doses of 1600 mg/day or 1602 mg/day. Preferably, the patient may be receiving pirfenidone for treatment of idiopathic pulmonary fibrosis. Alternatively, the patient may be suffering from a condition for which pirfenidone administration may be beneficial. Optionally, patients may receive reduced doses or discontinue treatment for a time period, and then resume administration of pirfenidone.

The methods disclosed herein are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described herein (including those described in the examples), unless stated otherwise.

Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

It will be appreciated that the invention provides pirfenidone as a medicament wherein the administration pattern of the medicament comprises administering according to any of the treatment methods described herein.

It will be appreciated that the invention provides pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to any of the treatment regimes as described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration. Pirfenidone is packaged and presented for use in a treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to such treatment regimes. Pirfenidone is administered to the patient in accordance with the treatment regimes as described above. The patient is one who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration.

In particular, the invention includes pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Optionally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

It will be appreciated that the invention provides the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to

any of the treatment regimes as described above with respect to any of the methods. The medicaments manufactured according to this aspect of the invention are for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration in accordance with such treatment regimes. The medicament so manufactured is administered to the patient in accordance with the treatment regimes as described above. The patient is one who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration.

In particular, the invention includes the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Optionally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

In respect of the aspects of the invention relating to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, the preferences expressed with respect to the preferred embodiments of the aspect of the invention relating to a method for administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis apply in the same way. Similarly, the examples relate to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, as well as to a method for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis.

EXAMPLES

The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1

Pirfenidone Dosing Regimen

Patients begin pirfenidone treatment by receiving escalating doses of pirfenidone over a period of 15 days until the full maintenance dose is reached. Specifically, from days 1 to 7, patients are administered one capsule of 267 mg pirfenidone three times per day. During days 8 to 14, patients receive two capsules of 267 mg pirfenidone three times per day. From day 15 onward, patients are treated with three capsules of 267 mg pirfenidone three times per day. Pirfenidone is administered orally, and each dose should be taken with food. If the patient is unable to eat, then the pirfenidone dose should be taken with milk or juice (excluding grapefruit juice).

Pirfenidone is known to cause photosensitivity reactions; therefore, throughout the treatment period, patients should use sun block that protects against at least UV-A with a sun protective factor (SPF) of 50. In addition, patients should wear appropriate clothing to minimize sun exposure, and if possible, avoid other medications known to cause photosensitivity reactions.

Once the full maintenance dose is reached, pirfenidone is administered orally to patients three times per day to provide a daily dose of 2403 mg pirfenidone. Each of the three doses of 801 mg pirfenidone includes three capsules of 267 mg pirfenidone each. The contents of the pirfenidone 267 mg capsules are pirfenidone (82.15%); croscarmellose sodium (8.15%); microcrystalline cellulose (7.39%); povidine, USP, EP (1.85%); and magnesium stearate (0.46%).

Patients are treated with pirfenidone for up to 72 weeks. Some patients are treated longer than 72 weeks. At weeks 2, 4, 6, 12, and every 12 weeks (±2 weeks) thereafter during the treatment period, with the exception of week 72 and the treatment completion visit, patients are examined and histories are collected as detailed in the steps below.

1. Patient history is collected to include review of adverse effects (AEs) and severe adverse effects (SAEs), use of concomitant medications, use of oxygen, hospitalizations, IPF exacerbations or acute respiratory decompensation, and dosing.

2. Patients receive a physical examination, and vital signs and weight are measured.

3. Pulmonary function is assessed by spirometry before and after administration of bronchodilators. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) are measured.

4. Clinical laboratory tests are performed, including hematology, serum chemistries, pregnancy tests for women of childbearng capacity, and urinalysis with microscopic examination.

5. Questionnaires are administered, including the University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ), St. George's Hospital Respiratory Questionnaire (SGRQ), and the World Health Organization Quality of Life (WHO QOL) questionnaire. After week 72, only the UCSD SOBQ and SGRQ are obtained at the scheduled 12 week visits.

Additionally, every 24 weeks starting with Week 12 (for example, weeks 12, 36, and 60), electrocardiogram (ECG) measurements are obtained. ECG data is obtained before administering bronchodilators for the pulmonary function test (PFT) measurements. At the week 36 visit, pharmacokinetic (PK) data is obtained for selected patients.

If a patient experiences a Grade 1 or greater elevation in alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin at baseline or after the start of pirfenidone dosing up to and including week 6, an additional safety chemistry blood test must be obtained between weeks 8 and 10.

Example 2

Modification of Pirfenidone Dosing Regimen in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to one capsule of 267 mg pirfenidone three times per day. While

receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

At any time after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 capsules per day. After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose also can be re-escalated in a manner consistent with the initial dose escalation, up to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly or every 2 weeks, or every 3 weeks, or every month to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 3

Temporary Discontinuation of Pirfenidone Dosing in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is discontinued. Following discontinuation of the pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. Pirfenidone dosing is discontinued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The pirfenidone dose can be discontinued for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, if the patient has been off drug for 14 days or more, the pirfenidone dose is re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 or 9 capsules per day, i.e. 1602 mg/day or 2403 mg/day. Alternatively, after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose is re-instituted at a dose of 6 capsules per day, i.e. 1602 mg/day, and re-escalated after 1 week to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly, or every 2 weeks, or every month, to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 4

Modification of Pirfenidone Dosing Regimen to 2 Capsules Three Times Per Day in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to two capsules of 267 mg pirfenidone three times per day, i.e. 1602 mg/day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After 1 week of treatment at 1602 mg/day, if AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated to the maximum of 9 capsules per day, i.e. 2403 mg.

Example 5

No Modification of Pirfenidone Dosing Regime in Response to a Grade 1 or Grade 2 Liver Function Test (LFT) Elevations

Patients were treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, some patients exhibited abnormal liver function test results. As described in Example 1, serum chemistry tests were performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphate (ALP), and gamma-glutamyl transferase (GGT).

If a patient exhibited a Grade 1 or Grade 2 increase in any one of AST, ALT, or bilirubin, the pirfenidone dose was not reduced for some patients. The patient continued to receive the full target dose of 2403 mg/day. While receiving the full target dose, the patient was monitored for AST, ALT, and bilirubin levels.

Example 6

Incidence of Liver Function Abnormality and Dosing Regimen Response

Grade 1 Abnormalities in Liver Function

In a study of 345 patients with idiopathic pulmonary fibrosis receiving pirfenidone three times per day for a total daily dose of 2403 mg/day, 49 patients without a baseline liver function abnormality exhibited a Grade 1 elevation in AST or ALT levels after pirfenidone administration. Of the 49 patients, three patients with a Grade 1 liver function test elevation had a treatment emergent adverse event of increased AST or ALT. In one patient, study drug dose was reduced to

1602 mg/day for the remainder of study participation (from Day 51 to Day 602), and the Grade 1 AST or ALT abnormality returned to Grade 0. For the second patient, study drug dose was reduced to 1602 mg/day and then increased to 2403 mg/day for remainder of study participation, and ALT returned to Grade 0. The third patient had study drug dose reduced to 801 mg/day, ultimately completing study at 1602 mg/day, at which time ALT returned to Grade 0. The remaining patients (46 patients) received no dose modification.

Grade 2 Abnormalities in Liver Function

Fifteen patients developed a Grade 2 liver function test abnormality in AST and/or ALT levels after pirfenidone administration of 2403 mg/day. Of the fifteen patients, 12 had reported treatment emergent adverse events of increased AST or ALT or hepatitis. The liver function test elevations for the remaining three patients were not documented as an adverse event (discussed below).

Of the twelve patients, two patients received continued administration of pirfenidone at the full daily dose of 2403 mg/day. The liver function test of one patient resolved to a Grade 0. The other patient had a history of steatosis and a Grade 1 abnormality prior to pirfenidone treatment and underwent a dose reduction for unrelated reasons (rash and diarrhea), not for abnormal liver function tests, and ended the study with a Grade 1 elevation.

Two patients had a temporary dose reduction or a temporary discontinuation of pirfenidone, and were rechallenged and escalated back to full dose. They completed the study at the full dose of 2403 mg/day with normal liver enzymes.

Seven patients underwent a permanent dose reduction of pirfenidone, in some cases after a temporary discontinuation of drug; by completion of the study, 3 patients were receiving 801 mg/day and 4 patients were receiving 1602 mg/day. With the exception of one patient, rechallenge with a higher dose was not attempted with these patients. The patient that was rechallenged received the full dose of 2403 mg/day, but the dose was later reduced due to a recurrence of Grade 2 elevation in ALT levels. All seven patients completed the study with resolution of transaminases, except for one patient that had a Grade 1 elevation at study completion.

One patient discontinued treatment due to abnormal liver function tests in AST and/or ALT levels. The dose for this patient was initially decreased to 1602 mg/day, then discontinued, and then resumed at 1602 mg/day. For this patient, however, treatment was permanently discontinued because a Grade 2 elevation of AST coincided with a Grade 3 ALT elevation in liver function tests.

Of the three patients whose liver function test elevations were not documented as an adverse event, one had Grade 1 AST and ALT elevation at baseline, and experienced a Grade 1 elevation of AST at the last documented assessment. This patient received no dose modification after a Grade 2 elevation in AST and/or ALT levels. A second patient with a Grade 2 transaminase elevation had treatment temporarily discontinued for acute cerebral artery occlusion. Transaminase levels returned to normal once the dose was escalated back to 2403 mg/day, and the patient completed the study on full dose with normal transaminases. The third patient had no liver function test abnormalities while on treatment until Day 422, then the patient experienced a Grade 2 AST and Grade 1 ALT elevation with respiratory failure due to IPF. Study drug was discontinued the same day for respiratory failure. The patient was hospitalized on Day 434 and died on Day 439 due to respiratory failure.

Grade 3 Abnormalities in Liver Function

Four patients developed Grade 3 liver function abnormality in AST and/or ALT levels after pirfenidone administration, all of who had a treatment emergent adverse event of either increased AST and/or ALT. Two of the four patients discontinued study drug for elevated liver function tests. In both instances, the abnormalities had not resolved, with Grade 2 and Grade 3 abnormalities last documented. The two other patients had Grade 1 abnormalities at screening and/or baseline. One patient discontinued for lung transplant at which time the last documented values showed a Grade 1 abnormality. The other patient interrupted study drug (investigator decision), and subsequently discontinued study drug (sponsor decision). The AST and ALT elevations had normalized at the last documented value.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art. Although methods have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used.

All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

What is claimed is:

1. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising

(a) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day.

2. The method of claim **1** wherein prior to step (a) pirfenidone is discontinued until biomarkers of liver function are within normal limits.

3. The method of claim **1**, wherein the pirfenidone is administered three times per day with food.

4. The method of claim **1**, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase, aspartate transaminase, bilirubin, and alkaline phosphatase.

5. The method of claim **1** further comprising the step of measuring one or more biomarkers of liver function during step (a).

6. The method of claim **1**, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase.

7. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising (a) administering to said patient pirfenidone at doses of 1600 mg/day or 1602 mg/day.

8. The method of claim **7** wherein prior to step (a) pirfenidone is discontinued until biomarkers of liver function are within normal limits.

9. The method of claim **7** wherein prior to step (a) pirfenidone is administered at about 800 mg/day or 801 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

10. The method of claim **7** wherein prior to step (a) pirfenidone is discontinued for about one week, or until biomarkers of liver function are within normal limits, followed by administering about 800 mg/day or 801 mg/day pirfenidone for about one week.

11. The method of claim **7**, wherein the pirfenidone is administered three times per day with food.

12. The method of claim **7**, wherein said one or more biomarkers of liver function is selected from the group con

sisting of alanine transaminase, aspartate transaminase, bilirubin, and alkaline phosphatase.

13. The method of claim **7** further comprising the step of measuring one or more biomarkers of liver function during step (a).

14. The method of claim **7**, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,635,707 B1
APPLICATION NO. : 12/553292
DATED : December 22, 2009
INVENTOR(S) : Williamson Z. Bradford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

At Item (73), "Intermune" should be -- InterMune --.

In the Specification:

At Column 6, line 54, "synoviitis" should be -- synovitis --.

At Column 6, line 55, "tenosynoviitis" should be -- tenosynovitis --.

At Column 14, line 28, "childbearng" should be -- childbearing --.

Signed and Sealed this

Ninth Day of February, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT 3

US007767700B2

(12) **United States Patent**
Bradford

(10) **Patent No.: US 7,767,700 B2**
(45) **Date of Patent: *Aug. 3, 2010**

(54) **METHOD OF PROVIDING PIRFENIDONE THERAPY TO A PATIENT**

(75) Inventor: **Williamson Ziegler Bradford**, Ross, CA (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 470 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/959,338**

(22) Filed: **Dec. 18, 2007**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **514/350**; 514/345

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to methods for decreasing adverse events associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy. The invention discloses an optimized dose escalation scheme that results in the patient having increased tolerance to adverse events associated with the administration of pirfenidone. The invention also discloses a starter pack that may be used in conjunction with the dose escalation scheme.

19 Claims, 7 Drawing Sheets

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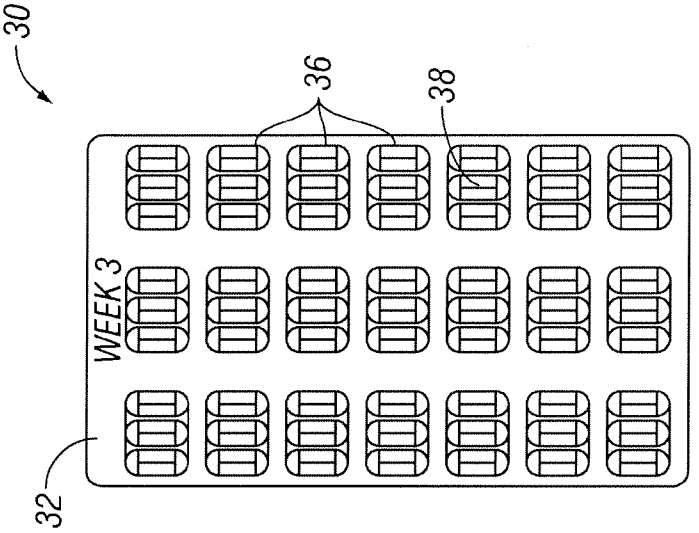

FIG. 3

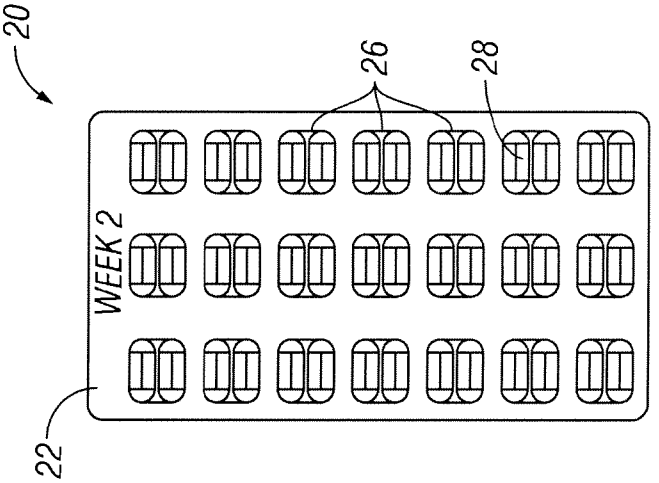

FIG. 2

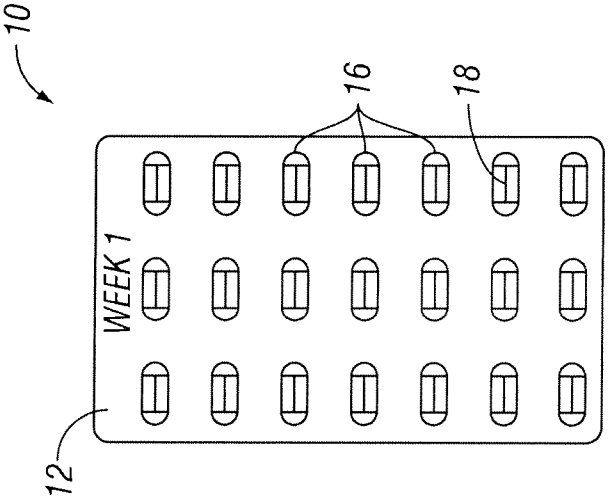

FIG. 1

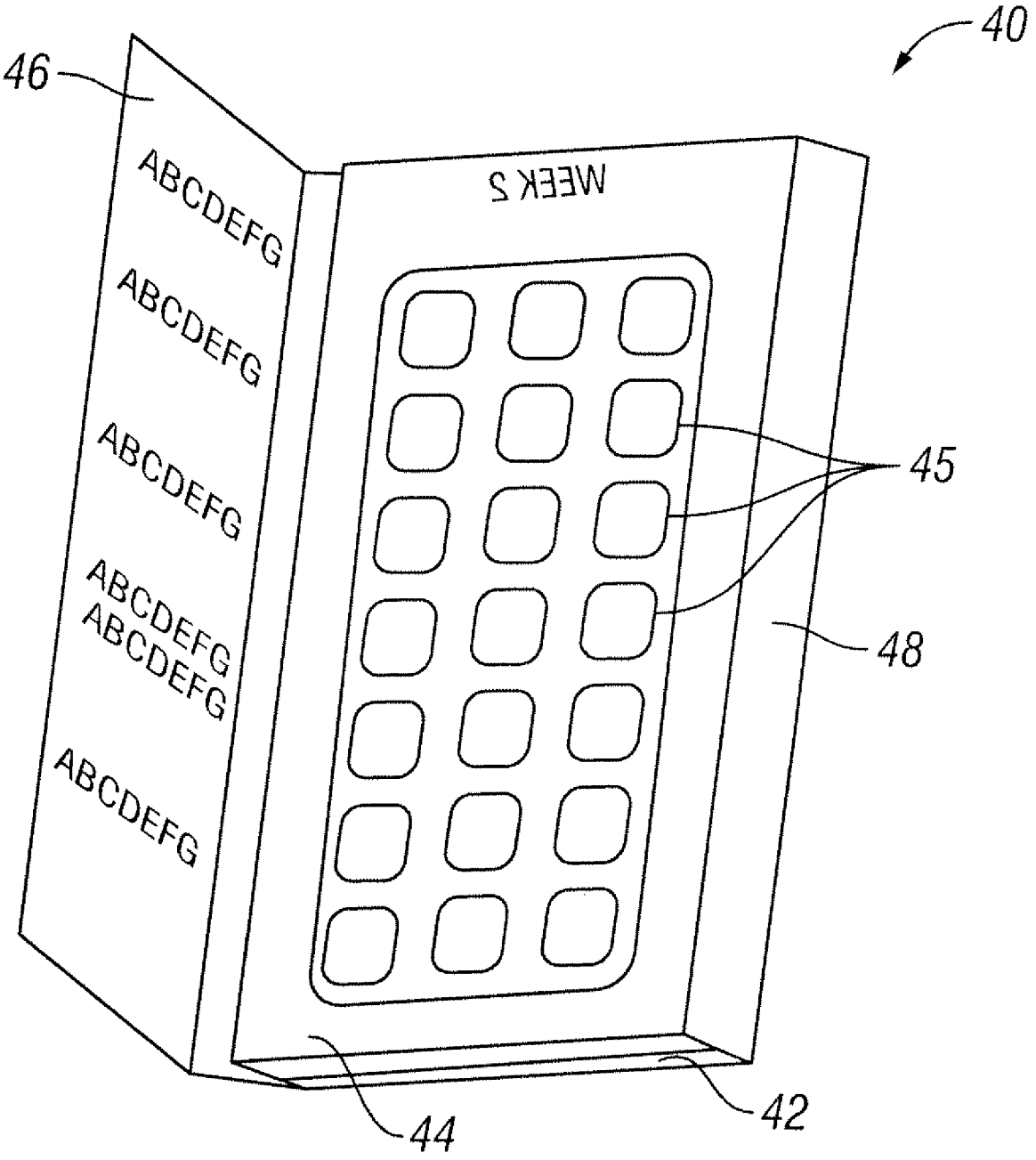
40
46
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
WEEK 2
45
48
44
42

FIG. 4

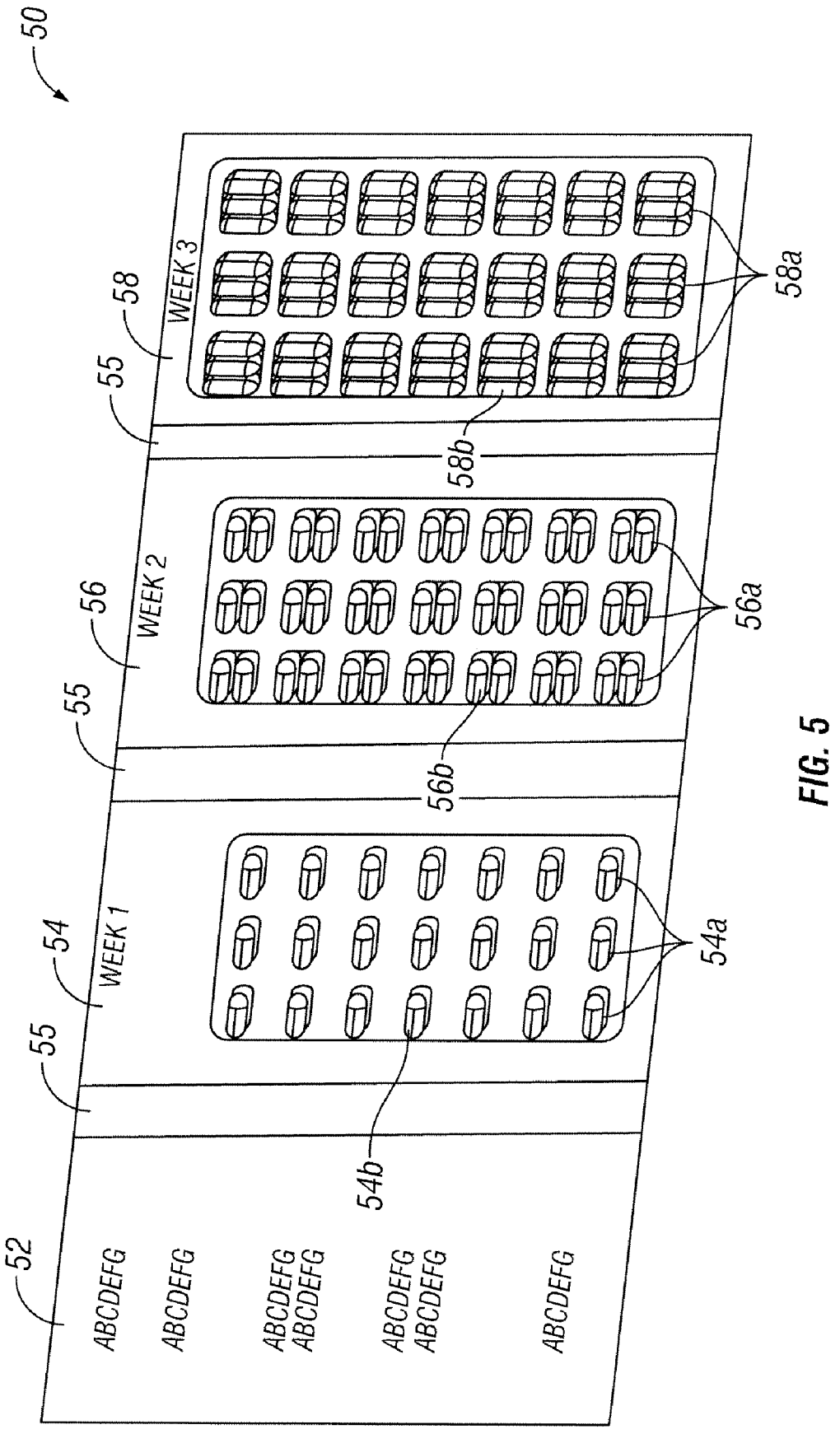
50
WEEK 3
58
55
58a
58b
WEEK 2
56
55
56a
56b
WEEK 1
54
55
54a
54b
52
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG

FIG. 5

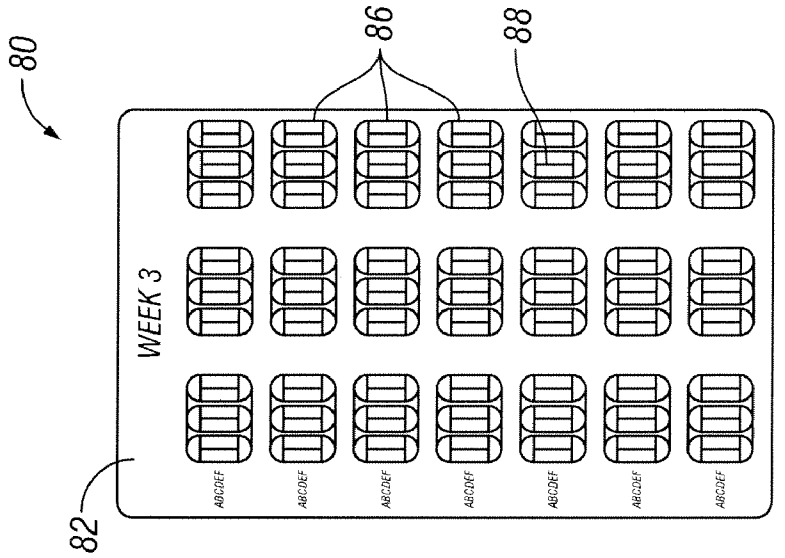

FIG. 8

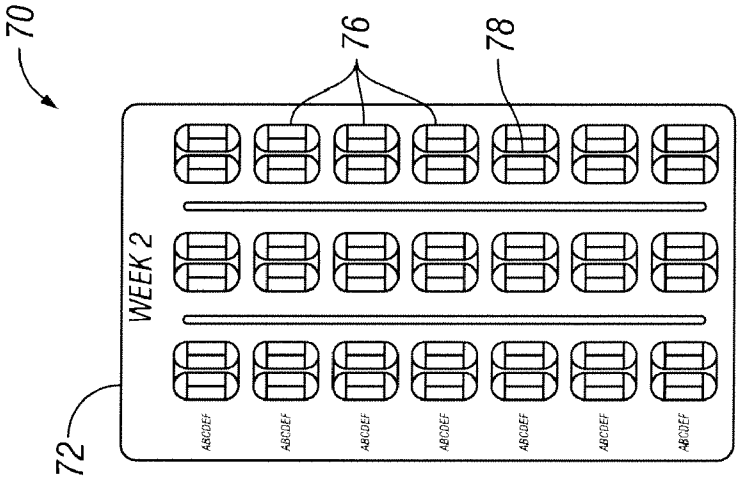

FIG. 7

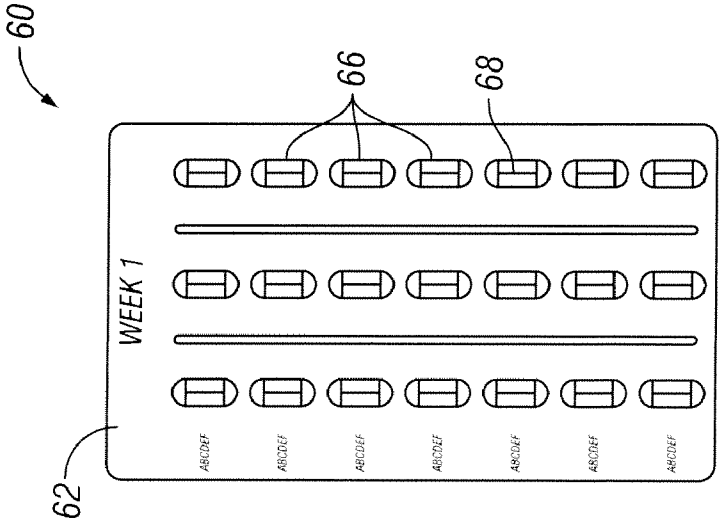

FIG. 6

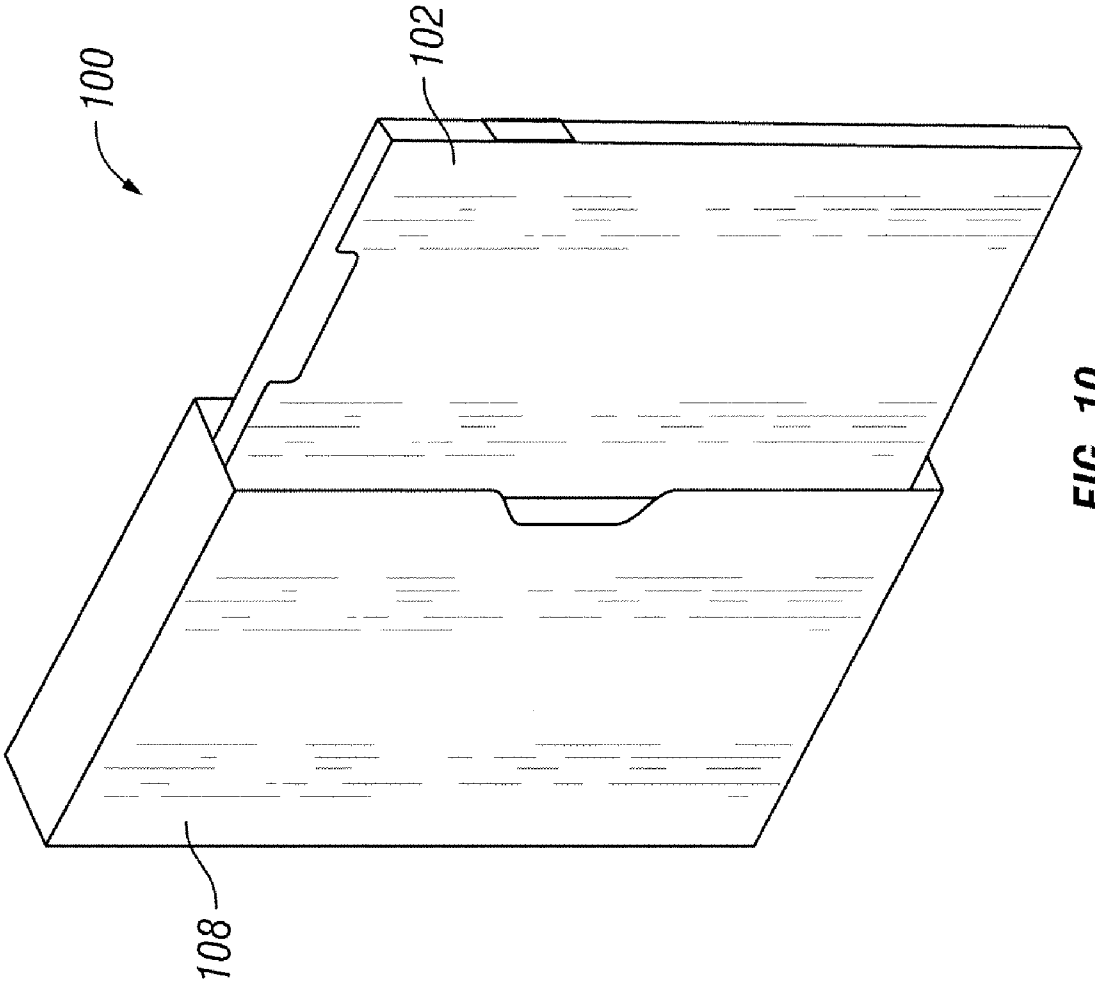

FIG. 10

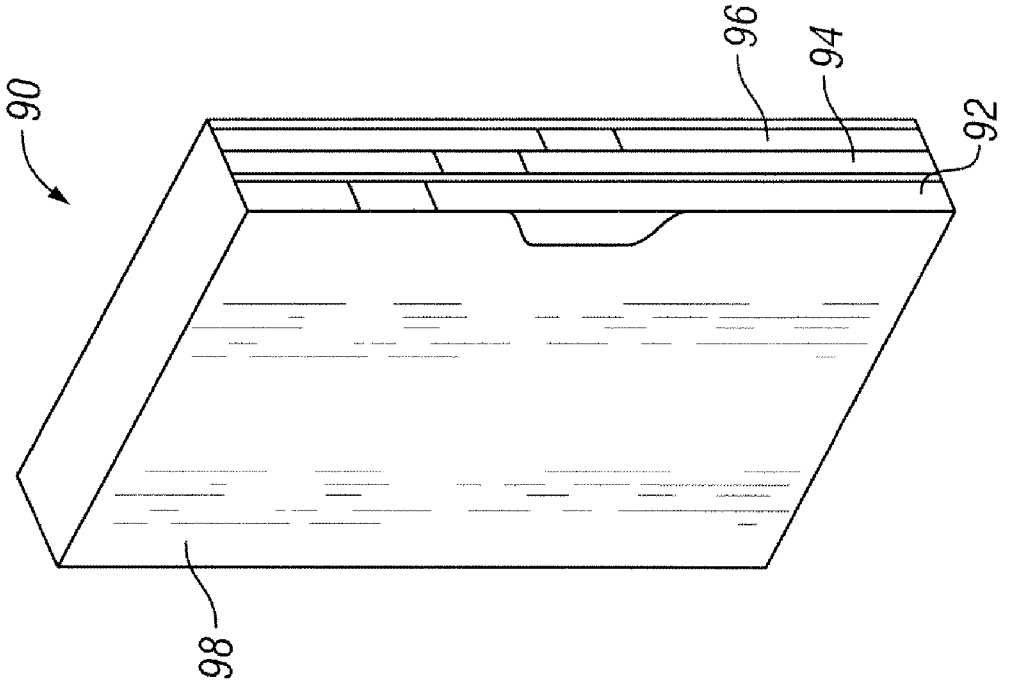

FIG. 9

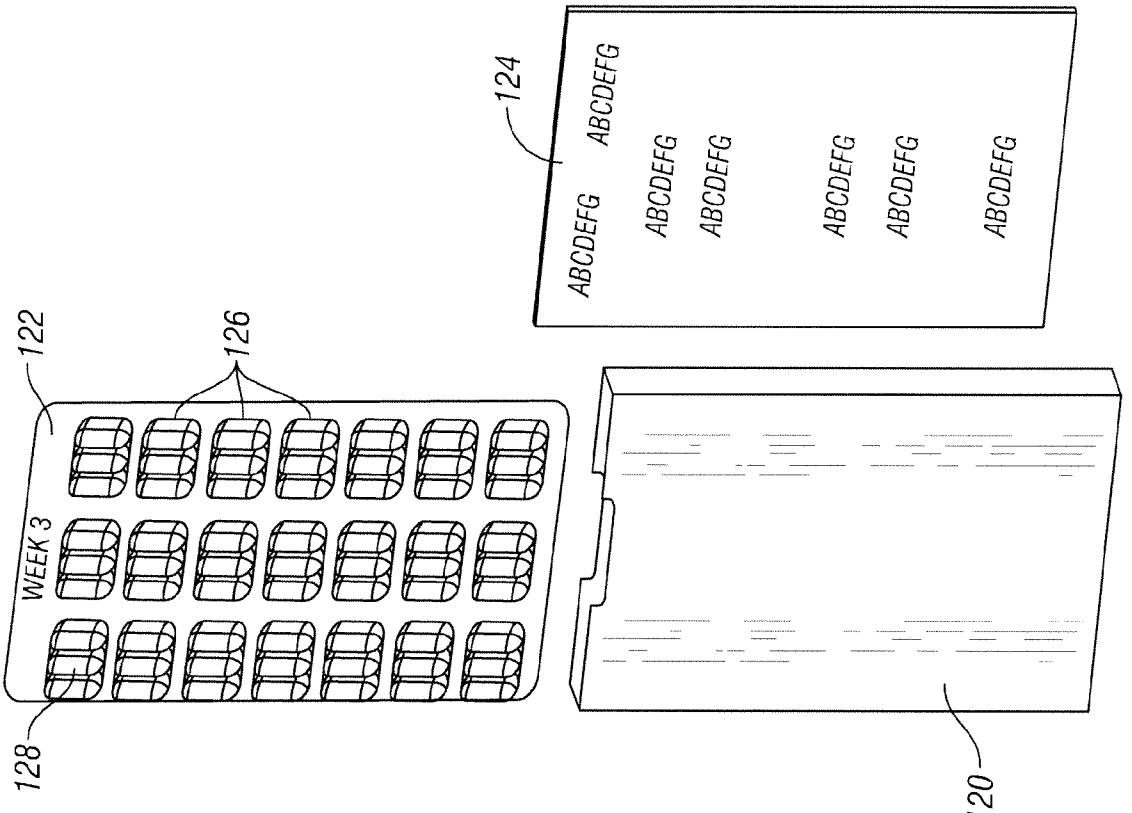
124
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
122
126
WEEK 3
128
120

FIG. 12

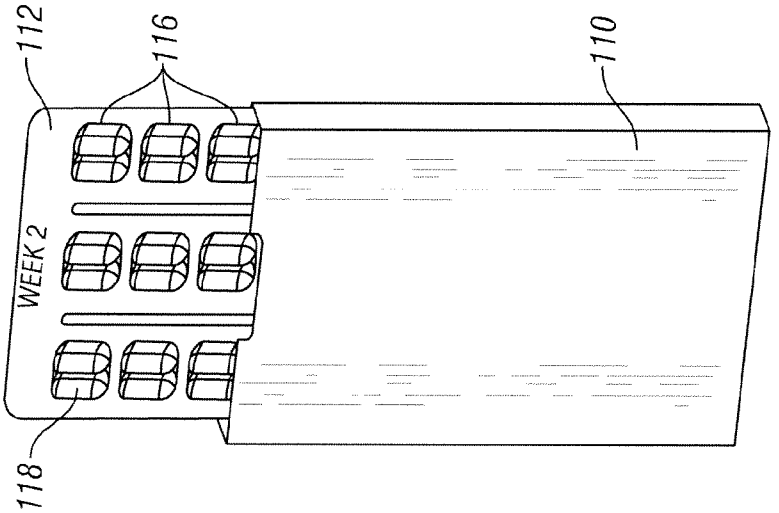
112
116
110
WEEK 2
118

FIG. 11

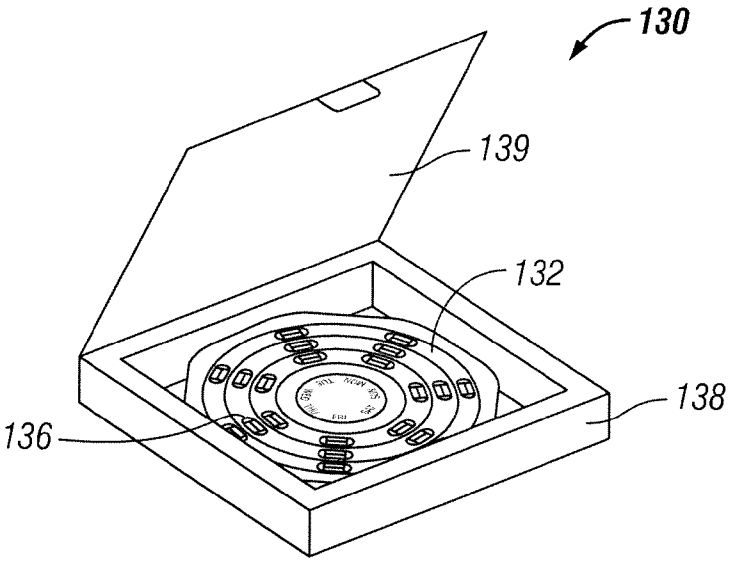

FIG. 13

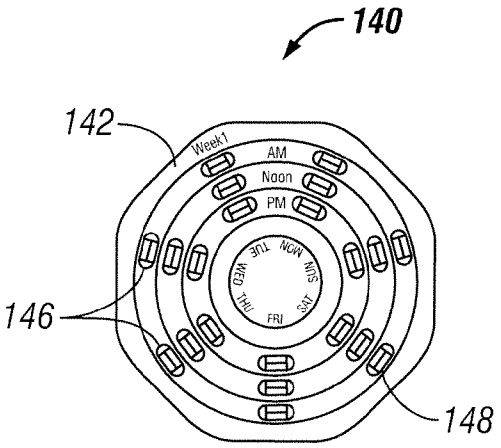

FIG. 14

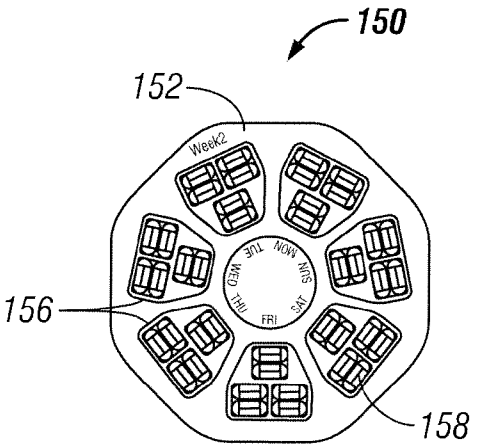

FIG. 15

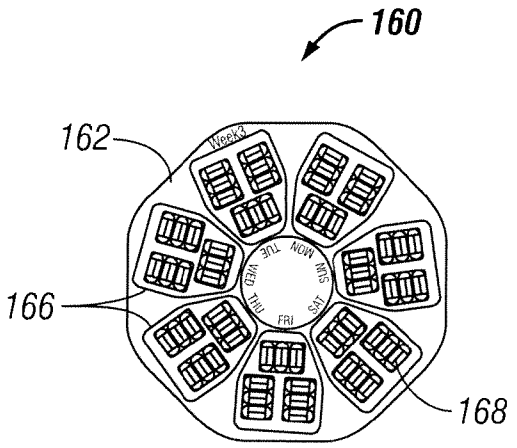

FIG. 16

METHOD OF PROVIDING PIRFENIDONE THERAPY TO A PATIENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 60/870,593, filed Dec. 18, 2006, the disclosure of which is incorporated by reference in its entirety.

BACKGROUND

1. Field of the Invention

The invention relates to methods for decreasing adverse events associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy.

2. Description of the Related Art

Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 Daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Several pirfenidone Investigational New Drug Applications (INDs) are currently on file with the U.S. Food and Drug Administration. Phase II human investigations are ongoing or have recently been completed for pulmonary fibrosis, renal glomerulosclerosis, and liver cirrhosis. There have been other Phase II studies that used pirfenidone to treat benign prostate hypertrophy, hypertrophic scarring (keloids), and rheumatoid arthritis.

Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

It is understood that one mechanism by which pirfenidone exerts its therapeutic effects is modulating cytokine actions. Pirfenidone is a potent inhibitor of fibrogenic cytokines and TNF-α. It is well documented that pirfenidone inhibits excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., *Australian and New England J Opthalmology* 26:S74-S76 (1998). Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., *Int'l J Immunopharmacology* 20:685-695 (1998).

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy include gastrointestinal upset, nausea, fatigue, somnolence, dizziness, headache, and photosensitivity rash. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related. The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at these higher doses.

Currently, adverse events following administration of pirfenidone are alleviated by dose reduction or discontinuation of pirfenidone. In a recent study, for adverse events rated Grade 2 or worse, the dosage was reduced in a stepwise manner: from 9 tablets having 200 mg of pirfenidone per day to 6 tablets having 200 mg of pirfenidone per day and 6 tablets having 200 mg of pirfenidone per day to 3 tablets having 200 mg of pirfenidone per day. Azuma, A. et al., *Am J Respir Crit. Care Med* 171:1040-47 (2005) ("Azuma study"). More specifically, if, after a period of 14 days of observation with reduced dosage, the adverse event persisted or increased, the dosage was further reduced by one more step—from 6 tablets per day to 3 tablets per day. If the adverse event persisted or increased despite reducing the dosage to 3 tablets per day, the study medication was discontinued.

The Azuma study discloses a dose-titration schedule for all patients wherein patients received a 200-mg dose of pirfenidone three times a day for the first two days; then a 400-mg dose of pirfenidone three times a day for the following two days; and then a maximum 600-mg dose of pirfenidone three times a day for the remainder of treatment. Thus, the maximum dose obtained by the Azuma study was only 1,800 mg/day of pirfenidone. Additionally, the dose-titration schedule of the Azuma study reaches the full maximum dosage of pirfenidone after only four days of treatment. There is significant reason to believe that the Azuma dose escalation does not optimally match the rate of dose escalation with the rate at which a patient develops sufficient tolerance to reduce the incidence of adverse events. Thus, there remains an unmet clinical need for a method of administering higher doses of pirfenidone to a patient in a manner that eliminates or minimizes adverse events, such as nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, somnolence, and other undesirable side effects.

SUMMARY

The present invention overcomes the unmet clinical need by providing an improved, optimized dose escalation scheme for the administration of pirfenidone. The dose escalation scheme of the present invention provides pirfenidone in an amount such that the full maximum dosage is not reached for at least one week. In a preferred embodiment, the full maximum dosage of pirfenidone is not reached until about Day 15 of treatment. The method of the present invention allows for a maximum dosage of 2,403 mg of pirfenidone per day to be administered to a patient and also reduces the incidence of adverse events associated with the administration of pirfenidone by more accurately matching dose escalation with tolerance development in the patient. Indeed, it has been observed that even as the dosage escalates using the dosing escalation scheme described herein, adverse events, such as somnolence, decrease.

The present invention discloses a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in a first amount for the duration of a first period of time; providing a second daily dosage of pirfenidone to the patient in a second amount for a second period of time; and providing a final daily dosage of pirfenidone to the patient in a final amount for a final period of time, wherein the first and second periods of time together total at least about 7 days, more preferably about 8, 9, 10, 11 or 12 days, and most preferably about 13 or 14 days. In some embodiments, the first and second periods can together total up to about 15 or about 20 or 21 days.

In one embodiment, the first amount is about 801 mg/day; the second amount is about 1,602 mg/day; and the third

amount is about 2,403 mg/day. In another embodiment, the first period of time is about 7 days; the second period of time is about 7 days; and the third period of time is in the range of about 1 day up to an unlimited number of days. In specific embodiments, the third period of time lasts at least about 1 month, at least about 2 months, at least about 3 months, at least about a year, at least about 18 months, at least about 2 years, or more than 2 years, at least about 3 years, at least about 4 years, at least about 5 years, or as long as therapy with pirfenidone is needed.

The present invention also discloses a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. Advantageously, the compartments can be arranged in columns and in rows, although other arrangements are also contemplated.

In one exemplary embodiment, the starter pack comprises rows designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. In one embodiment, the starter pack may comprise separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day. In one embodiment, each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone. In another embodiment, each week of treatment may be designated on a separate panel. In another embodiment, each panel contained within the starter pack may be approximately the same size. In another embodiment, the starter pack has compartments arranged such that a user of the starter pack may administer the pirfenidone in accordance with the dose escalation method taught by the present invention.

Also contemplated is use of pirfenidone in preparation of a medicament for the treatment of a fibrosis condition comprising administration of pirfenidone according to a dosing regimen as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a structure of a portion of a starter pack for the first week of treatment.

FIG. **2** shows a structure of a portion of a starter pack for the second week of treatment.

FIG. **3** shows a structure of a portion of a starter pack for the third week of treatment.

FIG. **4** shows a starter pack having multiple panels that are folded.

FIG. **5** shows a starter pack having multiple panels in an unfolded position.

FIG. **6** shows another structure of a portion of a starter pack for the first week of treatment.

FIG. **7** shows another structure of a portion of a starter pack for the second week of treatment.

FIG. **8** shows another structure of a portion of a starter pack for the third week of treatment.

FIG. **9** shows a starter pack having a casing material holding three different containers in such a manner that a user can easily slide a container out of the casing material.

FIG. **10** shows a starter pack wherein a container is partially pulled out from the casing material.

FIG. **11** shows a container comprising a panel having a plurality of compartments for containing a dosage amount of pirfenidone.

FIG. **12** shows a container wherein the panel has been pulled outside of the container.

FIG. **13** shows a starter pack having a casing material holding at least one circular panel containing pirfenidone.

FIG. **14** shows another structure of a portion of a circular starter pack for the first week of treatment.

FIG. **15** shows another structure of a portion of a circular starter pack for the second week of treatment.

FIG. **16** shows another structure of a portion of a circular starter pack for the third week of treatment.

DETAILED DESCRIPTION

The present invention discloses a method of providing pirfenidone therapy to a patient with an escalating dosage regimen that mitigates adverse events associated with the use of pirfenidone and, it is believed, better matches the development of tolerance to potentially adverse effects of the drug with increases in the dosage. In one embodiment of the present invention is a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in a first amount for the duration of a first period of time; providing a second daily dosage of pirfenidone to the patient in a second amount for a second period of time; and providing a final daily dosage of pirfenidone to the patient in a final amount for a final period of time. The sum of the first and second periods of time is preferably at least about 7 days, more preferably about 8, 9, 10, 11, or 12 days, and most preferably about 13 or 14 days. In some embodiments, the first and second periods can together total up to about 15 or about 20 or 21 days. Although it is also contemplated that the first and second periods together can total more than 21 days, and can (for example) be 22, 24, 26, or 30 days, it is believed that the longer dose escalation periods are less than optimal, due to the decrease in therapeutic benefit to the patient resulting from the delay in administering the full therapeutic dosage.

Although the present disclosure exemplifies dose escalation regimens having three steps, it is also possible to have more steps in the same amount of time, so that the dosage escalates in smaller steps. Indeed, if desired, each dose can be incrementally larger than the previous dose, or the dose can escalate every day, every two days, or every three or four days, for example. Regardless of the dose escalation step size, the use of an initial dose and an ending dose in the amounts discussed below is particularly preferred.

In one embodiment, the first amount is in the range of about 400 mg/day to about 1,200 mg/day. In another embodiment, the first amount is in the range of about 700 mg/day to about 900 mg/day. In another embodiment, the first amount is in the range of about 780 mg/day to about 820 mg/day. In another embodiment, the first amount is about 801 mg/day.

In one embodiment, the second amount is in the range of about 1,200 mg/day to about 2,000 mg/day. In another embodiment, the second amount is in the range of about 1,500 mg/day to about 1,700 mg/day. In another embodiment, the second amount is in the range of about 1,580 mg/day to about 1,620 mg/day. In another embodiment, the second amount is about 1,602 mg/day.

In one embodiment, the third amount is in the range of about 2,000 mg/day to about 3,000 mg/day. In another embodiment, the third amount is in the range of about 2,300 mg/day to about 2,400 mg/day. In another embodiment, the third amount is in the range of about 2,380 mg/day to about 2,420 mg/day. In another embodiment, the third amount is about 2,403 mg/day.

In one embodiment, the first period of time is in the range of about 3 days to about 10 days. In another embodiment, the

first period of time is about 6 to about 8 days. In another embodiment, the first period of time is about 7 days.

In one embodiment, the second period of time is in the range of about 3 days to about 10 days. In another embodiment, the second period of time is about 6 to about 8 days. In another embodiment, the second period of time is about 7 days.

In one embodiment, the final period of time is in the range of about 1 day to an unlimited number of days. Preferably, the final period of time will be however long the duration of treatment with pirfenidone should last.

In one embodiment of the present invention is a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in an amount of 801 mg/day over the course of Day 1 to Day 7; providing a second daily dosage of pirfenidone to the patient in an amount of 1602 mg/day over the course of Day 8 to Day 14; and providing a final daily dosage of pirfenidone to the patient in an amount of 2403 mg/day on the beginning of Day 15 and continuing with the 2403 mg/day dosage on each day following Day 15.

In one embodiment, the patient is administered one capsule (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day over the course of Day 1 to Day 7, to provide a daily dosage of 801 mg pirfenidone; then the patient is administered two capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day over the course of Day 8 to Day 14, to provide a daily dosage of 1602 mg pirfenidone; and then the patient is administered three capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day on Day 15 and each day thereafter, to provide a daily dosage of 2403 mg pirfenidone where the therapy continues after Day 15.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In another embodiment of the present invention, there is provided a starter pack comprising pirfenidone. Starter packs are a relatively easy method for singulating, transporting, storing and finally dispensing oral solid drugs. Such packs include, for instance, a planar transparent piece of plastic provided with "blisters" or convex protrusions configured in rows and columns. Each of the blisters or convex protrusions is sized to receive a singulated dosage amount of the particular oral solid drug being dispensed.

Typically, at least one backing layer is fastened to a solid receiving side of the blister pack. This layer is a low strength retaining barrier. This low strength retaining layer stretches across the backs of the blisters and retains the singulated oral dosage amounts individually sealed within each of the blisters.

Dispensing of drugs from such blister packs is easy to understand. The consumer presses down on a blister from the convex side of the blister. Such pressure bears directly against the singulated oral dosage amount contained in the blister. The singulated oral solid drug is then forced through the low strength retaining barrier. This low strength retaining barrier at least partially tears and breaks away. During this partial breaking and tearing away, the singulated oral dosage amount is partially—but typically not totally—ejected from its individual blister. Preferably, it is during this partial ejection that the oral solid drug is grasped by the user and consumed as directed. The result is a safe, sterile dispensing of the drug in desired single dosage amounts from the blister pack.

The starter pack of the present invention may comprise various dosage amounts of pirfenidone designated within blisters or other individual compartments so that the patient will take the proper dosage amount of the drug each day. The starter pack may comprise many different forms. One embodiment of the starter pack is shown in FIGS. **1-3**. FIG. **1** shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**10**) for the first week of treatment may comprise a panel (**12**) having a plurality of compartments (**16**) for containing a dosage amount (**18**) of pirfenidone. The compartments (**16**) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. In an embodiment where the starter pack comprises columns and rows, each daily dosage may be represented in a singular row or a singular column.

FIG. **2** shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**20**) for the second week of treatment may comprise a panel (**22**) having a plurality of compartments (**26**) for containing a dosage amount (**28**) of pirfenidone. The compartments (**26**) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**16**) for the first week of treatment. The dosage amount (**28**) of pirfenidone for the second week may be greater than the dosage amount (**18**) of the first week.

FIG. **3** shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (**30**) for the third week of treatment may comprise a panel (**32**) having a plurality of compartments (**36**) for containing a dosage amount (**38**) of pirfenidone. The compartments (**36**) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**26**) for the second week of treatment. The dosage amount (**38**) of pirfenidone for the third week may be greater than the dosage amount (**28**) of the second week.

Although FIGS. **1-3** show a starter pack wherein a panel represents one week of dosages, it is contemplated that a panel may be constructed to comprise more or less compartments. For instance, a panel may be constructed to hold dosage amounts for three days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for six days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for ten days of treatment. Any number of days and dosages in a single panel are contemplated by the inventors. Preferably, the starter pack may be designed so that the user administers pirfenidone according to the dose escalation scheme of the present invention.

In one embodiment, the starter pack comprises panels giving dosage amounts of pirfenidone for the first week of treatment and the second week of treatment. In another embodiment, the starter pack further comprises a panel giving dosage amounts of pirfenidone for the third week of treatment. In another embodiment, the starter pack comprises a panel or an insert that gives instructions to a patient for administering the proper dosage amount of pirfenidone.

In one embodiment, the starter pack may comprise only dosage amounts for the first week of treatment and the second week of treatment. Preferably, such a starter pack may also comprise instructions to the patient for administering the pirfenidone from a bottle for therapy after dose escalation is completed. It is contemplated that the user of the starter pack will continue therapy with pirfenidone pills from a bottle after dose escalation is completed.

The size of the starter pack and the panels that comprise the starter pack may be typical of similar starter packs already

known. In a preferred embodiment, each panel within a starter pack is approximately of similar size dimensions as the other panels of the starter pack.

In some embodiments, the starter pack comprises a unitary structure, wherein the unitary structure comprises more than one panel and each panel may comprise dosage amounts for one week of treatment. In some embodiments, the starter pack comprises a panel that has printed instructions thereon. FIG. **4** shows a starter pack (**40**) having multiple panels (**42**, **44**, **46**) that are folded. The starter pack has at least one region (**48**) capable of folding so that the separate panels (**42**, **44**, **46**) can be stacked upon one another while the starter pack (**40**) maintains its unitary structure. In some embodiments, the starter pack may comprise panels (**42**, **44**) having compartments for containing dosages of pirfenidone. The dosages may be pushed through the low strength retaining barrier at points (**45**) opposite the location of the blisters.

FIG. **5** shows a fully unfolded starter pack (**50**) comprising four panels (**52**, **54**, **56**, **58**). The Week 1 panel (**54**) may have compartments (**54***a*) that comprise a dosage amount (**54***b*) of pirfenidone related to the first week of treatment. The Week 2 panel (**56**) may have compartments (**56***a*) that comprise a dosage amount (**56***b*) of pirfenidone related to the second week of treatment. Optionally, a panel for the dosage amounts of Week 3 may be included. The Week 3 panel (**58**) may have compartments (**58***a*) that comprise a dosage amount (**58***b*) of pirfenidone related to the third week of usage. The other panel (**52**) may be left blank or provided with instructions or any other type of indicia. In some embodiments, the starter pack (**50**) may comprise an adhesive seal or a sticker that holds the starter pack in folded form until the adhesive seal or sticker is broken by a user. The starter pack may comprise regions (**55**) capable of folding so that the separate panels (**52**, **54**, **56**, **58**) can be stacked upon one another while the starter pack (**50**) maintains its unitary structure.

In one embodiment, one panel (**54**) may comprise compartments (**54***a*) giving the dosage amount (**54***b*) for Days 1-7 of the dose escalation scheme and the second panel (**56**) may comprise compartments (**56***a*) giving the dosage amount (**56***b*) for Days 8-14 of the dose escalation scheme. In another embodiment, an optional third panel (**58**) may be further provided to comprise compartments (**58***a*) giving the dosage amount (**58***b*) for Days 15-21 of the dose escalation scheme.

FIG. **6** shows a portion of another starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**60**) for the first week of treatment may comprise a panel (**62**) having a plurality of compartments (**66**) for containing a dosage amount (**68**) of pirfenidone. The compartments (**66**) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. Additionally, instructions may be provided on the starter pack (**60**) indicating the proper day and time the dosage amount (**68**) should be administered.

FIG. **7** shows a portion of another starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**70**) for the second week of treatment may comprise a panel (**72**) having a plurality of compartments (**76**) for containing a dosage amount (**78**) of pirfenidone. The compartments (**76**) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**66**) for the first week of treatment. The dosage amount (**78**) of pirfenidone for the second week may be greater than the dosage amount (**68**) of the first week. Additionally, instructions may be provided on the starter pack (**70**) indicating the proper day and time the dosage amount (**78**) should be administered.

FIG. **8** shows a portion of another starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (**80**) for the third week of treatment may comprise a panel (**82**) having a plurality of compartments (**86**) for containing a dosage amount (**88**) of pirfenidone. The compartments (**86**) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**76**) for the second week of treatment. The dosage amount (**88**) of pirfenidone for the third week may be greater than the dosage amount (**78**) of the second week. Additionally, instructions may be provided on the starter pack (**80**) indicating the proper day and time the dosage amount (**88**) should be administered.

In some embodiments, the starter pack may comprise a casing material that holds separate panels, wherein at least one panel comprises a plurality of compartments for containing a dosage amount of pirfenidone. In some embodiments, the panel may be located within a container having flat outer surfaces so that the container may easily be slid in and out of the casing material. FIG. **9** shows a starter pack (**90**) having a casing material (**98**) holding three different containers (**92**, **94**, **96**) in such a manner that a user can easily slide a container out of the casing material (**98**). In one embodiment, each container may comprise a panel that comprises a plurality of compartments that hold a dosage amount of pirfenidone. In some embodiments, the panels may further comprise instructions or indicia so that a user can administer pirfenidone according to the dose escalation scheme. In some embodiments, a panel may be provided separately for providing indicia or instructions on using the drug. In some embodiments, indicia or instructions may be provided on one or more of the containers (**92**, **94**, **96**).

FIG. **10** shows a starter pack (**100**) comprising a casing material (**108**) and at least one container (**102**). The container (**102**) is partially pulled out from the casing material (**108**) and may comprise a panel having a plurality of compartments for containing a dosage amount of pirfenidone. For example, the container (**102**) may comprise any of the panels shown in FIGS. **1-3** and FIGS. **6-8**. Preferably, each panel will be approximately the same size for easy and compact insertion into the casing material (**108**).

FIG. **11** shows a container (**110**) comprising a panel (**112**) having a plurality of compartments (**116**) for containing a dosage amount (**118**) of pirfenidone. The panel (**112**) is partially pulled out from the container (**110**) and can be slid in and out for easy use. FIG. **12** shows a container (**120**) wherein the panel (**122**) having a plurality of compartments (**126**) for containing a dosage amount (**128**) of pirfenidone has been completely pulled from the container (**120**). Instructions may be provided on a separate sheet (**124**) within the container (**120**) in addition to the panel (**122**). Alternatively, instructions or other indicia may be printed directly on the container (**120**) or the panel (**122**).

One embodiment of the present invention is a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. In one embodiment, the starter pack comprises a row designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. In one embodiment, the starter pack may comprise separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day. In one embodiment, each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three

compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone. In another embodiment, each week of treatment may be designated on a separate panel. In another embodiment, each panel contained within the starter pack may be approximately the same size. In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention.

In one embodiment, the starter pack further comprises additional rows for Days 15, 16, 17, 18, 19, 20, and 21. In another embodiment, each of the three compartments corresponding to Days 15, 16, 17, 18, 19, 20, and 21 separately contain three pills of 267-mg pirfenidone. The addition of the rows for Days 15, 16, 17, 18, 19, 20, and 21 is for the purpose of training the patient as to the correct amount of dosage that will be needed after the starter pack is finished and the patient begins taking pills from another source, such as a pill bottle. By providing the starter pack with a third week at the full dosage of pirfenidone, the patient will be better accustomed to taking the 2,403 mg/day dosage from Day 15 and each Day thereafter as required by the pirfenidone therapy method of the present invention.

In another embodiment, the starter pack comprises a circular form. FIG. **13** shows a container (**130**) comprising a base (**138**) that holds at least one panel (**132**) having a plurality of compartments (**136**) for containing a dosage amount of pirfenidone. The panel (**132**) is circular in shape with compartments (**136**) extending in a radial pattern from the center and wherein each radius designates its own Day for treatment with pirfenidone. The dosages for AM, noon, and PM may be separated in a manner shown in FIG. **13**. The container (**130**) also comprises a lid (**139**) so that at least one panel (**132**) containing pirfenidone can be stored within the container (**130**) and sealed.

FIG. **14** shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**140**) for the first week of treatment may comprise a circular panel (**142**) having a plurality of compartments (**146**) for containing a dosage amount (**148**) of pirfenidone. The compartments (**146**) may be arranged so that they extend radially from the center of the pane (**142**). The panel (**142**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

FIG. **15** shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**150**) for the second week of treatment may comprise a circular panel (**152**) having a plurality of compartments (**156**) for containing a dosage amount (**158**) of pirfenidone. The compartments (**156**) may be arranged so that they extend radially from the center or so that they fit within a panel. The panel (**152**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

FIG. **16** shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The panel for the third week of therapy is optionally provided. The starter pack (**160**) for the third week of treatment may comprise a circular panel (**162**) having a plurality of compartments (**166**) for containing a dosage amount (**168**) of pirfenidone. The compartments (**146**) may be arranged so that they extend radially from the center of the pane (**162**). The panel (**162**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention. Of course, as an alternative to blister packs, the doses can be contained in any other type of compartment, such as plastic bags or other containers fastened together in book form; plastic containers with snap-open lids arranged in a row or other geometric pattern, or any of a wide variety of other dosage-containing packages.

In one embodiment, a method for administering pirfenidone therapy to a patient comprises initially administering a predetermined starting dosage of pirfenidone to the patient and escalating the dosage administered to the patient over a predetermined time to a predetermined full dosage of pirfenidone. In some embodiments, the predetermined time is measured from the initial starting dosage and is between about 7 and 20 days. In some embodiments, the predetermined time is 13 or 14 days. In some embodiments, the starting dosage is about 801 mg/day. In some embodiments, the full dosage is about 2,403 mg/day. In some embodiments, the dosages are split into three daily oral administrations.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

What is claimed is:

1. An initial dose escalation regimen method for providing pirfenidone therapy to a patient for the treatment of idiopathic pulmonary fibrosis, comprising:

providing pirfenidone to a patient at a first oral daily dosage of 801 mg for days one to seven of the dose escalation regimen;

providing a second oral daily dosage of 1602 mg pirfenidone for days eight to fourteen of the dose escalation regimen; and

providing a third oral daily dosage of 2403 mg pirfenidone for at least day fifteen of the dose escalation regimen, wherein the patient is provided pirfenidone for the treatment of idiopathic pulmonary fibrosis.

2. The method of claim **1**, further comprising instructing the patient to administer the dosage with food.

3. The method of claim **1**, wherein each daily dosage is provided as a plurality of dosage forms comprising sub-daily dosages.

4. The method of claim **3**, wherein each daily dosage is split into three divided doses provided three times a day.

5. The method of claim **1**, wherein each oral daily dosage is provided in capsule form.

6. The method of claim **5**, wherein each capsule comprises 267 mg of pirfenidone.

7. A method of reducing the incidence of photosensitivity reaction adverse events in a patient receiving pirfenidone therapy for the treatment of idiopathic pulmonary fibrosis, comprising use of an initial dose escalation regimen comprising the steps of:

providing pirfenidone to the patient at a first oral daily dosage of 801 mg of pirfenidone for days one to seven of the dose escalation regimen; providing a second oral daily dosage of 1602 mg pirfenidone for days eight to

fourteen of the dose escalation regimen; and providing a third oral daily dosage of 2403 mg pirfenidone for at least day fifteen of the dose escalation regimen.

8. The method of claim **7**, further comprising instructing the patient to administer the dosage with food.

9. The method of claim **7**, wherein each daily dosage is provided as a plurality of dosage forms comprising sub-daily dosages.

10. The method of claim **9**, wherein each daily dosage is split into three divided doses provided three times a day.

11. The method of claim **7**, wherein each oral daily dosage is provided in capsule form.

12. The method of claim **11**, wherein each capsule comprises 267 mg of pirfenidone.

13. In a method of treating a patient with pirfenidone for idiopathic pulmonary fibrosis, the improvement comprising: reducing the incidence of photosensitivity reaction adverse events in the patient receiving pirfenidone therapy by use of an initial dose escalation regimen comprising providing pirfenidone to a patient at a first oral daily dosage of 801 mg of pirfenidone for days one to seven of the dose escalation regimen; providing a second oral daily dosage of 1602 mg pirfenidone for days eight to fourteen of the dose escalation regimen; and providing a third oral daily dosage of 2403 mg pirfenidone for at least day fifteen of the dose escalation regimen.

14. The method of claim **13**, further comprising instructing the patient to administer the dosage with food.

15. The method of claim **13**, wherein each daily dosage is provided as a plurality of dosage forms comprising sub-daily dosages.

16. The method of claim **15**, wherein each daily dosage is split into three divided doses provided three times a day.

17. The method of claim **13**, wherein each oral daily dosage is provided in capsule form.

18. The method of claim **17**, wherein each capsule comprises 267 mg of pirfenidone.

19. The method of claim **13**, comprising reducing the incidence of photosensitivity reaction adverse events to about 12%.

* * * * *

EXHIBIT 4

US007816383B1

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 7,816,383 B1**
(45) **Date of Patent: Oct. 19, 2010**

(54) **METHODS OF ADMINISTERING PIRFENIDONE THERAPY**

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(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

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A61K 31/15	(2006.01)
A01N 33/24	(2006.01)
A01N 33/02	(2006.01)
A61K 31/135	(2006.01)

(52) **U.S. Cl.** **514/350**; 514/354; 514/640; 514/646

(58) **Field of Classification Search** 514/350, 514/354, 640, 646

See application file for complete search history.

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Dolophine® Hydrochloride (methadone hydrochloride) package insert.

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Lexotan® (bromazepam) package insert.

Malarone® (atovaquone and proguanil hydrochloride) package insert.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes.

20 Claims, 1 Drawing Sheet

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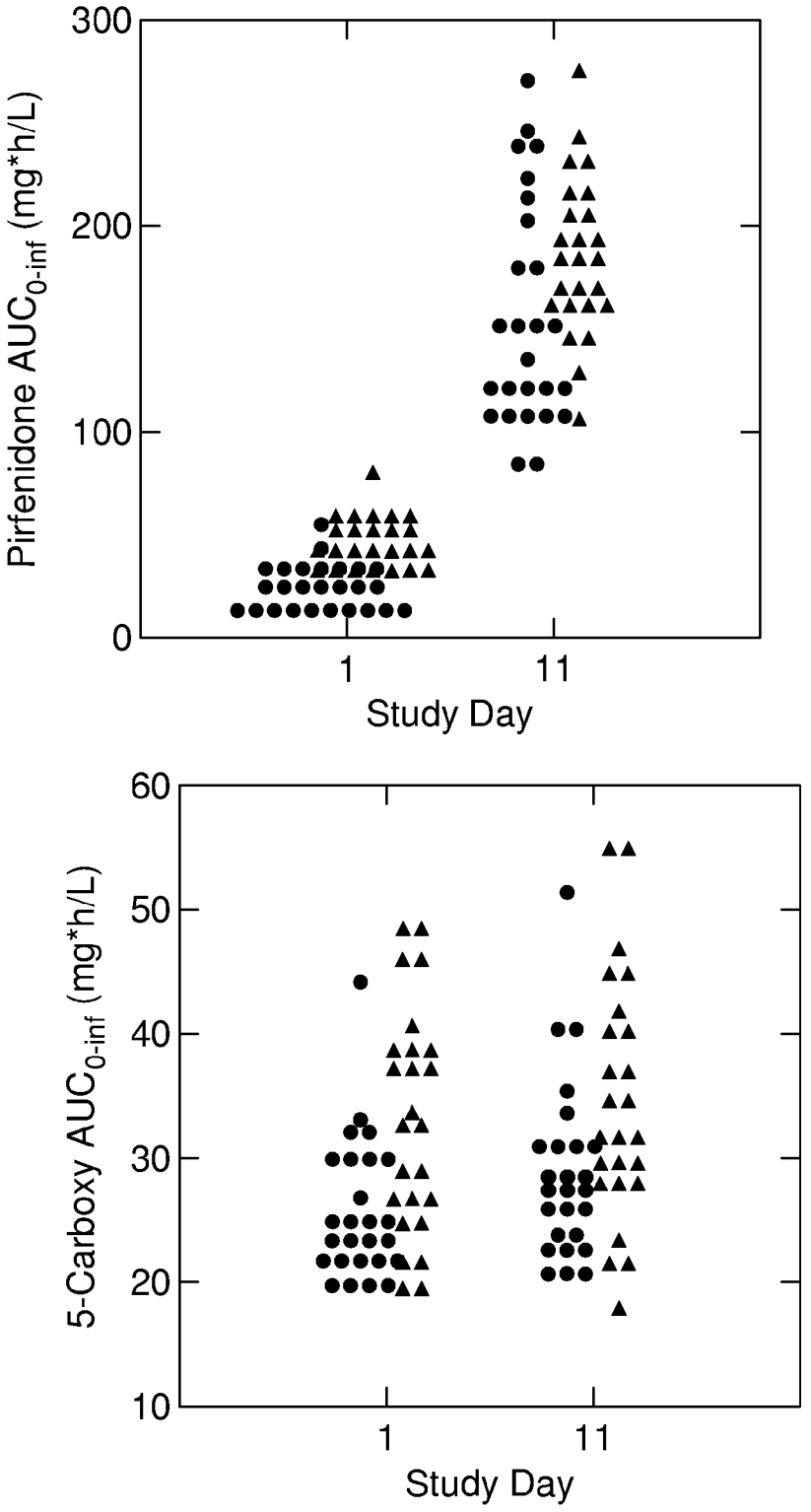
300
200
100
0
Pirfenidone AUC0-inf (mg*h/L)
1
11
Study Day
60
50
40
30
20
10
5-Carboxy AUC0-inf (mg*h/L)
1
11
Study Day

Figure 1

METHODS OF ADMINISTERING PIRFENIDONE THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/266,815, filed Dec. 4, 2009, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy involving avoiding adverse drug interactions with fluvoxamine, a strong inhibitor of CYP1A2.

BACKGROUND

Pirfenidone is small molecule with a molecular weight of 185.23 daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved in Japan for treatment of idiopathic pulmonary fibrosis (IPF) under the trade name Pirespa®.

Pirfenidone has been shown to be metabolized by various isoforms of the cytochrome P450 (CYP) protein [See the Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008]. Specifically, several cytochrome P450 (CYP) isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Fluvoxamine belongs to a class of therapeutics known as selective serotonin reuptake inhibitors (SSRIs). The SSRIs are a group of antidepressants with similar pharmacologic effects, but with different chemical structures. Fluvoxamine has been approved for treatment of social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), and has been prescribed to treat major depression, and other anxiety disorders such as panic disorder and post-traumatic stress disorder [McClellan et al., (Drugs October 2000). "Fluvoxamine An Updated Review of its Use in the Management of Adults with Anxiety Disorders". *Adis Drug Evaluation* 60 (4): 925-954]. In addition to fluvoxamine, other clinically available SSRIs are citalopram, fluoxetine, paroxetine and sertraline. The elimination of these lipophilic compounds proceeds predominantly via oxidation catalysed by CYP in the liver. SSRIs have the potential for inhibition of CYP enzymes [Brosen, The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clin Invest* 71(12):1002-1009, 1993]. Jeppesen et al. reported that fluvoxamine is a potent inhibitor of CYP1A2 in humans in vivo [Jeppesen et al., Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol* 51: 73-78, 1996]. Fluvoxamine has also been shown to be a very potent inhibitor of CYP1A2 in vitro [Brosen et al., Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 45:1211-1214, 1993; Rasmussen et al., Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 39:151-159, 1995].

SUMMARY OF THE INVENTION

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient may have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered may be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage may be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone may be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day may be administered as follows: 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of fluvoxamine.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of fluvoxamine to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient is receiving fluvoxamine, and fluvoxamine is discontinued concurrent with starting administration of pirfenidone. In another embodiment, fluvoxamine is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of fluvoxamine therapy is provided, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not fluvoxamine. In one aspect, the alternative therapy that is not fluvoxamine is a drug that is not a moderate to strong inhibitor of CYP1A2. Preferably, such drug is not a moderate to strong inhibitor of both CYP1A2, and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19. In some examples, the alternative drug is selected from the group consisting of Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Prozac Weekly), Paroxetine (Paxil, Paxil CR, Pexeva), and/or Sertraline (Zoloft).

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and advising the patient in any one, two, three or more of the following ways:

(a) advising the patient that fluvoxamine should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) advising the patient that use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) advising the patient that co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or.

(f) advising the patient that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the method further includes advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax). In yet further embodiments, the method also includes avoiding administering a strong CYP1A2 inhibitor, or discontinuing administration of a strong CYP1A2 inhibitor.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION OF THE INVENTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 50-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor [Hemeryck et al., Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: An Update. *Current Drug Metabolism* 3(1): 13-37, 2002].

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine. Adverse drug interactions represent 3-5% of preventable in-hospital adverse drug reactions, and are an important contributor to the number of emergency room visits and hospital admissions [Leape L L et al., JAMA 1995; 274(1):**35-43**; Raschetti R et al. Eur J Clin Pharmacol 1999; 54(12):**959-963**].

Data reported herein show that co-administration of pirfenidone with fluvoxamine resulted in an average 6-fold increase in exposure (AUC, or area under the curve) to pirfenidone. It also resulted in an average 2-fold increase in Cmax, the mean maximum plasma concentration. Depending on the circumstances, FDA draft guidance suggests that a drug-drug interaction is present when comparisons indicate twofold or greater systemic exposure for a drug when given in combination with the second drug, compared to when given alone. FDA Preliminary Concept Paper, "Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling," Oct. 1, 2004.

DEFINITIONS

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and

ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, a patient in need of "fluvoxamine therapy" is understood to be a patient in need of "selective serotonin reuptake inhibitor (SSRI) therapy." Such patients include patients suffering from social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), depression, anxiety disorders, panic disorder and post-traumatic stress disorder.

For CYP enzymes, the FDA generally defines a "strong inhibitor" as one that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates (not limited to sensitive CYP substrate) in clinical evaluations. The FDA generally defines a "moderate inhibitor" as one that caused a >2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.

CYP Inhibitors and Substrates

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, such as fluvoxamine. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme that metabolizes pirfenidone, e.g. selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

As yet other alternatives, in any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a strong inhibitor of CYP1A2 or a substrate for CYP1A2.

CYP1A2 metabolizes many commonly used drugs including theophylline, imipramine, propranolol, and clozapine. These drugs are commonly referred to as "substrates" for CYP1A2. Additional CYP1A2 substrates include but are not limited to acetominophen, amitriptyline, caffeine, chlordiazepoxide, cinacalcet, clomipramine, clopidogrel, cyclobenzaprine, desipramine, diazepam, duloxetine, erlotinib, estradiol, flutamide, haloperidol, levobupivacaine, methadone, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, ramelteon, riluzole, ropinirole, ropivacaine, tacrine, tizanidine, verapamil, and warfarin.

Inhibitors of CYP1A2 include fluvoxamine, cimetidine, amiodarone, echinacea, enoxacin, norfloxacin, oral contraceptives, tacrine, ticlopidine, and many fluoroquinolone antibiotics. Moderate inhibitors of CYP1A2 include ciprofloxacin, mexiletine, propafenone and zileuton. Additional inhibitors of CYP1A2 include atazanavir, citalopram, clarithromycin, dilitiazem, erythromycin, ethinyl estradiol, isoniazid, ketoconazole, methoxsalen, nalidixic acid, norethindrone, omeprazole, paroxetine, tipranavir, and troleandomycin. Other inhibitors of CYP1A2 include acyclovir, caffeine, famotidine, flutamide, grapefruit juice, lidocaine, lomefloxacin, moclobemide, ofloxacin, perphenazine, phenacetin, propafenone, ropinirole, tocamide, and verapamil.

Inhibitors of CYP3A4 include amiodarone, cimetidine, ciprofloxacin, delavirdine, fluvoxamine, miconazole, and voriconazole (VFEND). Strong inhibitors of CYP3A4 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin. Moderate inhibitors of CYP3A4 include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil. Additional inhibitors of CYP3A4 include acitretin, cyclosporine, danazol, diethyldithiocarbamate, efavirenz, ethinyl estradiol, fluoxetine, gestodene, imatinib, isoniazid, metronidazole, methylpredisolone, mifepristone, nicardipine, nifedipine, norethindrone, norfloxacin, norfluoxetine, oxiconazole, pomegranate, prednisone, quinine, ranolazine, roxithromycin, sertraline, Synercid, troleandomycin, zafirlukast, and zileuton. Other inhibitors of CYP3A4 include doxycycline, echinacea, and enoxacin.

Inhibitors of CYP2C9 include cimetidine, delavirdine, efavirenz, fenofibrate (Tricor), fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, leflunomide, modafinil, sertraline, voriconazole (VFEND), and zafirlukast (Accolate). Moderate inhibitors of CYP2C9 include amiodarone, fluconazole and oxandrolone. Additional CYP2C9 inhibitors include atazanavir, chloramphenicol, clopidogrel, cotrimoxazole, cranberry, disulfuram, fluorouracil, gemfibrozil, ginkgo, imatinib, itraconazole, lovastatin, metronidazole, omeprazole, paroxetine, sulfonamides, triclopidine, and

tipranavir. Other inhibitors of CYP2C9 include anastrazole, phenylbutazone, sulfamethoxazole, sulfaphenazole, tamoxifen, teniposide, valproic acid, and 5-fluorouracil.

Inhibitors of CYP2D6 include amiodarone, bupropion, celecoxib, chlorpheniramine, cimetidine, cinacalcet, citalopram, clomipramine, desipramine, diphenhydramine, halofantrine, haloperidol, methadone, moclobemide, propafenone, ritonavir, sertraline, and thioridazine. Strong CYP2D6 inhibitors include fluoxetine, paroxetine and quinidine, while moderate CYP2D6 inhibitors include duloxetine and terbinafine. Additional inhibitors of CYP2D6 include chloroquine, cocaine, darifenacin, escitalopram, fluphenazine, hydroxychloroquine, imatinib, levomepromazine, norfluoxetine, perphenazine, pomegranate, propoxyphene, propranolol, quinacrine, ranitidine, ranolazine, and tipranavir. Other inhibitors of CYP2D6 include amitriptyline, chlorpromazine, doxepin, fluvoxamine, goldenseal, hydroxyzine, imipramine, metoclopramide, pimozide, and ticlopidine (Ticlid).

Inhibitors of CYP2C19 include delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, indomethacin, isoniazid (INH), modafinil (Provigil), oxcarbazepine, ticlopidine, topiramate, and voriconazole (VFEND) A strong inhibitor of CYP2C19 is omeprazole. Additional inhibitors of CYP2C19 include citalopram, fluvastatin, ketoconazole, lansoprazole, letrozole, paroxetine, sertraline, telmisartan, and tipranavir. Other inhibitors of CYP2C19 include artemisinin, chloramphenicol, and oral contraceptives.

Inhibitors of CYP2B6 include clopidogrel (Plavix), efavirenz, fluoxetine, fluvoxamine, ketoconazole, memantine, nelfinavir, oral contraceptives, paroxetine, ritonavir, thiotepa, and ticlopidine (Ticlid).

Avoiding or Discontinuing Administration of a Drug to Avoid Adverse Drug Interactions with Pirfenidone

As used herein, "avoiding" means "refraining from." Merriam-Webster Online Dictionary, 11th ed., 24 Nov. 2009. In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4, or a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a strong CYP1A2 inhibitor.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a CYP1A2 substrate.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug being discontinued is a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a strong CYP1A2 inhibitor to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of the drug that is a CYP inhibitor and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the drug that is a CYP inhibitor is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP inhibitor is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which fluvoxamine is discontinued to avoid an adverse drug interaction, fluvoxamine is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, fluvoxamine is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the fluvoxamine is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of fluvoxamine therapy.

In some embodiments in which the drug being discontinued is a CYP inhibitor, the drug is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the drug that is a CYP inhibitor is discontinued

within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the drug that is a CYP inhibitor is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the drug upon discontinuation.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of the CYP1A2 substrate to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug that is a CYP1A2 substrate is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP1A2 substrate is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which a CYP1A2 substrate is discontinued to avoid an adverse drug interaction, the CYP1A2 substrate is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the CYP1A2 substrate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the CYP1A2 substrate is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP1A2 substrate therapy.

Selecting an Alternative Drug to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In another embodiment, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

In some embodiments, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a strong CYP1A2 inhibitor, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a strong CYP1A2 inhibitor.

In yet other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP1A2 substrate, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP1A2 substrate.

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a strong CYP1A2 inhibitor can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 substrate can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with fluvoxamine is contraindicated. In some embodiments, the patient is advised that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and fluvoxamine concurrently is provided wherein the patient is administered a therapeutically effective amount of fluvoxamine and a dosage of pirfenidone that is decreased relative to a patient not taking fluvoxamine. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered fluvoxamine. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 concurrently is provided wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In related aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In yet other aspects, a method of administering pirfenidone and a strong CYP1A2 inhibitor concurrently is provided wherein the patient is administered a therapeutically effective amount of the strong CYP1A2 inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking the strong CYP1A2 inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the strong CYP1A2 inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the strong CYP1A2 inhibitor.

In various embodiments, a method of administering pirfenidone and a CYP1A2 substrate concurrently is provided wherein the patient is administered a therapeutically effective amount of the CYP1A2 substrate and a dosage of pirfenidone that is decreased relative to a patient not taking the CYP1A2 substrate. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP1A2 substrate. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the CYP1A2 substrate.

In some embodiments, the amount of pirfenidone being administered is 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 50 to about 2400 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 267 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 534 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1068 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1335 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1869 mg, about 1900 mg, about 1950 mg, about

2000 mg, about 2050 mg, about 2100 mg, about 2136 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of administering a SSRI to a patient in need thereof is provided, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2, and a CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a strong CYP1A2 inhibitor to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 substrate to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of administering pirfenidone therapy to a patient receiving fluvoxamine therapy is provided, comprising administering to the patient a therapeutically effective amount of fluvoxamine and administering to the patient a daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day, e.g. 1600 mg or 1602 mg per day. In some embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine. Similarly, in any of the foregoing embodiments relating to other CYP inhibitors or CYP substrates, the daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day may be, e.g. 1600 mg or 1602 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) use of fluvoxamine should be avoided or discontinued,

(b) co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or

(f) strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the information or recommendation may include that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax).

In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are strong CYP1A2 inhibitors can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are CYP1A2 substrates can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19 should be avoided or discontinued, or are contraindicated, or should be used with caution. In yet further embodiments, the information or recommendation may include that administering a strong CYP1A2 inhibitor should be avoided or discontinued, or are contraindicated, or should be used with caution. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 substrates should be avoided or discontinued, or are contraindicated, or should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

In some embodiments, a kit is provided comprising fluvoxamine and a package insert, package label, instructions, or other labeling comprising any one, two, three or more of the following warnings:

(a) use of fluvoxamine and pirfenidone is contraindicated

(b) use of pirfenidone in patients being treated with fluvoxamine is contraindicated, and/or

(c) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone.

(d) co-administration of pirfenidone and fluvoxamine resulted in an average 2-fold increase in peak serum concentration of pirfenidone.

In some embodiments, a method of treating a patient in need of fluvoxamine is provided comprising providing or delivering any of the kits disclosed herein comprising fluvoxamine to a hospital, physician or patient.

In related aspects, the invention provides a method of administering a SSRI to a patient in need thereof, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1

An open-label Phase 1 study was performed to determine the impacts of fluvoxamine on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design. The study was a Phase 1, open-label, parallel-group study in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Smoking induces CYP1A2 activity. Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking status).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results. Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5-carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5-carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5-carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5-carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a]p-value < 0.00001 (paired t-test)

[b]p-value = 0.168 (paired t-test)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5-carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)
Non-smokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

What is claimed is:

1. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding co-administration of fluvoxamine, wherein said patient is also in need of fluvoxamine therapy.

2. The method of claim **1** wherein the patient has idiopathic pulmonary fibrosis (IPF).

3. The method of claim **1** wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

4. The method of claim **1** wherein 800 or 801 mg of pirfenidone is administered to the patient three times per day, with food.

5. A method of administering pirfenidone therapy to a patient in need thereof, comprising first discontinuing administration of fluvoxamine to avoid an adverse drug interaction with pirfenidone, and then administering to the patient a therapeutically effective amount of pirfenidone.

6. The method of claim **5** wherein the patient has idiopathic pulmonary fibrosis (IPF).

7. The method of claim **5** wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

8. The method of claim **5** wherein 800 or 801 mg of pirfenidone is administered to the patient three times per day, with food.

9. The method of claim **5** wherein the fluvoxamine is discontinued within 1 month prior to starting pirfenidone therapy.

10. The method of claim **5** wherein the fluvoxamine is discontinued within 2 weeks prior to starting pirfenidone therapy.

11. A method of administering pirfenidone therapy to a patient with IPF, wherein said patient is also in need of fluvoxamine therapy, comprising administering to the patient a daily dosage of 2400 mg or 2403 mg pirfenidone per day while avoiding fluvoxamine co-administration, and any one or more of the following:

(a) advising the patient that fluvoxamine should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) advising the patient that use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone, or

(f) advising the patient that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

12. The method of claim **11** wherein the patient is advised that fluvoxamine should be avoided or discontinued.

13. The method of claim **11** wherein the patient is advised that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone.

14. The method of claim **11** wherein the patient is advised that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone.

15. The method of claim **11** wherein the patient is advised that use of pirfenidone in patients being treated with fluvoxamine is contraindicated.

16. The method of claim **11** wherein the patient is advised that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone.

17. The method of claim **16** further comprising advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax).

18. The method of claim **11** wherein the patient is advised that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

19. The method of claim **18** further comprising avoiding administering a strong CYP1A2 inhibitor.

20. The method of claim **18** further comprising discontinuing administration of a strong CYP1A2 inhibitor.

* * * * *

EXHIBIT 5

US007910610B1

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 7,910,610 B1**
(45) **Date of Patent: *Mar. 22, 2011**

(54) **METHODS OF ADMINISTERING PIRFENIDONE THERAPY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/901,245**

(22) Filed: **Oct. 8, 2010**

Related U.S. Application Data

(63) Continuation of application No. 12/684,879, filed on Jan. 8, 2010, now Pat. No. 7,816,383.

(60) Provisional application No. 61/266,815, filed on Dec. 4, 2009.

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(52) **U.S. Cl.** **514/350**; 514/354; 514/640; 514/646

(58) **Field of Classification Search** 514/350, 514/354, 640, 646

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes.

11 Claims, 1 Drawing Sheet

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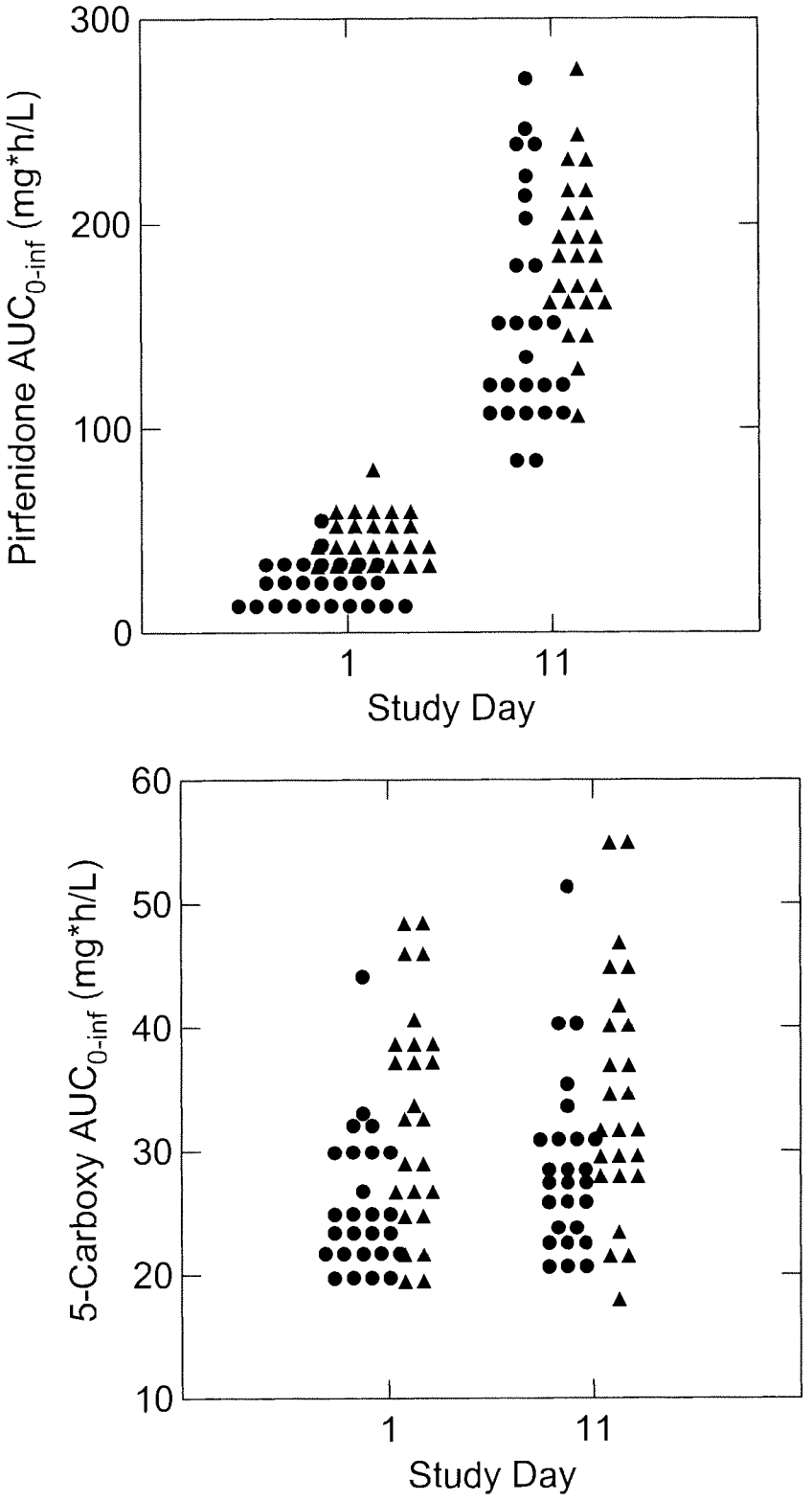
300
200
100
0
Pirfenidone $AUC_{0\text{-}inf}$ (mg*h/L)
1
11
Study Day
60
50
40
30
20
10
5-Carboxy $AUC_{0\text{-}inf}$ (mg*h/L)
1
11
Study Day

Figure 1

METHODS OF ADMINISTERING PIRFENIDONE THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/684,879, filed Jan. 8, 2010, now U.S. Pat. No. 7,816,383, which claims the priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/266,815, filed Dec. 4, 2009, each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy involving avoiding adverse drug interactions with fluvoxamine, a strong inhibitor of CYP1A2.

BACKGROUND

Pirfenidone is small molecule with a molecular weight of 185.23 daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved in Japan for treatment of idiopathic pulmonary fibrosis (IPF) under the trade name Pirespa®.

Pirfenidone has been shown to be metabolized by various isoforms of the cytochrome P450 (CYP) protein [See the Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008]. Specifically, several cytochrome P450 (CYP) isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Fluvoxamine belongs to a class of therapeutics known as selective serotonin reuptake inhibitors (SSRIs). The SSRIs are a group of antidepressants with similar pharmacologic effects, but with different chemical structures. Fluvoxamine has been approved for treatment of social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), and has been prescribed to treat major depression, and other anxiety disorders such as panic disorder and post-traumatic stress disorder [McClellan et al., (Drugs October 2000). "Fluvoxamine An Updated Review of its Use in the Management of Adults with Anxiety Disorders". *Adis Drug Evaluation* 60 (4): 925-954]. In addition to fluvoxamine, other clinically available SSRIs are citalopram, fluoxetine, paroxetine and sertraline. The elimination of these lipophilic compounds proceeds predominantly via oxidation catalysed by CYP in the liver. SSRIs have the potential for inhibition of CYP enzymes [Brosen, The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clin Invest* 71(12):1002-1009, 1993]. Jeppesen et al. reported that fluvoxamine is a potent inhibitor of CYP1A2 in humans in vivo [Jeppesen et al., Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol* 51: 73-78, 1996]. Fluvoxamine has also been shown to be a very potent inhibitor of CYP1A2 in vitro [Brosen et al., Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 45:1211-1214, 1993; Rasmussen et al., Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 39:151-159, 1995].

SUMMARY OF THE INVENTION

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient may have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered may be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage may be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone may be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day may be administered as follows: 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of fluvoxamine.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of fluvoxamine to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient is receiving fluvoxamine, and fluvoxamine is discontinued concurrent with starting administration of pirfenidone. In another embodiment, fluvoxamine is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of fluvoxamine therapy is provided, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not fluvoxamine. In one aspect, the alternative therapy that is not fluvoxamine is a drug that is not a moderate to strong inhibitor of CYP1A2. Preferably, such drug is not a moderate to strong inhibitor of both CYP1A2, and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19. In some examples, the alternative drug is selected from the group consisting of Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Prozac Weekly), Paroxetine (Paxil, Paxil CR, Pexeva), and/or Sertraline (Zoloft).

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and advising the patient in any one, two, three or more of the following ways:

(a) advising the patient that fluvoxamine should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both

CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19., can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) advising the patient that use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) advising the patient that co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or.

(f) advising the patient that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the method further includes advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax). In yet further embodiments, the method also includes avoiding administering a strong CYP1A2 inhibitor, or discontinuing administration of a strong CYP1A2 inhibitor.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION OF THE INVENTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing a well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 5 O-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor [Hemeryck et al., Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: An Update. *Current Drug Metabolism* 3(1): 13-37, 2002].

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine. Adverse drug interactions represent 3-5% of preventable in-hospital adverse drug reactions, and are an important contributor to the number of emergency room visits and hospital admissions [Leape L L et al., JAMA 1995;274(1):35-43; Raschetti R et al. Eur J Clin Pharmacol 1999;54(12):959-963].

Data reported herein show that co-administration of pirfenidone with fluvoxamine resulted in an average 6-fold increase in exposure (AUC, or area under the curve) to pirfenidone. It also resulted in an average 2-fold increase in Cmax, the mean maximum plasma concentration. Depending on the circumstances, FDA draft guidance suggests that a drug-drug interaction is present when comparisons indicate twofold or greater systemic exposure for a drug when given in combination with the second drug, compared to when given alone. FDA Preliminary Concept Paper, "Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling," Oct. 1, 2004.

Definitions

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; her-

niated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, a patient in need of "fluvoxamine therapy" is understood to be a patient in need of "selective serotonin reuptake inhibitor (SSRI) therapy." Such patients include patients suffering from social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), depression, anxiety disorders, panic disorder and post-traumatic stress disorder.

For CYP enzymes, the FDA generally defines a "strong inhibitor" as one that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates (not limited to sensitive CYP substrate) in clinical evaluations. The FDA generally defines a "moderate inhibitor" as one that caused a >2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.

CYP Inhibitors and Substrates

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, such as fluvoxamine. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme that metabolizes pirfenidone, e.g. selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

As yet other alternatives, in any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a strong inhibitor of CYP1A2 or a substrate for CYP1A2.

CYP1A2 metabolizes many commonly used drugs including theophylline, imipramine, propranolol, and clozapine. These drugs are commonly referred to as "substrates" for CYP1A2. Additional CYP1A2 substrates include but are not limited to acetominophen, amitriptyline, caffeine, chlordiazepoxide, cinacalcet, clomipramine, clopidogrel, cyclobenzaprine, desipramine, diazepam, duloxetine, erlotinib, estradiol, flutamide, haloperidol, levobupivacaine, methadone, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, ramelteon, riluzole, ropinirole, ropivacaine, tacrine, tizanidine, verapamil, and warfarin.

Inhibitors of CYP1A2 include fluvoxamine, cimetidine, amiodarone, echinacea, enoxacin, norfloxacin, oral contraceptives, tacrine, ticlopidine, and many fluoroquinolone antibiotics. Moderate inhibitors of CYP1A2 include ciprofloxacin, mexiletine, propafenone and zileuton. Additional inhibitors of CYP1A2 include atazanavir, citalopram, clarithromycin, dilitiazem, erythromycin, ethinyl estradiol, isoniazid, ketoconazole, methoxsalen, nalidixic acid, norethindrone, omeprazole, paroxetine, tipranavir, and troleandomycin. Other inhibitors of CYP1A2 include acyclovir, caffeine, famotidine, flutamide, grapefruit juice, lidocaine, lomefloxacin, moclobemide, ofloxacin, perphenazine, phenacetin, propafenone, ropinirole, tocainide, and verapamil.

Inhibitors of CYP3A4 include amiodarone, cimetidine, ciprofloxacin, delavirdine, fluvoxamine, miconazole, and voriconazole (VFEND). Strong inhibitors of CYP3A4 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin. Moderate inhibitors of CYP3A4 include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil. Additional inhibitors of CYP3A4 include acitretin, cyclosporine, danazol, diethyldithiocarbamate, efavirenz, ethinyl estradiol, fluoxetine, gestodene, imatinib, isoniazid, metronidazole, methylpredisolone, mifepristone, nicardipine, nifedipine, norethindrone, norfloxacin, norfluoxetine, oxiconazole, pomegranate, prednisone, quinine, ranolazine, roxithromycin, sertraline, Synercid, troleandomycin, zafirlukast, and zileuton. Other inhibitors of CYP3A4 include doxycycline, echinacea, and enoxacin.

Inhibitors of CYP2C9 include cimetidine, delavirdine, efavirenz, fenofibrate (Tricor), fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, leflunomide, modafinil, sertraline, voriconazole (VFEND), and zafirlukast (Accolate). Moderate inhibitors of CYP2C9 include amiodarone, fluconazole and oxandrolone. Additional CYP2C9 inhibitors include atazanavir, chloramphenicol, clopidogrel, cotrimoxazole, cranberry, disulfiram, fluorouracil, gemfibrozil, ginkgo, imatinib, itraconazole, lovastatin, metronidazole, omeprazole, paroxetine, sulfonamides, triclopidine, and tipranavir. Other inhibitors of CYP2C9 include anastrazole, phenylbutazone, sulfamethoxazole, sulfaphenazole, tamoxifen, teniposide, valproic acid, and 5-fluorouracil.

Inhibitors of CYP2D6 include amiodarone, bupropion, celecoxib, chlorpheniramine, cimetidine, cinacalcet, citalopram, clomipramine, desipramine, diphenhydramine, halofantrine, haloperidol, methadone, moclobemide, pro-

pafenone, ritonavir, sertraline, and thioridazine. Strong CYP2D6 inhibitors include fluoxetine, paroxetine and quinidine, while moderate CYP2D6 inhibitors include duloxetine and terbinafine. Additional inhibitors of CYP2D6 include chloroquine, cocaine, darifenacin, escitalopram, fluphenazine, hydroxychloroquine, imatinib, levomepromazine, norfluoxetine, perphenazine, pomegranate, propoxyphene, propranolol, quinacrine, ranitidine, ranolazine, and tipranavir. Other inhibitors of CYP2D6 include amitriptyline, chlorpromazine, doxepin, fluvoxamine, goldenseal, hydroxyzine, imipramine, metoclopramide, pimozide, and ticlopidine (Ticlid).

Inhibitors of CYP2C19 include delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, indomethacin, isoniazid (INH), modafinil (Provigil), oxcarbazepine, ticlopidine, topiramate, and voriconazole (VFEND) A strong inhibitor of CYP2C19 is omeprazole. Additional inhibitors of CYP2C19 include citalopram, fluvastatin, ketoconazole, lansoprazole, letrozole, paroxetine, sertraline, telmisartan, and tipranavir. Other inhibitors of CYP2C19 include artemisinin, chloramphenicol, and oral contraceptives.

Inhibitors of CYP2B6 include clopidogrel (Plavix), efavirenz, fluoxetine, fluvoxamine, ketoconazole, memantine, nelfinavir, oral contraceptives, paroxetine, ritonavir, thiotepa, and ticlopidine (Ticlid).

Avoiding or Discontinuing Administration of a Drug to Avoid Adverse Drug Interactions with Pirfenidone

As used herein, "avoiding" means "refraining from." *Merriam-Webster Online Dictionary,* 11th ed., 24 Nov. 2009. In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4, or a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a strong CYP1A2 inhibitor.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a CYP1A2 substrate.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug being discontinued is a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a strong CYP1A2 inhibitor to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of the drug that is a CYP inhibitor and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the drug that is a CYP inhibitor is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP inhibitor is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which fluvoxamine is discontinued to avoid an adverse drug interaction, fluvoxamine is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, fluvoxamine is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the fluvoxamine is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of fluvoxamine therapy.

In some embodiments in which the drug being discontinued is a CYP inhibitor, the drug is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the drug that is a CYP inhibitor is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at

least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the drug that is a CYP inhibitor is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the drug upon discontinuation.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of the CYP1A2 substrate to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug that is a CYP1A2 substrate is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP1A2 substrate is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which a CYP1A2 substrate is discontinued to avoid an adverse drug interaction, the CYP1A2 substrate is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the CYP1A2 substrate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the CYP substrate is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP1A2 substrate therapy.

Selecting an Alternative Drug to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In another embodiment, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

In some embodiments, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a strong CYP1A2 inhibitor, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a strong CYP1A2 inhibitor.

In yet other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP1A2 substrate, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP1A2 substrate.

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a strong CYP1A2 inhibitor can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 substrate can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with fluvoxamine is contraindicated. In some embodiments, the patient is advised that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and fluvoxamine concurrently is provided wherein the patient is administered a therapeutically effective amount of fluvoxamine and a dosage of pirfenidone that is decreased relative to a patient not taking fluvoxamine. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered fluvoxamine. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 concurrently is provided wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In related aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In yet other aspects, a method of administering pirfenidone and a strong CYP1A2 inhibitor concurrently is provided wherein the patient is administered a therapeutically effective amount of the strong CYP1A2 inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking the strong CYP1A2 inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the strong CYP1A2 inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the strong CYP1A2 inhibitor.

In various embodiments, a method of administering pirfenidone and a CYP1A2 substrate concurrently is provided wherein the patient is administered a therapeutically effective amount of the CYP1A2 substrate and a dosage of pirfenidone that is decreased relative to a patient not taking the CYP1A2 substrate. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP1A2 substrate. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the CYP1A2 substrate.

In some embodiments, the amount of pirfenidone being administered is 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 50 to about 2400 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 267 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 534 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1068 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1335 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1869 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2136 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of administering a SSRI to a patient in need thereof is provided, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2, and a CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1 , CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a strong CYP1A2 inhibitor to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 substrate to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of administering pirfenidone therapy to a patient receiving fluvoxamine therapy is provided, comprising administering to the patient a therapeutically effective amount of fluvoxamine and administering to the patient a daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day, e.g. 1600 mg or 1602 mg per day. In some embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine. Similarly, in any of the foregoing embodiments relating to other CYP inhibitors

or CYP substrates, the daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day may be, e.g. 1600 mg or 1602 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) use of fluvoxamine should be avoided or discontinued,

(b) co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or

(f) strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the information or recommendation may include that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax).

In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1 , CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are strong CYP1A2 inhibitors can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are CYP1A2 substrates can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19 should be avoided or discontinued, or are contraindicated, or should be used with caution. In yet further embodiments, the information or recommendation may include that administering a strong CYP1A2 inhibitor should be avoided or discontinued, or are contraindicated, or should be used with caution. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 substrates should be avoided or discontinued, or are contraindicated, or should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

In some embodiments, a kit is provided comprising fluvoxamine and a package insert, package label, instructions, or other labeling comprising any one, two, three or more of the following warnings:

(a) use of fluvoxamine and pirfenidone is contraindicated

(b) use of pirfenidone in patients being treated with fluvoxamine is contraindicated, and/or

(c) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone.

(d) co-administration of pirfenidone and fluvoxamine resulted in an average 2-fold increase in peak serum concentration of pirfenidone.

In some embodiments, a method of treating a patient in need of fluvoxamine is provided comprising providing or delivering any of the kits disclosed herein comprising fluvoxamine to a hospital, physician or patient.

In related aspects, the invention provides a method of administering a SSRI to a patient in need thereof, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1

An open-label Phase 1 study was performed to determine the impacts of fluvoxamine on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design. The study was a Phase 1, open-label, parallel-group study in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Smoking induces CYP1A2 activity. Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each subject was to receive a single 801-mg dose of pirfenidone on

Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking status).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results. Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5-carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5-carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5-carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5-carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126 -206)	29.4 (25.4 -36.5)

[a]p-value < 0.00001 (paired t-test)

[b]p-value = 0.168 (paired t-test)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5-carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12 -8.25)	1.13 (1.04 -1.19)
Nonsmokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26 -4.68)	1.03 (0.978 -1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

What is claimed is:

1. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone while avoiding co-administration of a strong cytochrome P450 1A2 (CYP1A2) inhibitor, wherein said patient is also in need of therapy with a strong CYP1A2 inhibitor.

2. The method of claim **1** wherein the patient has idiopathic pulmonary fibrosis (IPF).

3. The method of claim **1** wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

4. The method of claim **1** wherein 800 or 801 mg of pirfenidone is administered to the patient three times per day, with food.

5. A method of administering pirfenidone therapy to a patient in need thereof, comprising discontinuing administration of a strong CYP1A2 inhibitor to avoid an adverse drug interaction with pirfenidone, and administering to the patient a therapeutically effective amount of pirfenidone.

6. The method of claim **5** wherein the patient has idiopathic pulmonary fibrosis (IPF).

7. The method of claim **5** wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

8. The method of claim **5** wherein 800 or 801 mg of pirfenidone is administered to the patient three times per day, with food.

9. The method of claim **5** wherein the strong CYP1A2 inhibitor is discontinued within 1 month prior to starting pirfenidone therapy.

10. The method of claim **5** wherein the strong CYP1A2 inhibitor is discontinued within 2 weeks prior to starting pirfenidone therapy.

11. The method of claim **1** or **5** wherein the patient is advised that co-administration of pirfenidone with the strong CYP1A2 inhibitor can alter the therapeutic effect or adverse reaction profile of pirfenidone.

* * * * *

EXHIBIT 6

US008013002B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,013,002 B2**
(45) **Date of Patent: *Sep. 6, 2011**

(54) **METHODS OF ADMINISTERING PIRFENIDONE THERAPY**

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(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/049,894**

(22) Filed: **Mar. 16, 2011**

(65) **Prior Publication Data**

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(63) Continuation of application No. 12/901,245, filed on Oct. 8, 2010, now Pat. No. 7,910,610, which is a continuation of application No. 12/684,879, filed on Jan. 8, 2010, now Pat. No. 7,816,383.

(60) Provisional application No. 61/266,815, filed on Dec. 4, 2009.

(51) **Int. Cl.**

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A61K 31/44	(2006.01)
A61K 31/15	(2006.01)
A61K 31/135	(2006.01)

(52) **U.S. Cl.** **514/350**; 514/354; 514/640; 514/646

(58) **Field of Classification Search** 514/350, 514/354, 640, 646

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes.

11 Claims, 1 Drawing Sheet

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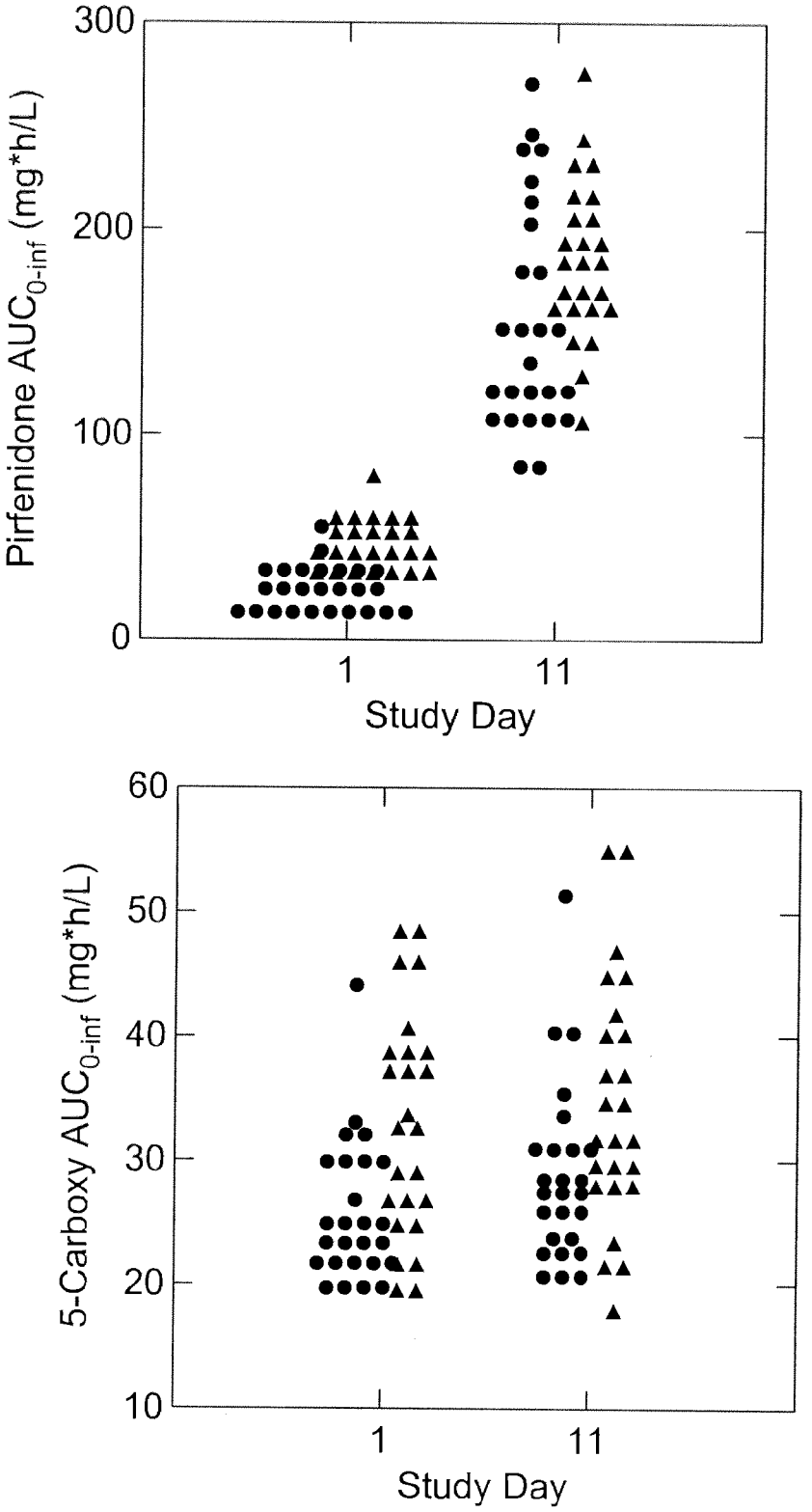
300
200
100
0
Pirfenidone AUC0-inf (mg*h/L)
1
11
Study Day
60
50
40
30
20
10
5-Carboxy AUC0-inf (mg*h/L)
1
11
Study Day

Figure 1

METHODS OF ADMINISTERING PIRFENIDONE THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/901,245, filed Oct. 8, 2010, now U.S. Pat. No. 7,910,610, which is a continuation of U.S. patent application Ser. No. 12/684,879, filed Jan. 8, 2010, now U.S. Pat. No. 7,816,383, which claims the priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/266,815, filed Dec. 4, 2009, each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy involving avoiding adverse drug interactions with fluvoxamine, a strong inhibitor of CYP1A2.

BACKGROUND

Pirfenidone is small molecule with a molecular weight of 185.23 daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved in Japan for treatment of idiopathic pulmonary fibrosis (IPF) under the trade name Pirespa®.

Pirfenidone has been shown to be metabolized by various isoforms of the cytochrome P450 (CYP) protein [See the Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008]. Specifically, several cytochrome P450 (CYP) isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Fluvoxamine belongs to a class of therapeutics known as selective serotonin reuptake inhibitors (SSRIs). The SSRIs are a group of antidepressants with similar pharmacologic effects, but with different chemical structures. Fluvoxamine has been approved for treatment of social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), and has been prescribed to treat major depression, and other anxiety disorders such as panic disorder and post-traumatic stress disorder [McClellan et al., (Drugs October 2000). "Fluvoxamine An Updated Review of its Use in the Management of Adults with Anxiety Disorders". *Adis Drug Evaluation* 60 (4): 925-954]. In addition to fluvoxamine, other clinically available SSRIs are citalopram, fluoxetine, paroxetine and sertraline. The elimination of these lipophilic compounds proceeds predominantly via oxidation catalysed by CYP in the liver. SSRIs have the potential for inhibition of CYP enzymes [Brosen, The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clin Invest* 71(12):1002-1009, 1993]. Jeppesen et al. reported that fluvoxamine is a potent inhibitor of CYP1A2 in humans in vivo [Jeppesen et al., Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol* 51: 73-78, 1996]. Fluvoxamine has also been shown to be a very potent inhibitor of CYP1A2 in vitro [Brosen et al., Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 45:1211-1214, 1993; Rasmussen et al., Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 39:151-159, 1995].

SUMMARY OF THE INVENTION

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient may have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered may be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage may be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone may be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day may be administered as follows: 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of fluvoxamine.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of fluvoxamine to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient is receiving fluvoxamine, and fluvoxamine is discontinued concurrent with starting administration of pirfenidone. In another embodiment, fluvoxamine is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of fluvoxamine therapy is provided, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not fluvoxamine. In one aspect, the alternative therapy that is not fluvoxamine is a drug that is not a moderate to strong inhibitor of CYP1A2. Preferably, such drug is not a moderate to strong inhibitor of both CYP1A2, and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19. In some examples, the alternative drug is selected from the group consisting of Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Prozac Weekly), Paroxetine (Paxil, Paxil CR, Pexeva), and/or Sertraline (Zoloft).

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and advising the patient in any one, two, three or more of the following ways:

(a) advising the patient that fluvoxamine should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19., can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) advising the patient that use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) advising the patient that co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or.

(f) advising the patient that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the method further includes advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax). In yet further embodiments, the method also includes avoiding administering a strong CYP1A2 inhibitor, or discontinuing administration of a strong CYP1A2 inhibitor.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION OF THE INVENTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 5 O-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor [Hemeryck et al., Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: An Update. *Current Drug Metabolism* 3(1): 13-37, 2002].

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine. Adverse drug interactions represent 3-5% of preventable in-hospital adverse drug reactions, and are an important contributor to the number of emergency room visits and hospital admissions [Leape L L et al., JAMA 1995;274(1):35-43; Raschetti R et al. Eur J Clin Pharmacol 1999;54(12):959-963].

Data reported herein show that co-administration of pirfenidone with fluvoxamine resulted in an average 6-fold increase in exposure (AUC, or area under the curve) to pirfenidone. It also resulted in an average 2-fold increase in Cmax, the mean maximum plasma concentration. Depending on the circumstances, FDA draft guidance suggests that a drug-drug interaction is present when comparisons indicate twofold or greater systemic exposure for a drug when given in combination with the second drug, compared to when given alone. FDA Preliminary Concept Paper, "Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling," Oct. 1, 2004.

Definitions

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic

pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, a patient in need of "fluvoxamine therapy" is understood to be a patient in need of "selective serotonin reuptake inhibitor (SSRI) therapy." Such patients include patients suffering from social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), depression, anxiety disorders, panic disorder and post-traumatic stress disorder.

For CYP enzymes, the FDA generally defines a "strong inhibitor" as one that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates (not limited to sensitive CYP substrate) in clinical evaluations. The FDA generally defines a "moderate inhibitor" as one that caused a >2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.

CYP Inhibitors and Substrates

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, such as fluvoxamine. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme that metabolizes pirfenidone, e.g. selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

As yet other alternatives, in any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a strong inhibitor of CYP1A2 or a substrate for CYP1A2.

CYP1A2 metabolizes many commonly used drugs including theophylline, imipramine, propranolol, and clozapine. These drugs are commonly referred to as "substrates" for CYP1A2. Additional CYP1A2 substrates include but are not limited to acetominophen, amitriptyline, caffeine, chlordiazepoxide, cinacalcet, clomipramine, clopidogrel, cyclobenzaprine, desipramine, diazepam, duloxetine, erlotinib, estradiol, flutamide, haloperidol, levobupivacaine, methadone, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, ramelteon, riluzole, ropinirole, ropivacaine, tacrine, tizanidine, verapamil, and warfarin.

Inhibitors of CYP1A2 include fluvoxamine, cimetidine, amiodarone, echinacea, enoxacin, norfloxacin, oral contraceptives, tacrine, ticlopidine, and many fluoroquinolone antibiotics. Moderate inhibitors of CYP1A2 include ciprofloxacin, mexiletine, propafenone and zileuton. Additional inhibitors of CYP1A2 include atazanavir, citalopram, clarithromycin, dilitiazem, erythromycin, ethinyl estradiol, isoniazid, ketoconazole, methoxsalen, nalidixic acid, norethindrone, omeprazole, paroxetine, tipranavir, and troleandomycin. Other inhibitors of CYP1A2 include acyclovir, caffeine, famotidine, flutamide, grapefruit juice, lidocaine, lomefloxacin, moclobemide, ofloxacin, perphenazine, phenacetin, propafenone, ropinirole, tocainide, and verapamil.

Inhibitors of CYP3A4 include amiodarone, cimetidine, ciprofloxacin, delavirdine, fluvoxamine, miconazole, and voriconazole (VFEND). Strong inhibitors of CYP3A4 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin. Moderate inhibitors of CYP3A4 include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil. Additional inhibitors of CYP3A4 include acitretin, cyclosporine, danazol, diethyldithiocarbamate, efavirenz, ethinyl estradiol, fluoxetine, gestodene, imatinib, isoniazid, metronidazole, methylpredisolone, mifepristone, nicardipine, nifedipine, norethindrone, norfloxacin, norfluoxetine, oxiconazole, pomegranate, prednisone, quinine, ranolazine, roxithromycin, sertraline, Synercid, troleandomycin, zafirlukast, and zileuton. Other inhibitors of CYP3A4 include doxycycline, echinacea, and enoxacin.

Inhibitors of CYP2C9 include cimetidine, delavirdine, efavirenz, fenofibrate (Tricor), fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, leflunomide, modafinil, sertraline, voriconazole (VFEND), and zafirlukast (Accolate). Moderate inhibitors of CYP2C9 include amiodarone, fluconazole and oxandrolone. Additional CYP2C9 inhibitors include atazanavir, chloramphenicol, clopidogrel, cotrimoxazole, cranberry, disulfiram, fluorouracil, gemfibrozil, ginkgo, imatinib, itraconazole, lovastatin, metronidazole, omeprazole, paroxetine, sulfonamides, triclopidine, and tipranavir. Other inhibitors of CYP2C9 include anastrazole, phenylbutazone, sulfamethoxazole, sulfaphenazole, tamoxifen, teniposide, valproic acid, and 5-fluorouracil.

Inhibitors of CYP2D6 include amiodarone, bupropion, celecoxib, chlorpheniramine, cimetidine, cinacalcet, citalopram, clomipramine, desipramine, diphenhydramine, halofantrine, haloperidol, methadone, moclobemide, propafenone, ritonavir, sertraline, and thioridazine. Strong CYP2D6 inhibitors include fluoxetine, paroxetine and quinidine, while moderate CYP2D6 inhibitors include duloxetine and terbinafine. Additional inhibitors of CYP2D6 include chloroquine, cocaine, darifenacin, escitalopram, fluphenazine, hydroxychloroquine, imatinib, levomepromazine, norfluoxetine, perphenazine, pomegranate, propoxyphene, propranolol, quinacrine, ranitidine, ranolazine, and tipranavir. Other inhibitors of CYP2D6 include amitriptyline, chlorpromazine, doxepin, fluvoxamine, goldenseal, hydroxyzine, imipramine, metoclopramide, pimozide, and ticlopidine (Ticlid).

Inhibitors of CYP2C19 include delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, indomethacin, isoniazid (INH), modafinil (Provigil), oxcarbazepine, ticlopidine, topiramate, and voriconazole (VFEND) A strong inhibitor of CYP2C19 is omeprazole. Additional inhibitors of CYP2C19 include citalopram, fluvastatin, ketoconazole, lansoprazole, letrozole, paroxetine, sertraline, telmisartan, and tipranavir. Other inhibitors of CYP2C19 include artemisinin, chloramphenicol, and oral contraceptives.

Inhibitors of CYP2B6 include clopidogrel (Plavix), efavirenz, fluoxetine, fluvoxamine, ketoconazole, memantine, nelfinavir, oral contraceptives, paroxetine, ritonavir, thiotepa, and ticlopidine (Ticlid).

Avoiding or Discontinuing Administration of a Drug to Avoid Adverse Drug Interactions with Pirfenidone

As used herein, "avoiding" means "refraining from." *Merriam-Webster Online Dictionaiy,* 11th ed., 24 Nov. 2009. In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4, or a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a strong CYP1A2 inhibitor.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a CYP1A2 substrate.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug being discontinued is a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a strong CYP1A2 inhibitor to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of the drug that is a CYP inhibitor and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the drug that is a CYP inhibitor is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP inhibitor is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which fluvoxamine is discontinued to avoid an adverse drug interaction, fluvoxamine is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, fluvoxamine is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at east 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the fluvoxamine is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of fluvoxamine therapy.

In some embodiments in which the drug being discontinued is a CYP inhibitor, the drug is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the drug that is a CYP inhibitor is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at

least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the drug that is a CYP inhibitor is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the drug upon discontinuation.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of the CYP1A2 substrate to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug that is a CYP1A2 substrate is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP1A2 substrate is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which a CYP1A2 substrate is discontinued to avoid an adverse drug interaction, the CYP1A2 substrate is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the CYP1A2 substrate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the CYP1A2 substrate is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP1A2 substrate therapy.

Selecting an Alternative Drug to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In another embodiment, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

In some embodiments, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a strong CYP1A2 inhibitor, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a strong CYP1A2 inhibitor.

In yet other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP1A2 substrate, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP1A2 substrate.

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a strong CYP1A2 inhibitor can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 substrate can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with fluvoxamine is contraindicated. In some embodiments, the patient is advised that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 is contraindicated. In some embodiments, the patient is advised that pirfenidone should

be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and fluvoxamine concurrently is provided wherein the patient is administered a therapeutically effective amount of fluvoxamine and a dosage of pirfenidone that is decreased relative to a patient not taking fluvoxamine. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered fluvoxamine. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 concurrently is provided wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In related aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In yet other aspects, a method of administering pirfenidone and a strong CYP1A2 inhibitor concurrently is provided wherein the patient is administered a therapeutically effective amount of the strong CYP1A2 inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking the strong CYP1A2 inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the strong CYP1A2 inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the strong CYP1A2 inhibitor.

In various embodiments, a method of administering pirfenidone and a CYP1A2 substrate concurrently is provided wherein the patient is administered a therapeutically effective amount of the CYP1A2 substrate and a dosage of pirfenidone that is decreased relative to a patient not taking the CYP1A2 substrate. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP1A2 substrate. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the CYP1A2 substrate.

In some embodiments, the amount of pirfenidone being administered is 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 50 to about 2400 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 267 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 534 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1068 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1335 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1869 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2136 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1

mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of administering a SSRI to a patient in need thereof is provided, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2, and a CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a strong CYP1A2 inhibitor to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 substrate to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of administering pirfenidone therapy to a patient receiving fluvoxamine therapy is provided, comprising administering to the patient a therapeutically effective amount of fluvoxamine and administering to the patient a daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day, e.g. 1600 mg or 1602 mg per day. In some embodiments, the dosage of pirfenidone is decreased

prior to administration of fluvoxamine. Similarly, in any of the foregoing embodiments relating to other CYP inhibitors or CYP substrates, the daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day may be, e.g. 1600 mg or 1602 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) use of fluvoxamine should be avoided or discontinued,

(b) co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or

(f) strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the information or recommendation may include that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax).

In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are strong CYP1A2 inhibitors can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are CYP1A2 substrates can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19 should be avoided or discontinued, or are contraindicated, or should be used with caution. In yet further embodiments, the information or recommendation may include that administering a strong CYP1A2 inhibitor should be avoided or discontinued, or are contraindicated, or should be used with caution. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 substrates should be avoided or discontinued, or are contraindicated, or should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

In some embodiments, a kit is provided comprising fluvoxamine and a package insert, package label, instructions, or other labeling comprising any one, two, three or more of the following warnings:

(a) use of fluvoxamine and pirfenidone is contraindicated

(b) use of pirfenidone in patients being treated with fluvoxamine is contraindicated, and/or

(c) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone.

(d) co-administration of pirfenidone and fluvoxamine resulted in an average 2-fold increase in peak serum concentration of pirfenidone.

In some embodiments, a method of treating a patient in need of fluvoxamine is provided comprising providing or delivering any of the kits disclosed herein comprising fluvoxamine to a hospital, physician or patient.

In related aspects, the invention provides a method of administering a SSRI to a patient in need thereof, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1

An open-label Phase 1 study was performed to determine the impacts of fluvoxamine on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design. The study was a Phase 1, open-label, parallel-group study in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Smoking induces CYP1A2 activity. Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each

subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking status).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results. Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5-carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5-carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5-carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5-carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a]p-value < 0.00001 (paired t-test)
[b]p-value = 0.168 (paired t-test)
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5-carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94–2.25) for pirfenidone and 0.369 (0.349–0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)
Nonsmokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

What is claimed is:

1. A method of administering pirfenidone and fluvoxamine concurrently to a patient in need thereof comprising administering a therapeutically effective amount of fluvoxamine to the patient and administering a therapeutically effective amount of pirfenidone to the patient, wherein the amount of the pirfenidone is about 801 mg/day.

2. The method of claim **1** wherein the pirfenidone is administered three times per day.

3. The method of claim **2** wherein the patient has idiopathic pulmonary fibrosis (IPF).

4. The method of claim **3** wherein the pirfenidone is administered to the patient with food.

5. The method of claim **1** further comprising discontinuing co-administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

6. A method of providing pirfenidone therapy to a patient in need thereof comprising titrating the dosage of pirfenidone administered to the patient downward from a dose of about 2400 mg/day, while co-administering fluvoxamine, wherein the dose of pirfenidone is reduced by about 1600 mg/day.

7. The method of claim **6** wherein about 800 mg/day of pirfenidone is administered to the patient.

8. The method of claim **6** wherein the pirfenidone is administered three times per day.

9. The method of claim **8** wherein the patient has idiopathic pulmonary fibrosis (IPF).

10. The method of claim **9** wherein the pirfenidone is administered to the patient with food.

11. The method of claim **6** further comprising discontinuing co-administration of fluvoxamine and administering about 2400 mg/day of pirfenidone.

* * * * *

EXHIBIT 7

US008084475B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,084,475 B2**
(45) **Date of Patent: Dec. 27, 2011**

(54) **PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450**

(75) Inventors: **Williamson Ziegler Bradford**, Ross, CA (US); **Javier Szwarcberg**, San Francisco, CA (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/684,543**

(22) Filed: **Jan. 8, 2010**

(65) **Prior Publication Data**

US 2011/0172277 A1 Jul. 14, 2011

Related U.S. Application Data

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(51) **Int. Cl.**
A01N 43/40 (2006.01)
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **514/350**; 514/354; 514/345

(58) **Field of Classification Search** 514/350, 514/354, 345
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with pirfenidone and CYP inducers, such as smoking.

11 Claims, 1 Drawing Sheet

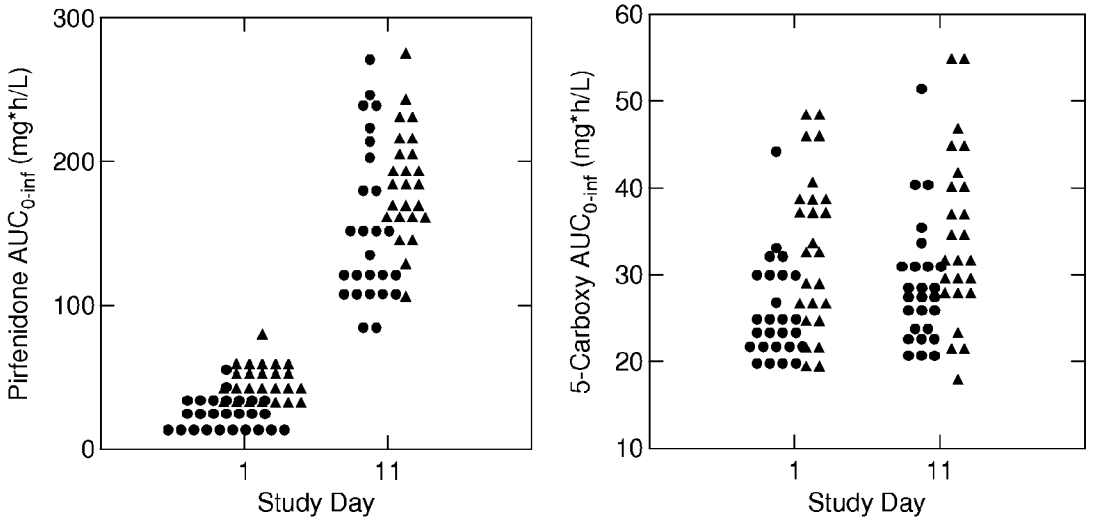
300
200
100
0
Pirfenidone AUC0-inf (mg*h/L)
1
11
Study Day
60
50
40
30
20
10
5-Carboxy AUC0-inf (mg*h/L)
1
11
Study Day

Figure 1

PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/266,753, filed Dec. 4, 2009, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy, involving increased effectiveness of pirfenidone through the avoidance of inducers of cytochrome P450 (CYP) proteins which metabolize pirfenidone. More specifically, the invention is related to methods of administering pirfenidone therapy involving the avoidance of inducers of CYP1A2.

BACKGROUND

Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Pirfenidone has anti-fibrotic properties via: decreased TGF-β expression, decreased TNF-α expression, decreased PDGF expression, and decreased collagen expression.

Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy (>10%) are nausea, rash, dyspepsia, dizziness, vomiting, and photosensitivity reaction, and anorexia. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related. The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at higher doses. In comparison to studies performed to determine the effects of pirfenidone therapy on patients, relatively little was known about the effects of pirfenidone when used in combination with other therapeutics.

Pirfenidone has been shown to be metabolized by isoforms of the cytochrome P450 (CYP) protein (Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008). Specifically, several CYP isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Activity of CYPs in patients who smoke is significantly increased over their non-smoking counterparts.

SUMMARY

The invention disclosed herein is based upon the discovery of an adverse reaction in patients taking pirfenidone who also smoke.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient can have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered can be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage can be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone can be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day can be administered as follows: 800 mg or 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration of an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone ("CYP inducer"). In some cases, the use or administration of the CYP inducer is avoided for at least 2.5 hours after administration of the pirfenidone. In various cases, the CYP inducer that metabolizes pirfenidone is CYP1A2. Induction of CYP1A2 activity has been reported as a consequence of cigarette smoking, dietary factors, several drugs, chronic hepatitis, and exposure to polybrominated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Landi et al. IARC Sci Publ. 1999; (148): 173-95. In addition to, or in the alternative to smoking, the CYP inducers to be discontinued or avoided can be selected from the group consisting of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, and ritonavir. The CYP inducers to be discontinued or avoided can additionally or alternatively be charbroiled foods and/or cruciferous vegetables. The CYP inducers to be discontinued or avoided can additionally or alternatively be selected from the group consisting of phenobarbital, phenyloin, primidone, and St. John's wort.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing use or administration of a CYP inducer that metabolizes pirfenidone to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient discontinues use or administration of the CYP inducer concurrent with starting administration of pirfenidone. In another embodiment, the use or administration of the CYP inducer is discontinued within at least 3 days to within 4 weeks prior to or after starting pirfenidone therapy. This time period can, for example, permit adequate time for tapering and withdrawal without adverse effects, if such tapering is useful for the CYP inducer. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of a CYP inducer that metabolizes pirfenidone and administering a

therapeutically effective amount of pirfenidone. In some embodiments, when the patient is a smoker (e.g., has not quit smoking), the patient avoids smoking for at least 2.5 hours after administration of pirfenidone.

In some embodiments, the patient is a smoker and discontinues smoking. In various embodiments, the method further comprises administering to the smoker patient a nicotine replacement therapy or other smoking cessation therapy. The nicotine replacement therapy can comprise one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. The method can additionally or alternatively comprise administering buproprion hydrochloride (Zyban®) or varenciline (Chantix®).

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone comprises administering a therapeutically effective amount of pirfenidone to the patient, and any one, two, three, or more of the following:

(a) advising the patient that CYP inducers that metabolize pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

For the patient who smokes, the method can further comprise advising the patient to consider nicotine replacement therapy in place of smoking and/or encouraging the patent to stop smoking before treatment with pirfenidone.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 50-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carci-

noma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

Preferably, a CYP inducer that metabolizes pirfenidone is one that decreases plasma AUC values of pirfenidone by 30% or more. A strong CYP inducer that metabolizes pirfenidone is preferably one that decreases plasma AUC values of pirfenidone by 50% or more.

In some embodiments, the effect of a CYP inducer on metabolism of pirfenidone in an individual patient is normalized based upon the patient's body surface area (BSA). BSA can be calculated using a patient's height and weight. In specific embodiments, the normalized effect of the CYP inducer is an at least 30% or at least 50% decrease in AUC values of pirfenidone.

CYP Inducers

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to smoking but also to any other activity or drug that induces a CYP that metabolizes pirfenidone, including CYP1A2. The CYP inducer can be charbroiled meats or cruciferous vegetables. Additionally or alternatively, the CYP inducer can be one or more of phenobarbital, phenyloin, primidone, or St. John's wort. Additionally or alternatively, the CYP inducer can be one or more of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, or ritonavir.

Avoiding or Discontinuing Administration of a CYP Inducer to Avoid Adverse Drug Interactions with Pirfenidone

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration of a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2). In some embodiments, the CYP inducer is smoking (e.g., inhalation of the smoke of burning organic material, particularly tobacco or marijuana), as the result of polycyclic aromatic hydrocarbons which are contained in such smoke.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a CYP1A2 inducer to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of a CYP inducer and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the CYP inducer is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the CYP inducer is discontinued within at least 3 days to 4 weeks prior to or after starting pirfenidone therapy. This time period, for example, can permit adequate time for tapering and withdrawal without adverse effects.

In embodiments in which the CYP inducer is discontinued to avoid an adverse drug interaction, the CYP inducer preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP inducer.

In embodiments where the CYP inducer cannot be or is not discontinued prior pirfenidone therapy, the CYP inducer is preferably discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

In embodiments in which the patient discontinues smoking to avoid an adverse drug interaction, the smoking preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the smoking.

In embodiments in which the patient cannot or does not discontinue smoking prior to pirfenidone therapy, the smoking preferably is discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or

at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

The patient preferably avoids use of the CYP inducer to allow sufficient time for the dose of pirfenidone to be substantially absorbed by the patient's body. Pirfenidone has a serum half life in humans of about 2 to 3 hours. Thus, the patient preferably avoids use of the CYP inducer, for example, for at least 2.5 hours after administration of the pirfenidone. The patient can also avoid use of the CYP inducer for at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone. For example in embodiments where the patient is a smoker, the patient can avoid smoking for at least 2.5 hours, at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone.

Selecting an Alternative Drug or Therapy to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP inducer, such as an inducer of CYP1A2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP inducer.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient who smokes and in need of pirfenidone therapy, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering a stop-smoking therapy, for example nicotine replacement therapy. The nicotine replacement therapy can be any nicotine source and can include a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. Additionally or alternatively, the method can include administration of a drug to assist in smoking cessation. Non-limiting examples of smoking cessation drugs include, but are not limited to, bupropion hydrochloride (Zyban®) or varenicline (Chantix®).

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that administration of pirfenidone and smoking can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients who smoke can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that use of pirfenidone in patients who smoke resulted in a 50% decrease is exposure to pirfenidone.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2) is provided wherein the patient is administered a therapeutically effective amount of the inducer and a dosage of pirfenidone that is increased relative to a patient not taking the inducer. In some aspects, such an increased dosage of pirfenidone is greater than 2400 mg/day. For example, the increased dosage is about 2670 mg per day, 2937 mg per day, 3204 mg per day, 3471 mg per day, or 3738 mg per day (e.g., 10, 11, 12, 13, or 14 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP inducer. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is increased prior to administration of the CYP inducer.

In embodiments wherein the patient avoids or discontinues use of the CYP inducer, preferably the amount of pirfenidone being administered is 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 2400 mg to about 3800 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2670 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2937 mg, about 2950 mg, about 3000 mg, about 3050 mg, about 3100 mg, about 3150 mg, about 3200 mg, about 3204 mg, about 3250 mg, about 3300 mg, about 3350 mg, about 3400 mg, about 3450 mg, about 3471 mg, about 3500 mg, about 3550 mg, about 3600 mg, about 3650 mg, about 3700 mg, about 3738 mg, about 3750 mg, and about 3800 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP inducer that metabolizes pirfenidone to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is an inducer of CYP1A2 to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 inducer to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) advising the patient that strong CYP inducers that metabolize pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism. In some embodiments, the information or recommendation may include that co-administration of pirfenidone with inducers of CYP that metabolize pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that administration of pirfenidone to a patient who smokes can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with CYP1A2 inducers can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be avoided. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be discontinued. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

An open-label Phase 1 study was performed to determine the impacts of a strong CYP1A2 inhibitor and a CYP1A2 inducer on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design. The study was a Phase 1, open-label, parallel-group study designed to investigate the impact of CYP1A2 inhibition and induction on the pharmacokinetics and safety of pirfenidone in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model

was defined, $AUC_{0-\infty}$ co estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results. Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5 carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5 carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5 carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a] p-value < 0.00001 (paired t-test)

[b] p-value = 0.168 (paired t-test)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5 carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)
Nonsmokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

The relationship between smoking status and exposure to pirfenidone and 5 carboxy pirfenidone were examined using the $AUC_{0-\infty}$ estimates from Day 1. Due to the high degree of correlation between BSA and other demographic variables (sex, creatinine clearance (mL/min) (CLcr), age) and the pharmacologic plausibility of a relationship between exposure and body size, $AUC_{0-\infty}$ was first normalized to body surface area before application of multiple linear regression. Smoking status was the only significant predictor of the variability in pirfenidone $AUC_{0-\infty}$ normalized to BSA. Smoking status had a pronounced effect in that smokers would be predicted to have a ~50% drop in $AUC_{0-\infty}$ after accounting for differences in BSA. For 5 carboxy-pirfenidone $AUC_{0-\infty}$, the only significant predictors were age and CLcr.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition and/or induction on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

Administration of pirfenidone to patients who smoke resulted in a significant decrease in exposure ($AUC_{0-\infty}$) to

pirfenidone, and was, on average, about 50% the exposure of pirfenidone in patients that didn't smoke.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

Examples of Embodiments of the Invention Include

1. A method of administering pirfenidone therapy to a patient in need thereof comprising administering to the patient a therapeutically effective amount of pirfenidone and avoiding use or administration of a strong inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone.

2. The method of paragraph 1, wherein the strong inducer of CYP is avoided for at least 2.5 hours after administration of the pirfenidone.

3. The method of paragraph 2, wherein the patient is a smoker and avoids smoking for at least 2.5 hours after administration of the pirfenidone.

4. A method of administering pirfenidone therapy to a patient in need thereof, wherein the patient is receiving an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone, comprising discontinuing use or administration of the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone to avoid an adverse drug reaction and administering a therapeutically effective amount of pirfenidone.

5. The method of paragraph 4, wherein the inducer of CYP is discontinued prior to administration of pirfenidone.

6. The method of paragraph 5, wherein the inducer of CYP is discontinued within 4 weeks prior to the administration of pirfenidone.

7. The method of paragraph 4, wherein the inducer of CYP is discontinued concurrent to administration of pirfenidone.

8. The method of paragraph 1 or 4, wherein the patient is a smoker, comprising discontinuing smoking.

9. The method of paragraph 8, further comprising administering a nicotine replacement therapy to the patient.

10. The method of paragraph 9, wherein the nicotine replacement therapy comprises one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler.

11. The method of paragraph 8, further comprising administering to the patient bupropion hydrochloride (Zyban) or varenicline (Chantix).

12. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and any one or more of the following:

(a) advising the patient that strong inducers of a cytochrome P450 (CYP) that metabolizes pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with an inducer of CYP that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

13. The method of paragraph 12, wherein the patient is a smoker, and further comprising advising the patient to consider nicotine replacement therapy in place of smoking.

14. The method of any one of paragraphs 12-13, further comprising encouraging patients who smoke to stop smoking before treatment with pirfenidone.

15. The method of any one of paragraphs 1-14, wherein the therapeutically effective amount of pirfenidone is a total daily dose of about 2400 mg.

16. The method of any one of paragraphs 1-15, wherein the pirfenidone is administered three times a day, at a total daily dose of about 2400 mg.

17. The method of any one of paragraphs 1-16, wherein the CYP comprises CYP1A2.

18. The method of any one of paragraphs 1-17, wherein the patient suffers from idiopathic pulmonary fibrosis (IPF).

19. The method of any one of paragraphs 1-18, wherein the pirfenidone is co-administered with food.

20. The method of any one of paragraphs 1-19, wherein the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone is one or more of carbamazepine, charbroiled food, cigarette smoke, cruciferous vegetables, esomeprazole, griseofulvin, insulin, lansprazole, marijuana smoke, moricizine, omeprazole, phenobarbital, phenyloin, primidone rifampin, ritonavir, smoking, and St. John's wort.

What is claimed is:

1. A method of administering pirfenidone therapy to a patient in need thereof, wherein said patient is also in need of a strong inducer of CYP1A2 other than cigarette smoke, comprising (a) administering to the patient a therapeutically effective amount of pirfenidone and (b) avoiding concomitant administration of said strong inducer of CYP1A2.

2. The method of claim **1**, wherein the patient has idiopathic pulmonary fibrosis (IPF).

3. The method of claim **1**, wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

4. A method of administering pirfenidone therapy to a patient in need thereof, wherein said patient is receiving a strong inducer of CYP1A2 other than cigarette smoke, comprising (a) first discontinuing administration of the strong inducer of CYP1A2, and then (b) administering to the patient a therapeutically effective amount of pirfenidone.

5. The method of claim **4**, wherein the patient discontinues administration of said strong inducer of CYP1A2 concurrent to administration of pirfenidone.

6. The method of claim **4**, wherein the patient has idiopathic pulmonary fibrosis (IPF).

7. The method of claim **4**, wherein the therapeutically effective amount of pirfenidone is a daily dosage of 2400 mg or 2403 mg per day.

8. A method of increasing the effectiveness of pirfenidone in the treatment of idiopathic pulmonary fibrosis (IPF) in a patient that is receiving a CYP1A2 inducer, comprising discontinuing the CYP1A2 inducer within 4 weeks prior to pirfenidone administration to decrease the levels of CYP1A2 induction, and then administering pirfenidone.

9. The method of claim **8**, wherein the amount of pirfenidone is administered at a daily dosage of 2400 mg or 2403 mg per day.

10. The method of claim **8**, wherein the patient is a current smoker and smoking is discontinued within 4 weeks prior to pirfenidone administration.

11. The method of claim **10**, wherein the pirfenidone is administered at a daily dosage of 2400 mg or 2403 mg per day.

* * * * *

EXHIBIT 8

US008318780B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,318,780 B2**
(45) **Date of Patent: *Nov. 27, 2012**

(54) **METHODS OF ADMINISTERING PIRFENIDONE THERAPY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 13/049,894, filed on Mar. 16, 2011, now Pat. No. 8,013,002, which is a continuation of application No. 12/901,245, filed on Oct. 8, 2010, now Pat. No. 7,910,610, which is a continuation of application No. 12/684,879, filed on Jan. 8, 2010, now Pat. No. 7,816,383.

(60) Provisional application No. 61/266,815, filed on Dec. 4, 2009.

(51) **Int. Cl.**

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(58) **Field of Classification Search** 514/350, 514/354, 640, 646

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes.

24 Claims, 1 Drawing Sheet

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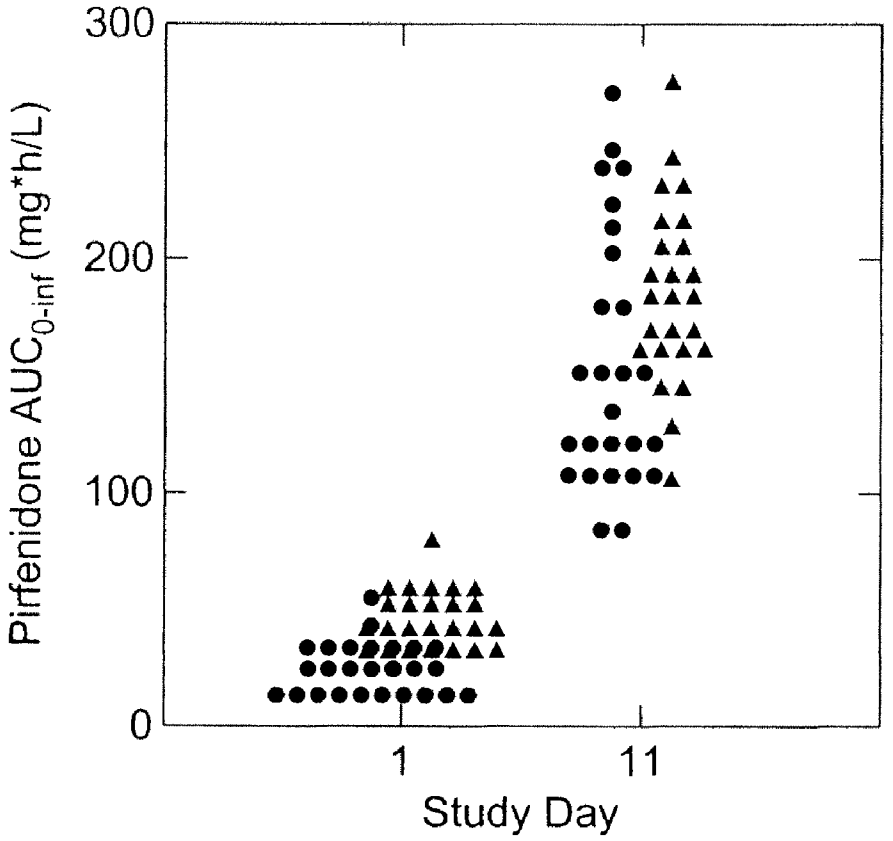
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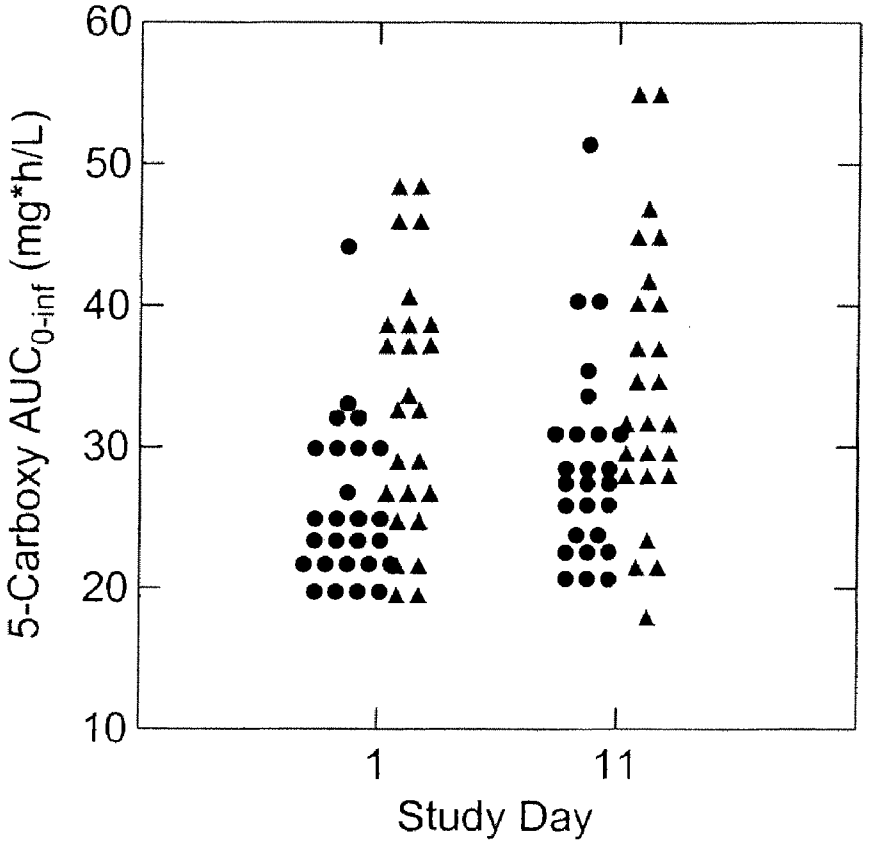
Study Day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5-Carboxy AUC_{0-inf} (mg*h/L)
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METHODS OF ADMINISTERING PIRFENIDONE THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/049,894, filed Mar. 16, 2011, now U.S. Pat. No. 8,013,002, which is a continuation of U.S. patent application Ser. No. 12/901,245, filed Oct. 8, 2010, now U.S. Pat. No. 7,910,610, which is a continuation of U.S. patent application Ser. No. 12/684,879, filed Jan. 8, 2010, now U.S. Pat. No. 7,816,383, which claims the priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 61/266,815, filed Dec. 4, 2009, each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy involving avoiding adverse drug interactions with fluvoxamine, a strong inhibitor of CYP1A2.

BACKGROUND

Pirfenidone is small molecule with a molecular weight of 185.23 daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved in Japan for treatment of idiopathic pulmonary fibrosis (IPF) under the trade name Pirespa®.

Pirfenidone has been shown to be metabolized by various isoforms of the cytochrome P450 (CYP) protein [Sec the Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008]. Specifically, several cytochrome P450 (CYP) isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Fluvoxamine belongs to a class of therapeutics known as selective serotonin reuptake inhibitors (SSRIs). The SSRIs are a group of antidepressants with similar pharmacologic effects, but with different chemical structures. Fluvoxamine has been approved for treatment of social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), and has been prescribed to treat major depression, and other anxiety disorders such as panic disorder and post-traumatic stress disorder [McClellan et al., (Drugs October 2000). "Fluvoxamine An Updated Review of its Use in the Management of Adults with Anxiety Disorders". *Adis Drug Evaluation* 60 (4): 925-954]. In addition to fluvoxamine, other clinically available SSRIs are citalopram, fluoxetine, paroxetine and scrtraline. The elimination of these lipophilic compounds proceeds predominantly via oxidation catalysed by CYP in the liver. SSRIs have the potential for inhibition of CYP enzymes [Brosen, The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clin Invest* 71(12):1002-1009, 1993]. Jeppesen et al. reported that fluvoxamine is a potent inhibitor of CYP1A2 in humans in vivo [Jeppesen et al., Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol* 51: 73-78, 1996]. Fluvoxamine has also been shown to be a very potent inhibitor of CYP1A2 in vitro [Brosen et al., Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 45:1211-1214, 1993; Rasmussen et al., Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 39:151-159, 1995].

SUMMARY OF THE INVENTION

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient may have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered may be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage may be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone may be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day may be administered as follows: 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of fluvoxamine.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of fluvoxamine to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient is receiving fluvoxamine, and fluvoxamine is discontinued concurrent with starting administration of pirfenidone. In another embodiment, fluvoxamine is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of fluvoxamine therapy is provided, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not fluvoxamine. In one aspect, the alternative therapy that is not fluvoxamine is a drug that is not a moderate to strong inhibitor of CYP1A2. Preferably, such drug is not a moderate to strong inhibitor of both CYP1A2, and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19. In some examples, the alternative drug is selected from the group consisting of Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac, Prozac Weekly), Paroxetine (Paxil, Paxil CR, Pexeva), and/or Sertraline (Zoloft).

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and advising the patient in any one, two, three or more of the following ways:

(a) advising the patient that fluvoxamine should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) advising the patient that use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) advising the patient that co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or.

(f) advising the patient that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the method further includes advising the patient that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax). In yet further embodiments, the method also includes avoiding administering a strong CYP1A2 inhibitor, or discontinuing administration of a strong CYP1A2 inhibitor.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION OF THE INVENTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 5 O-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor [Hemeryck et al., Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: An Update. *Current Drug Metabolism* 3(1): 13-37, 2002].

The invention disclosed herein is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine. Adverse drug interactions represent 3-5% of preventable in-hospital adverse drug reactions, and are an important contributor to the number of emergency room visits and hospital admissions [Leape L L et al., JAMA 1995; 274(1):35-43; Raschetti R et al. Eur J Clin Pharmacol 1999; 54(12):959-963].

Data reported herein show that co-administration of pirfenidone with fluvoxamine resulted in an average 6-fold increase in exposure (AUC, or area under the curve) to pirfenidone. It also resulted in an average 2-fold increase in Cmax, the mean maximum plasma concentration. Depending on the circumstances, FDA draft guidance suggests that a drug-drug interaction is present when comparisons indicate twofold or greater systemic exposure for a drug when given in combination with the second drug, compared to when given alone. FDA Preliminary Concept Paper, "Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling," Oct. 1, 2004.

Definitions

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic

pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal, carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, a patient in need of "fluvoxamine therapy" is understood to be a patient in need of "selective serotonin reuptake inhibitor (SSRI) therapy." Such patients include patients suffering from social anxiety disorder (social phobia), obsessive compulsive disorder (OCD), depression, anxiety disorders, panic disorder and post-traumatic stress disorder.

For CYP enzymes, the FDA generally defines a "strong inhibitor" as one that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates (not limited to sensitive CYP substrate) in clinical evaluations. The FDA generally defines a "moderate inhibitor" as one that caused a >2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.

CYP Inhibitors and Substrates

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, such as fluvoxamine. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. The embodiments may also apply to any other drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme that metabolizes pirfenidone, e.g. selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A 11 and/or CYP4F2.

As yet other alternatives, in any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to fluvoxamine but also to any other drug that is a strong inhibitor of CYP1A2 or a substrate for CYP1A2.

CYP1A2 metabolizes many commonly used drugs including theophylline, imipramine, propranolol, and clozapine. These drugs are commonly referred to as "substrates" for CYP1A2. Additional CYP1A2 substrates include but are not limited to acetominophen, amitriptyline, caffeine, chlordiazepoxide, cinacalcet, clomipramine, clopidogrel, cyclobenzaprine, desipramine, diazepam, duloxetine, erlotinib, estradiol, flutamide, haloperidol, levobupivacaine, methadone, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, ramelteon, riluzole, ropinirole, ropivacaine, tacrine, tizanidine, verapamil, and warfarin.

Inhibitors of CYP1A2 include fluvoxamine, cimetidine, amiodarone, echinacea, enoxacin, norfloxacin, oral contraceptives, tacrine, ticlopidine, and many fluoroquinolone antibiotics. Moderate inhibitors of CYP1A2 include ciprofloxacin, mexiletine, propafenone and zileuton. Additional inhibitors of CYP1A2 include atazanavir, citalopram, clarithromycin, dilitiazem, erythromycin, ethinyl cstradiol, isoniazid, ketoconazole, methoxsalen, nalidixic acid, norethindrone, omeprazole, paroxetine, tipranavir, and troleandomycin. Other inhibitors of CYP1A2 include acyclovir, caffeine, famotidine, flutamide, grapefruit juice, lidocaine, lomefloxacin, moclobemide, ofloxacin, perphenazine, phenacetin, propafenone, ropinirole, tocainide, and verapamil.

Inhibitors of CYP3A4 include amiodarone, cimetidine, ciprofloxacin, delavirdine, fluvoxamine, miconazole, and voriconazole (VFEND). Strong inhibitors of CYP3A4 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir and telithromycin. Moderate inhibitors of CYP3A4 include amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice and verapamil. Additional inhibitors of CYP3A4 include acitretin, cyclosporine, danazol, diethyldithiocarbamate, efavirenz, ethinyl estradiol, fluoxetine, gestodene, irnatinib, isoniazid, metronidazole, methylpredisolone, mifepristone, nicardipine, nifedipine, norethindrone, norfloxacin, norfluoxetine, oxiconazole, pomegranate, prednisone, quinine, ranolazine, roxithromycin, sertraline, Synercid, troleandomycin, zafirlukast, and zileuton. Other inhibitors of CYP3A4 include doxycycline, echinacea, and enoxacin.

Inhibitors of CYP2C9 include cimetidine, delavirdine, efavirenz, fenofibrate (Tricor), fluoxetine, fluvastatin, fluvoxamine, isoniazid, ketoconazole, leflunomide, modafinil, sertraline, voriconazole (VFEND), and zafirlukast (Accolate). Moderate inhibitors of CYP2C9 include amiodarone, fluconazole and oxandrolone. Additional CYP2C9 inhibitors include atazanavir, chlorarnphenicol, clopidogrel, cotrimoxazole, cranberry, disulfiram, fluorouracil, gemfibrozil, ginkgo, imatinib, itraconazole, lovastatin, metronidazole, omeprazole, paroxetine, sulfonamides, triclopidine, and tipranavir. Other inhibitors of CYP2C9 include anastrazole, phenylbutazone, sulfamethoxazole, sulfaphenazole, tamoxifen, teniposide, valproic acid, and 5-fluorouracil.

Inhibitors of CYP2D6 include amiodarone, bupropion, celecoxib, chlorpheniramine, cimetidine, cinacalcet, citalopram, clomipramine, desipramine, diphenhydramine, halofantrine, haloperidol, methadone, moclobemide, propafenone, ritonavir, sertraline, and thioridazine. Strong CYP2D6 inhibitors include fluoxetine, paroxetine and quinidine, while moderate CYP2D6 inhibitors include duloxetine and terbinafine. Additional inhibitors of CYP2D6 include chloroquine, cocaine, darifenacin, escitalopram, fluphenazine, hydroxychloroquine, imatinib, levomepromazine, norfluoxetine, perphenazine, pomegranate, propoxyphene, propranolol, quinacrine, ranitidine, ranolazine, and tipranavir. Other inhibitors of CYP2D6 include amitriptyline, chlorpromazine, doxepin, fluvoxamine, goldenseal, hydroxyzine, imipramine, metoclopramide, pimozide, and ticlopidine (Ticlid).

Inhibitors of CYP2C19 include delavirdine, efavirenz, esomeprazole, felbamate, fluconazole, fluoxetine, fluvoxamine, indomethacin, isoniazid (INH), modafinil (Provigil), oxcarbazepine, ticlopidine, topiramate, and voriconazole (VFEND) A strong inhibitor of CYP2C19 is omeprazole. Additional inhibitors of CYP2C19 include citalopram, fluvastatin, ketoconazole, lansoprazole, letrozole, paroxetine, sertraline, telmisartan, and tipranavir. Other inhibitors of CYP2C19 include artemisinin, chloramphenicol, and oral contraceptives.

Inhibitors of CYP2B6 include clopidogrel (Plavix), efavirenz, fluoxetine, fluvoxamine, ketoconazole, memantine, nelfinavir, oral contraceptives, paroxetine, ritonavir, thiotepa, and ticlopidine (Ticlid).

Avoiding or Discontinuing Administration of a Drug to Avoid Adverse Drug Interactions with Pirfenidone

As used herein, "avoiding" moans "refraining from." *Merriam-Webster Online Dictionary,* 11th ed., 24 Nov. 2009. In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4, or a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a moderate-strong inhibitor of both CYP 1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a strong CYP1A2 inhibitor.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding administration of a CYP1A2 substrate.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug being discontinued is a drug that is a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6. In some embodiments, the drug is fluvoxamine.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a strong CYP1A2 inhibitor to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of the drug that is a CYP inhibitor and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the drug that is a CYP inhibitor is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP inhibitor is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which fluvoxamine is discontinued to avoid an adverse drug interaction, fluvoxamine is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, fluvoxamine is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the fluvoxamine is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of fluvoxamine therapy.

In some embodiments in which the drug being discontinued is a CYP inhibitor, the drug is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the drug that is a CYP inhibitor is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at

least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the drug that is a CYP inhibitor is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the drug upon discontinuation.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of the CYP1A2 substrate to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In some embodiments, the drug that is a CYP1A2 substrate is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the drug that is a CYP1A2 substrate is discontinued within at least 3 days to 1 month prior to or after starting pirfenidone therapy. This time period, for example, permits adequate time for tapering and withdrawal without adverse effects.

In some embodiments in which a CYP1A2 substrate is discontinued to avoid an adverse drug interaction, the CYP1A2 substrate is discontinued within at least 3 days prior to or after starting pirfenidone therapy. In various embodiments, the CYP1A2 substrate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to or after starting pirfenidone therapy. In some embodiments, the CYP1A2 substrate is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP1A2 substrate therapy.

Selecting an Alternative Drug to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2.

In another embodiment, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

In some embodiments, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, and/or CYP3A4.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a strong CYP1A2 inhibitor, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a strong CYP1A2 inhibitor.

In yet other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP1A2 substrate, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP1A2 substrate.

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with drugs that are a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2, can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a strong CYP1A2 inhibitor can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 substrate can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with fluvoxamine is contraindicated. In some embodiments, the patient is advised that co-administration of pirfenidone and fluvoxamine resulted in a 6-fold increase in exposure to pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 is contraindicated. In some embodiments, the patient is advised that pirfenidone should

be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, the patient is advised that use of pirfenidone in patients being treated with a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 is contraindicated. In some embodiments, the patient is advised that pirfenidone should be used with caution in patients taking a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and fluvoxamine concurrently is provided wherein the patient is administered a therapeutically effective amoun of fluvoxamine and a dosage of pirfenidone that is decreased relative to a patient not taking fluvoxamine. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered fluvoxamine. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of fluvoxamine.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 concurrently is provided wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In other aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In related aspects, a method of administering pirfenidone and a drug that is a moderate-strong inhibitor of both CYP 1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 concurrently is provided, wherein the patient is administered a therapeutically effective amount of the drug that is a CYP inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking such drug that is a CYP inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the drug that is a CYP inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the drug that is a CYP inhibitor.

In yet other aspects, a method of administering pirfenidone and a strong CYP1A2 inhibitor concurrently is provided wherein the patient is administered a therapeutically effective amount of the strong CYP1A2 inhibitor and a dosage of pirfenidone that is decreased relative to a patient not taking the strong CYP1A2 inhibitor. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the strong CYP1A2 inhibitor. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the strong CYP1A2 inhibitor.

In various embodiments, a method of administering pirfenidone and a CYP1A2 substrate concurrently is provided wherein the patient is administered a therapeutically effective amount of the CYP1A2 substrate and a dosage of pirfenidone that is decreased relative to a patient not taking the CYP1A2 substrate. In some aspects, such a decreased dosage of pirfenidone is less than 2400 mg/day. For example, the decreased dosage is about 2136 mg per day, 1869 mg per day, 1602 mg per day, 1335 mg per day, or 1068 mg per day (e.g., 8, 7, 6, 5, 4, or 3 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP1A2 substrate. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is decreased prior to administration of the CYP1A2 substrate.

In some embodiments, the amount of pirfenidone being administered is 2400 or 2403 g/day. Pirfenidone can be dosed at a total amount of about 50 to about 2400 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 267 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 534 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1068 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1335 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1869 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2136 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 g/kg. Specific ranges of doses in mg/kg include about 1 mg/kg

to about 20 mg/kg, about 5 g/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of administering a SSRI to a patient in need thereof is provided, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2, and a CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 g/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 g/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP1A1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and/or CYP3A4 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is a moderate-strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP3A4, CYP2B6 and/or CYP2D6 to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a strong CYP1A2 inhibitor to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 g/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 substrate to the patient does not result in an increased exposure to pirfenidone. In some embodiments, the dose is reduced by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 g/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of administering pirfenidone therapy to a patient receiving fluvoxamine therapy is provided, comprising administering to the patient a therapeutically effective amount of fluvoxamine and administering to the patient a daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day, e.g. 1600 mg or 1602 mg per day. In some embodiments, the dosage of pirfenidone is decreased

prior to administration of fluvoxamine. Similarly, in any of the foregoing embodiments relating to other CYP inhibitors or GYP substrates, the daily dosage of pirfenidone that is less than 2400 mg or 2403 mg per day may be, e.g. 1600 mg or 1602 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient downward relative to a previously administered dosage in the patient, wherein co-administration of fluvoxamine to the patient does not result in an increased exposure to pirfenidone,

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) use of fluvoxamine should be avoided or discontinued,

(b) co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) co-administration of pirfenidone with fluvoxamine can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(d) use of pirfenidone in patients being treated with fluvoxamine is contraindicated,

(e) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone, and/or

(f) strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

In some embodiments, the information or recommendation may include that co-administration of pirfenidone and fluvoxamine resulted in a 2-fold increase in average peak serum concentration of pirfenidone (Cmax).

In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, CYP2C19, CYP2B6, and/or CYP2D6 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are moderate to strong inhibitors of both CYP1A2 and another GYP enzyme selected from the group consisting of CYP 1A1, CYP2A6, CYP2B6, CYP2CS, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2 CYP3A4, CYP3A5, CYP4A11 and/or CYP4F2 can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are strong CYP1A2 inhibitors can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with drugs that are CYP1A2 substrates can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are moderate to strong inhibitors of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19 should be avoided or discontinued, or are contraindicated, or should be used with caution. In yet further embodiments, the information or recommendation may include that administering a strong CYP1A2 inhibitor should be avoided or discontinued, or are contraindicated, or should be used with caution. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 substrates should be avoided or discontinued, or are contraindicated, or should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

In some embodiments, a kit is provided comprising fluvoxamine and a package insert, package label, instructions, or other labeling comprising any one, two, three or more of the following warnings:

(a) use of fluvoxamine and pirfenidone is contraindicated

(b) use of pirfenidone in patients being treated with fluvoxamine is contraindicated, and/or

(c) co-administration of pirfenidone and fluvoxamine resulted in an average 6-fold increase in exposure to pirfenidone.

(d) co-administration of pirfenidone and fluvoxamine resulted in an average 2-fold increase in peak serum concentration of pirfenidone.

In some embodiments, a method of treating a patient in need of fluvoxamine is provided comprising providing or delivering any of the kits disclosed herein comprising fluvoxamine to a hospital, physician or patient.

In related aspects, the invention provides a method of administering a SSRI to a patient in need thereof, the improvement comprising discontinuing administration of fluvoxamine, for example, concurrent with starting administration of pirfenidone, and optionally administering an SSRI that is not a moderate to strong inhibitor of both CYP1A2 and another CYP enzyme selected from the group consisting of CYP3A4, CYP2C9, and/or CYP2C19.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

Example 1

An open-label Phase 1 study was performed to determine the impacts of fluvoxamine on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design. The study was a Phase 1, open-label, parallel-group study in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Smoking induces CYP1A2 activity. Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each

subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning d at bedtime

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking status).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results. Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5-carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5-carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5-carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5-carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a]p-value < 0.00001 (paired t-test)
[b]p-value = 0.168 (paired t-test)
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity;
SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5-carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)
Nonsmokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity;
SD = standard deviation.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

What is claimed is:

1. A method of administering pirfenidone to a patient in need thereof comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding concomitant use of a cytochrome P450 1A2 (CYP1A2) inhibitor that is a moderate to strong inhibitor of both (i) CYP1A2 and (ii) another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and CYP2D6, wherein the patient is also in need of said CYP1A2 inhibitor.

2. The method of claim **1** wherein the avoiding of the CYP1A2 inhibitor is to avoid an adverse drug interaction with pirfenidone.

3. The method of claim **1** wherein the patient is in need of an anti-fibrotic agent.

4. The method of claim **1** wherein the patient has idiopathic pulmonary fibrosis (IPF).

5. The method of claim **1** wherein the pirfenidone is administered at a total daily dosage of about 1600 mg.

6. The method of claim **3** wherein the pirfenidone is administered at a total daily dosage of about 1600 mg.

7. The method of claim **5** wherein the pirfenidone is administered three times per day.

8. The method of claim **1** wherein the pirfenidone is administered at a total daily dosage of about 2400 mg per day.

9. The method of claim **1** wherein the pirfenidone is administered at a total daily dosage of 2403 mg per day.

10. The method of claim **9** wherein the pirfenidone is administered three times per day.

11. A method of administering pirfenidone to a patient in need thereof, wherein said patient is in need of therapy with CYP1A2 inhibitor that is a moderate to strong inhibitor of both (i) CYP1A2 and (ii) another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and CYP2D6, comprising:

(a) discontinuing said CYP1A2 inhibitor and

(b) administering to the patient a therapeutically effective amount of pirfenidone.

12. The method of claim **11** wherein the patient has discontinued administration of the CYP1A2 inhibitor within 1 month prior to the start of pirfenidone therapy.

13. The method of claim **11** wherein the patient has discontinued administration of the CYP1A2 inhibitor within 2 weeks prior to the start of pirfenidone therapy.

14. The method of claim **11** wherein the discontinuing of the CYP1A2 inhibitor is to avoid an adverse drug interaction with pirfenidone.

15. The method of claim **11** wherein the patient is in need of an anti-fibrotic agent.

16. The method of claim **11** wherein the patient has idiopathic pulmonary fibrosis (IPF).

17. The method of claim **11** wherein the pirfenidone is administered at a total daily dosage of about 1600 mg.

18. The method of claim **11** wherein the pirfenidone is administered at a total daily dosage of about 2400 mg per day.

19. The method of claim **11** wherein the pirfenidone is administered at a total daily dosage of 2403 mg per day.

20. The method of claim **17** wherein the pirfenidone is administered three times per day.

21. The method of claim **19** wherein the pirfenidone is administered three times per day.

22. The method of claim **16** wherein the pirfenidone is administered at a total daily dosage of about 1600 mg.

23. The method of claim **16** wherein the pirfenidone is administered at a total daily dosage of 2403 mg per day.

24. A method of administering pirfenidone comprising administering to a patient with IPF pirfenidone at a total daily dose of 2403 mg per day, administered three times per day, and avoiding or discontinuing concomitant use of a CYP1A2 inhibitor that is a moderate to strong inhibitor of both (i) CYP1A2 and (ii) another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19 and CYP2D6, wherein the patient is also in need of said CYP1A2 inhibitor.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,318,780 B2
APPLICATION NO. : 13/224589
DATED : November 27, 2012
INVENTOR(S) : Williamson Z. Bradford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification:

At Column 1, line 54, "scrtaline" should be -- sertraline --.

At Column 5, line 3, "cachcxia" should be -- cachexia --.

At Column 7, line 33, "moans" should be -- means --.

At Column 11, line 18, "amoun" should be -- amount --.

Signed and Sealed this
Twenty-sixth Day of November, 2013

Margaret A. Focarino

Margaret A. Focarino
Commissioner for Patents of the United States Patent and Trademark Office

EXHIBIT 9

US008383150B2

(12) **United States Patent**
Radhakrishnan et al.

(10) **Patent No.: US 8,383,150 B2**
(45) **Date of Patent: *Feb. 26, 2013**

(54) **GRANULATE FORMULATION OF PIRFENIDONE AND PHARMACEUTICALLY ACCEPTABLE EXCIPIENTS**

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(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/162,048**

(22) Filed: **Jun. 16, 2011**

(65) **Prior Publication Data**

US 2012/0015984 A1 Jan. 19, 2012

Related U.S. Application Data

(63) Continuation of application No. 12/067,712, filed as application No. PCT/US2006/037057 on Sep. 22, 2006, now Pat. No. 7,988,994.

(60) Provisional application No. 60/720,257, filed on Sep. 22, 2005.

(51) **Int. Cl.**

A61K 9/48	(2006.01)
A61K 9/14	(2006.01)
A01N 43/40	(2006.01)

(52) **U.S. Cl.** **424/452**; 514/345; 424/451; 424/489

(58) **Field of Classification Search** 424/452, 424/451, 489; 514/345

See application file for complete search history.

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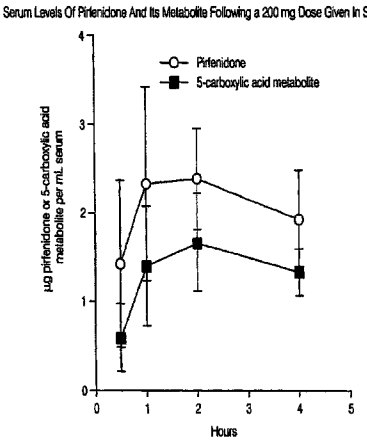
Primary Examiner — Aradhana Sasan

(74) *Attorney, Agent, or Firm* — Marshall, Gerstein & Borun LLP

(57) **ABSTRACT**

A capsule formulation of pirfenidone is provided that includes pharmaceutically acceptable excipients. In one embodiment, this capsule formulation is capable of sustaining desirable pharmacokinetic responses in a patient. Further provided are methods of treating fibrotic conditions and other cytokine-mediated disorders by administering pirfenidone capsules of such formulation to a patient in need.

27 Claims, 10 Drawing Sheets



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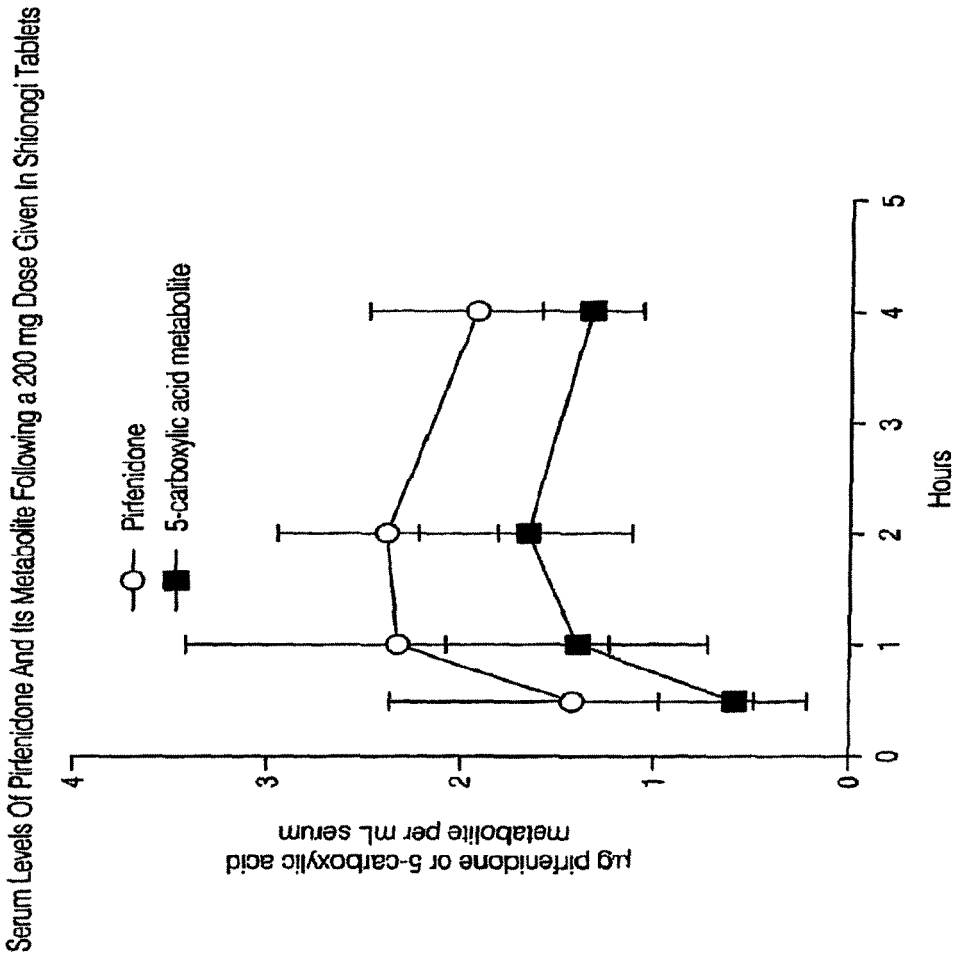
Serum Levels Of Pirfenidone And Its Metabolite Following a 200 mg Dose Given In Shionogi Tablets
Pirfenidone
5-carboxylic acid metabolite
μg pirfenidone or 5-carboxylic acid metabolite per mL serum
Hours
0
1
2
3
4
5

FIG. 1

Composition Table Of Shionogi Tablets

Compound	Function	Strength
		200 mg Tablet
Intragranular additions		
Pirfenidone	API	200.0
Lactose	Filler	56.0
Carmellose Calcium	Disintegrator	5.0
Hydroxymethyl cellulose	Binder	6.0
Extragranular additions		
Carmellose Calcium	Disintegrator	15.0
Magnesium Stearate	Lubricant	3.0
Core Tablet	**Total**	**285.0**
Hydroxylpropyl cellulose	Coating Base	
Triethylene citrate	Plasticizer	7.6
Titanium dioxide	Light Protectant	0.8
Coating Layer Total		3.0
Total		**296.4**

FIG. 2

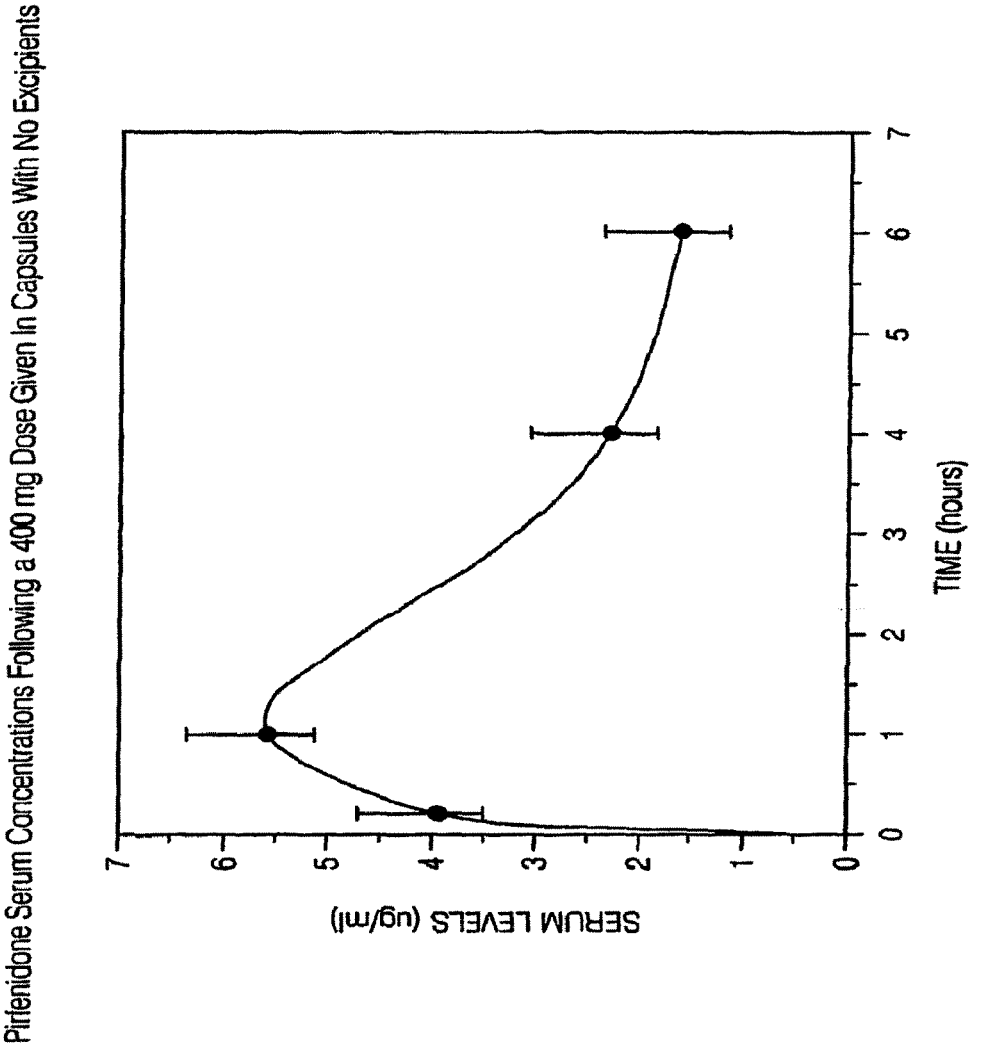
Pirfenidone Serum Concentrations Following a 400 mg Dose Given In Capsules With No Excipients
SERUM LEVELS (ug/ml)
TIME (hours)
0
1
2
3
4
5
6
7

FIG. 3

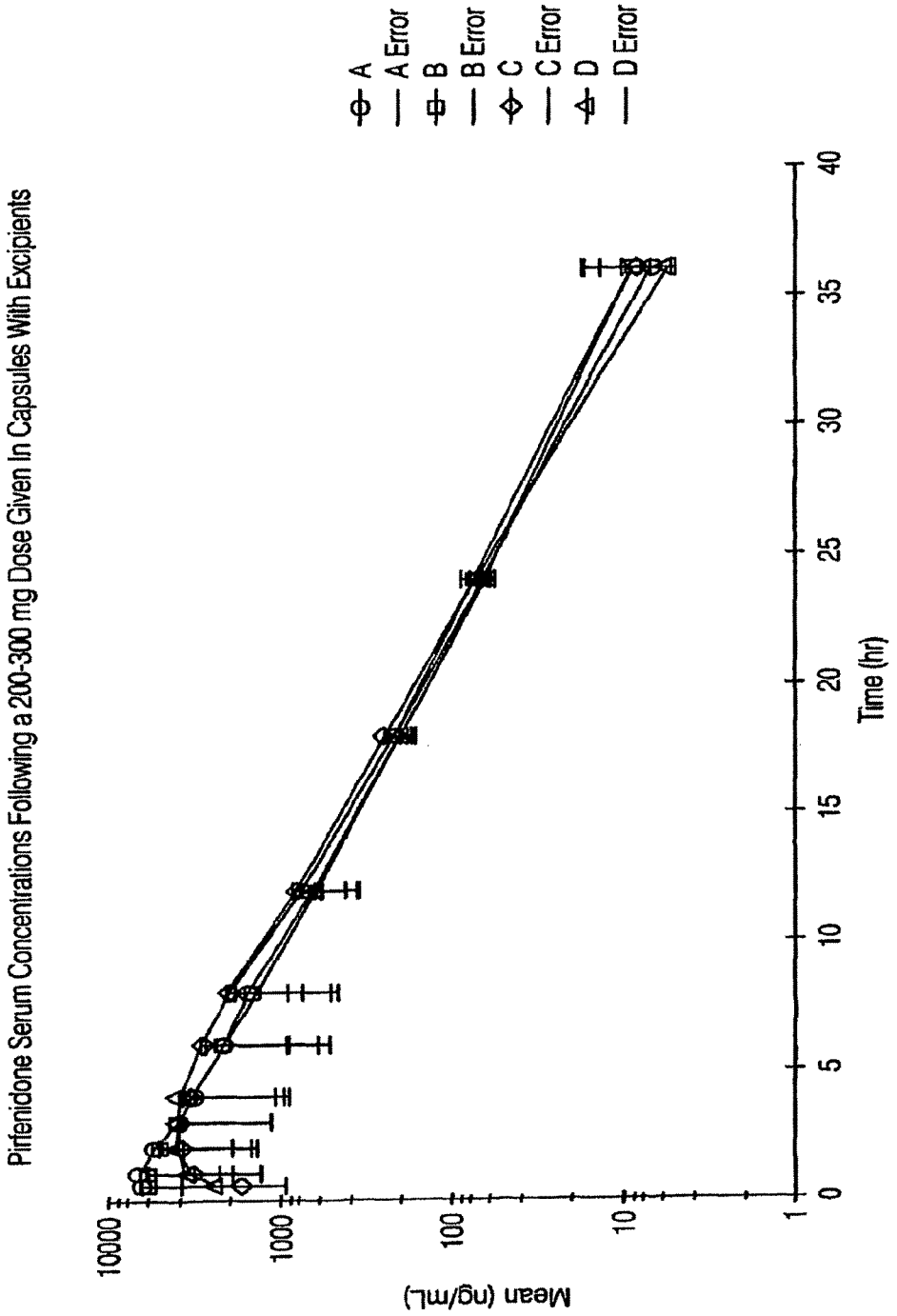
Pirfenidone Serum Concentrations Following a 200-300 mg Dose Given In Capsules With Excipients
A
A Error
B
B Error
C
C Error
D
D Error
Mean (ng/mL)
10000
1000
100
10
1
Time (hr)
0
5
10
15
20
25
30
35
40

FIG. 4

Comparison of PK Parameters Between Capsule of Pirfenidone Only and Capsules with Excipients

PK Parameters	Capsule Group I	Capsule Group II	Capsule of Pirfenidone Only
C_{max} (μg/mL)	8.05 ± 2.53	7.68 ± 1.86	6.28 ± 2.49
T_{max} (hr)	3.23 ± 1.42	2.73 ± 1.17	0.85 ± 0.32
AUC (μg/mL·hr)	62.4 ± 25.4	59.3 ± 22.8	20.8 ± 10.0
$T_{1/2}$ (hr)	3.00 ± 0.98	2.93 ± 0.94	2.20 ± 0.60

FIG. 5

FOMULATION USED IN HUMAN AND IN VITRO

Component	Quality Standard	Function	mg/Capsule
			267 mg capsule
Pirfenidone	In-house	Active ingredient	267
Croscarmellose, sodium	NF, Ph Eur, JP	Disintegrant	26.5
Microcrystalline cellulose	USP, Ph Eur, JP	Binder, Filler	24.0
Povidone	USP, Ph Eur, JP	Binder	6.0
Magnesium stearate	NF, Ph Eur, JP	Lubricant	1.5
Purified water	USP	Processing solvent	--
Gelatin capsule	USP, Ph Eur	--	--
Total weight per capsule			325.0

FIG. 6

REPRESENTATIVE 45 KG BATCH FORMULA-267 MG CAPSULE DOSAGE STRENGTH

Component	% (w/w)	kg
Pirfenidone	82.15	36.97
Croscarmellose Sodium	8.15	3.67
Microcrystalline Cellulose (Avicell PH 102)	7.39	3.32
Povidone (Nominal K Value: 30)	1.85	0.83
Magnesium Stearate	0.46	0.21
Purified Water	--	20.40
Total Weight (kg)	100	45.00

FIG. 7

Storage conditions: 25° C/60%RH

Attributes	Time (months)								
	0	1	2	3	6	9	12	18
Appearance	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay (%)	99.6	101.0	101.2	100.6	101.3	101.7	101.1	100.6
Dissolution % (RSD)	100 (2.1)	101 (2.5)	99 (2.8)	101 (4.5)	99 (4.6)	101 (1.2)	101 (1.6)	101 (1.7)
Impurities (HPLC) %	< 0.05[a]	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Moisture %	0.96	0.86	1.0	1.2	1.4	1.2	1.4	1.7

[a]No peaks detected at a Limit of Detection of 0.025µg/mL

FIG. 8A

Storage conditions: 30° C/65%RH

Attributes	Time (months)							
	0	1	2	3	6	9	12	18
Appearance	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay (%)	99.6	101.3	100.6	100.4	101.3	101.6	101.3	101.1
Dissolution % (RSD)	100 (2.1)	95 (4.2)	99 (1.3)	101 (3.8)	100 (3.8)	100 (2.1)	101 (2.3)	99 (4.1)
Impurities (HPLC) %	< 0.05[a]	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Moisture %	0.96	0.91	1.1	1.3	1.5	1.3	1.6	1.9

[a]No peaks detected at a Limit of Detection of 0.025µg/mL

FIG. 8B

Storage conditions: 40° C/75%RH

Attributes	Time (months)								
	0	1	2	3	6	9	12	18
Appearance	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay (%)	99.6	101.0	100.3	100.7	101.3	101.6	100.4	101.0
Dissolution % (RSD)	100 (2.1)	101 (1.5)	100 (3.7)	98 (4.8)	100 (3.8)	100 (1.8)	98 (3.3)	42 (7.5)
Impurities (HPLC) %	< 0.05[a]	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Moisture %	0.96	0.94	1.2	1.3	1.3	1.4	1.8	2.3

[a]No peaks detected at a Limit of Detection of 0.025 µg/mL

FIG. 8C

Representative Medicinal Product Components and Composition for 267 mg dose Capsule version II

Component	Quality Standard	Function	mg/capsule	% (w/w)
Pirfenidone	In-house[a]	Active ingredient	227.5	70.0
Croscarmellose, sodium	NF, Ph Eur, JP	Disintegrant	44.6	13.7
Microcrystalline cellulose[b]	USP, Ph Eur, JP	Binder, Filler	40.3	12.4
Povidone	USP, Ph Eur, JP	Binder	10.1	3.1
Magnesium stearate	NF, Ph Eur, JP	Lubricant	2.5	0.8
Purified water[c]	USP	Processing solvent	--	--
Gelatin capsule[d]	USP, Ph Eur	--	--	--
Total weight per capsule			325.0	100

FIG. 9A

Representative Medicinal Product Components and Composition for 267 mg dose Capsule version III

Component	Quality Standard	Function	mg/capsule	% (w/w)
Pirfenidone	In-house[a]	Active ingredient	308.8	95.0
Croscarmellose, sodium	NF, Ph Eur, JP	Disintegrant	7.4	2.3
Microcrystalline cellulose[b]	USP, Ph Eur, JP	Binder, Filler	6.7	2.1
Povidone	USP, Ph Eur, JP	Binder	1.7	0.5
Magnesium stearate	NF, Ph Eur, JP	Lubricant	0.4	0.1
Purified water[c]	USP	Processing solvent	--	--
Gelatin capsule[d]	USP, Ph Eur	--	--	--
Total weight per capsule			325.0	100

FIG. 9B

GRANULATE FORMULATION OF PIRFENIDONE AND PHARMACEUTICALLY ACCEPTABLE EXCIPIENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 12/067,712, filed Mar. 21, 2008, now U.S. Pat. No. 7,988,994, which is the U.S. National Phase Under 35 USC 371 of PCT/US2006/037057 filed Sep. 22, 2006, which in turn claims priority to U.S. Ser. No. 60/720,257 filed Sep. 22, 2005, the disclosures of which are hereby incorporated herein by reference.

BACKGROUND OF THE DISCLOSURE

1. Field of the Disclosure

The present disclosure relates in general to pirfenidone, a small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Specifically, the present disclosure relates to a capsule formulation of pirfenidone including pharmaceutically acceptable excipients. Further provided are methods of using such capsule formulation in the treatment of fibrotic conditions and other disorders mediated by cytokines.

2. Description of the Related Art

Pirfenidone is a non-peptide synthetic molecule with a molecular weight of 185.23 daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure is known. The synthesis of pirfenidone has been worked out. Pirfenidone is manufactured and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Pirfenidone has anti-fibrotic properties via: decreased TNF-α expression, decreased PDGF expression, and decreased collagen expression. Several pirfenidone Investigational New Drug Applications (INDs) are currently on file with the U.S. Food and Drug Administration. Phase II human investigations are ongoing or have recently been completed for pulmonary fibrosis, renal glomerulosclerosis, and liver cirrhosis. There have been other Phase II studies that used pirfenidone to treat benign prostate hypertrophy, hypertrophic scarring (keloids), and rheumatoid arthritis.

One important use of pirfenidone is known to be providing therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone demonstrates a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, remove pre-existing fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

It is understood that one mechanism by which pirfenidone exerts its therapeutic effects is modulating cytokine actions. Pirfenidone is a potent inhibitor of fibrogenic cytokines and TNF-α. It is well documented that pirfenidone inhibits excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., Australian and New England Journal Ophthalmology, 26; S74-S76, 1998. Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., International Journal Immunopharmacology, 20:685-695 (1998).

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various

formulations have been tested and adopted in clinical trials and other research and experiments. The effectiveness of a formulation may be determined by a plurality of factors, including the amount of pirfenidone it contains, the kinds and relative amounts of pharmacologically acceptable excipients used, and the target patient profile (e.g., the physiological and genetic conditions, disease prognosis, and demographic characteristics of the patient). Changes in these factors cause changes in pharmacokinetic (PK) responses in the patient. Thus, there is a need in general for effective pharmaceutical formulations that elicit desirable pharmacokinetic responses in patients thereby optimizing therapeutic actions of pirfenidone.

SUMMARY OF THE VARIOUS EMBODIMENTS

It is therefore an object of this disclosure to provide pharmaceutical formulations of pirfenidone capable of advantageous therapeutic actions. It is a related object to provide pharmaceutical formulations of pirfenidone capable of eliciting and sustaining desirable pharmacokinetic responses in the patient in need thereof. It is another object of this disclosure to provide methods for treating fibrotic conditions and other cytokine-mediated disorders using such formulations.

In accordance with this disclosure, there is provided, in one embodiment, a capsule having a pharmaceutical formulation of 5-methyl-1-phenyl-2-(1H)-pyridone (pirfenidone), which includes 5-30% of pharmaceutically acceptable excipients and 70-95% of pirfenidone by weight.

According to another embodiment, the excipients include disintegrators, binders, fillers, and lubricants. Examples of disintegrators include agar-agar, algins, calcium carbonate, carboxymethylcellulose, cellulose, clays, colloidal silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesium aluminium silicate, methylcellulose, polacrilin potassium, sodium alginate, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone hydroxypropylcellulose, sodium starch glycolate, and starch. Examples of binders include microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, and polyvinylpyrrolidone. Examples of fillers include calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol. Examples of lubricants include agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, and zinc stearate.

According to yet another embodiment, by weight 2-10% of the capsule is disintegrator, 2-30% is binder, 2-30% is filler, and 0.3-0.8% is lubricant. In another embodiment, by weight 2-10% of the capsule is disintegrator, 2-25% is binder, 2-25% is filler, and 0.3-0.8% is lubricant. According to still another embodiment, the excipients further include povidone. In a further embodiment, by weight 1-4% of the capsule is povidone. According to another embodiment, the capsule includes 100-400 mg Pirfenidone.

In accordance with this disclosure, there is provided, in another embodiment, a method for treating a fibrotic condition. The method comprises administering the aforementioned capsule to a patient suffering from the fibrotic condition. Examples of such fibrotic conditions include pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, dermal

fibrosis, coronary restenosis, and post-surgical adhesions. Examples of pulmonary fibrosis include idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndromes.

In accordance with this disclosure, there is provided, in yet another embodiment, a method for inhibiting actions of cytokines in a patient suffering from a disorder mediated by such cytokines. The method comprises administering the aforementioned capsule to the patient. Examples of such cytokines include TNF-α, TGF-β1, bFGF, PDGF, and EGF. Examples of such disorder include multiple sclerosis, arthritis, asthma, chronic rhinitis, and edema. In still another embodiment, the method further comprises administering one or more capsules to the patient one or more times a day, with a total daily intake of pirfenidone greater than 1200 mg. In various embodiments, the patient is given one or more capsules twice or three times a day.

In accordance with this disclosure, there is provided, in still another embodiment, a capsule having an effective amount of pirfenidone and pharmaceutically acceptable excipients. The capsule when administered in a patient is capable of sustaining a measurable pharmacokinetic response. The pharmacokinetic response is characterized by an increase in the T_{max} or AUC values than a pirfenidone capsule containing no pharmaceutically acceptable excipients. In various embodiments, treatment methods of administering such capsules are provided for patients suffering from fibrotic conditions such as idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndrome, and other disorders mediated by cytokines such as TNF-α, TGF-β1, bFGF, PDGF, and EGF.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows changes in the mean serum concentrations of pirfenidone and its metabolite 5-carboxylic acid over time in human subjects included in one of the previously reported pharmacokinetic studies: Shionogi Phase II.

FIG. **2** is a table that shows quantitative compositions of the pirfenidone tablets used in Shionogi Phase II.

FIG. **3** shows changes in pirfenidone serum concentrations over time in human subjects after a single dose of 400 mg pirfenidone delivered orally in capsules without excipients.

FIG. **4** shows changes in pirfenidone serum concentrations over time in human objects following a single dose of 200-300 mg pirfenidone delivered orally in capsules with excipients, according to one embodiment of this disclosure.

FIG. **5** is a table that shows the PK values of the capsules with excipients according to one embodiment of this disclosure, compared to the PK values of capsules without excipients of one of the previously reported PK studies.

FIG. **6** is a table that shows the formulation of pirfenidone/excipient-containing capsules used in the study depicted in FIG. **4** and the study depicted in FIG. **8***a-c*.

FIG. **7** is a table that lists the components used to prepare a representative batch of the pirfenidone/excipient formulation of FIG. **6**.

FIGS. **8***a-c* lists tables that show the stability of the pirfenidone/excipient formulation of FIG. **6** at 25° C. and 60% relative humidity (FIG. **8***a*), 35° C. and 65% relative humidity (FIG. **8***b*), and 40° C. and 75% relative humidity (FIG. **8***c*).

FIGS. **9***a* and **9***b* depict additional representative formulation of pirfenidone/excipient-containing capsules contemplated herein.

DETAILED DESCRIPTION OF THE VARIOUS EMBODIMENTS

Discussion of the Relevant Terms

Throughout the present disclosure relevant terms are to be understood consistently with their typical meanings established in the relevant art, i.e. the art of pharmaceutical chemistry, medicine, biology, genetics, molecular biology, biochemistry, physiology, genomics, pharmacogenomics, bioinformatics, computational biology, and cheminfomatics. However, further clarifications and descriptions are provided for certain terms as set forth below:

The terms pharmaceuticals, pharmaceutical products, drug products, drug chemicals, drug compounds, compounds, and chemicals, are used interchangeably throughout this disclosure.

API, as used herein, refers to active pharmaceutical ingredients. In various embodiments of this disclosure, the API of the capsule and tablet formulations is pirfenidone.

The terms pharmaceutically acceptable excipients, pharmaceutically compatible excipients, and excipients are used interchangeably in this disclosure. They refer to non-API substances such as disintegrators, binders, fillers, and lubricants used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

Disintegrators, as used herein, refer to one or more of agar-agar, algins, calcium carbonate, carboxymethylcellulose, cellulose, clays, colloidal silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesium aluminium silicate, methylcellulose, polacrilin potassium, sodium alginate, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone hydroxypropylcellulose, sodium starch glycolate, and starch.

Binders, as used herein, refer to one or more of microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, and polyvinylpyrrolidone.

Fillers, as used herein, refer to one or more of calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol.

Lubricants, as used herein, refer to one or more of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, and zinc stearate.

Capsule, as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products. In one embodiment, capsule is made of gelatin. Other suitable matrix substances such as total synthetic polymer chemicals having gelatin-like properties may be used to manufacture pirfenidone capsules according to alternative embodiments of this disclosure.

AUC, as used herein, refers to the area under the curve that represents changes in blood concentrations of pirfenidone over time.

C_{max}, as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of pirfenidone over time.

T_{max}, as used herein, refers to the time that it takes for pirfenidone blood concentration to reach the maximum value.

$T_{1/2}$, as used in this disclosure, refers to the time that it takes for pirfenidone blood concentration to decline to one-half of the maximum level.

Collectively AUC, C_{max}, T_{max}, and $T_{1/2}$ are the principle pharmacokinetic parameters that characterize the pharmacokinetic responses of a particular drug product such as pirfenidone in an animal or human subject.

Reported Pharmacokinetic Studies on Pirfenidone

Several pharmacokinetic studies on human subjects have been reported, including one in healthy adult males (Schmidt R M, Ritter A and Margolin S, 1974 Bioavailability of Pirfenidone Capsules Following Oral Administration (Human Volunteers) (60-244-73), Oct. 11, 1974. Affiliated Medical Research, Inc., Princeton, N.J., hereafter "Schmidt 1974"), and two in patients with pulmonary fibrosis (Nagai S, Hamada K, Shigematsu M, Taniyama M, Yamauchi S and Izumi T, 2002, Open Label Compassionate Use One Year-Treatment with Pirfenidone to Patients with Chronic Pulmonary Fibrosis, Intern Med 41: 1118-1123, hereafter "Nagai 2002"; and Azuma A, Nukiwa T, Tsuboi E et al, 2005, Double-Blind, Placebo Controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis, Am J Respir Crit. Care Med., hereafter "Shionogi Phase II").

One additional pharmacokinetic study was conducted on a single dose of four 100 mg capsules each containing 100% pirfenidone. Pirfenidone was administered orally to 10 healthy adult males at doses of 100, 200, and 400 mg. On day 1, a single dose of 100 mg was given to each subject. On day 3, a single dose of 200 mg was given to each subject. And on day 4, a last single dose of 400 mg was given to each subject. This last single dose of 400 mg was analyzed for pharmacokinetics. Blood plasma samples were collected before dosing and at 0.25, 1, 4, and 6 hr after dosing. Pirfenidone concentrations in plasma were determined by gas chromatography. The resulting values of pharmacokinetic parameters are: C_{max}=6.3+2.5 μg/mL, T_{max}=0.9±0.3 hrs, AUC_{6hr}=20.8±10.0 μg/mL-hr, and $T_{1/2}$=2.2±0.6 hrs.

Nagai 2002 involved 10 male patients with pulmonary fibrosis. The subjects underwent dose escalation starting with an initial dose of 400 mg for several days to a maintenance dose of 40 mg/kg/day. Pharmacokinetics analyses were done on each of the 10 subjects on day 1 when a dose of 400 mg was given. Plasma samples were collected at 0, 0.25, 1, 1.5, 2, 4, 6, 8, and 24 hr after dosing. The values of pharmacokinetic parameters were computed. C_{max} was 3.0 to 7.2 μg/mL, and AUC_{24hr} was 16.9 to 66.4 μg/mL·hr.

Shionogi Phase II involved serial sampling in a 15-patient subset of a pirfenidone cohort (13 males and 2 females). On day 1 a 200 mg single dose was given to each of the 15 patients, and serum samples were collected before dosing and at 0.5, 1, 2, and 3 hr after dosing. Blood concentrations of pirfenidone were determined by HPLC assay. FIG. **1** demonstrates changes in the observed mean serum concentrations of pirfenidone and its metabolite 5-carboxylic acid over time. The values of pharmacokinetic parameters were computed to be: C_{max}=2.7±0.7 μg/mL, T_{max}=1.8±1.1 hrs, AUC_{4hr}= 7.3±1.6 μg/mL·hr, and $T_{1/2}$=3.5±2.2 hrs.

The drug formulations in these previously reported studies were different. Schmidt 1974 used a capsule including 100% pirfenidone. Nagai 2002 and Shionogi Phase II used pirfenidone tablets that included certain pharmaceutically acceptable excipients. For example, the drug product used in Shionogi Phase II was formulated as compressed, coated tablets of 200 mg of pirfenidone. Shionogi Phase II tablets included pharmaceutically acceptable excipients. FIG. **2** is a table listing the ingredients of the Shionogi Phase II tablets and the quantities of each ingredient. As shown, the core tablet was 285 mg, of which 200 mg was API. Various amounts of disintegrator, filler, binder, and lubricant were included. With the addition of the coating, the total weight of the Shionogi Phase II tablet was 296.4 mg.

Schmidt 1974 examined the pharmacokinetics of single dose pirfenidone. Ten human volunteers were included in this study. At 15 minutes after oral ingestion of 400 mg pirfenidone, the average serum concentration of pirfenidone reached 3.97 mg/mL. At one hour, the average serum concentration was measured to be 5.57 mg/mL, and at six hour 1.63 mg/mL. FIG. **3** is a plot of serum pirfenidone levels over time summarizing this study. As shown, the maximum serum pirfenidone level was reached between one and three hours. The value of $T_{1/2}$ was calculated to be 2.87+0.22 hrs.

Capsule Formulation of Pirfenidone with Excipients

To those skilled in the pharmaceutical research and manufacturing, it is generally known that tablet formulations permit generous additions of non-API ingredients including excipients and coating substances, especially high percentage of fillers. However, the addition of non-API ingredients may limit the amount of API carried in each tablet. By contrast, capsule formulations tend to facilitate the inclusion of high percentage of API with no or less non-API components. Capsules may allow for inclusion of a larger amount of binders, instead of fillers as used more in tablets. Where high percentage of API is desired and specific excipients are not known to be essential, capsule formulations are often adopted.

To be sure, no capsule formulation of pirfenidone manufactured or reported to date contains excipients. The present disclosure provides a new pirfenidone capsule formulation with certain pharmaceutically acceptable excipients. According to one embodiment, this new capsule formulation is capable of eliciting advantageous pharmacokinetic responses in human subjects. In another embodiment, this new capsule formulation facilitates dissolution and improves flowability in the capsule manufacturing process.

This capsule formulation includes 100-400 mg pirfenidone. One or more pharmaceutically acceptable excipients are added in various embodiments. For example, in one embodiment, by weight 2-10% of the capsule is disintegrator, 2-30% is binder, 2-30% is filler, and 0.3-0.8% is lubricant. As described in the beginning of this Detailed Description, a multitude of substances may be suitably included as disintegrator, binder, filler, and lubricant. One example is to use magnesium stearate as lubricant, microcrystalline cellulose as binder, and croscarmellose as disintegrator. In a particular embodiment, the capsule formulation further includes povidone. By weight povidone may constitute 1-4% of the capsule.

The capsule shell may be made of hard gelatin in one embodiment. The shell may be clear or opaque, white or with color in various embodiments. The capsule is size 1 in a preferred embodiment. Other sizes may be adopted in alternative embodiments.

The manufacture of pirfenidone capsules based on the capsule formulation of the various embodiments includes a series of steps. These steps are: preparing pirfenidone granulation, fluid bed drying, milling, lubrication blend, encapsulation, and bulk packaging

The preparation of pirfenidone granulation may be done in the following sequence. First, povidone is mixed with water and dissolved using an overhead mixer. Second, pirfenidone is milled with croscarmellose and microcrystalline cellulose to break up any lumps. Third, the milled pirfenidone, croscarmellose, and microcrystalline cellulose are added into a high shear granulator and blended. Fourth, the povidone and water solution is added to the blend. Fifth, the pirfenidone granulation is blended for an additional period of time after the povidone and water solution have been completely added.

The fluid bed drying process may be performed on a Fluid Bed Dryer with an inlet temperature of 60° C. The milling process may be performed using a suitable miller such as Quadro Comil®. The lubrication blend process may be conducted with the addition of an appropriate amount of croscar-

mellose and magnesium stearate. The pirfenidone granulation may be further blended at this point. Next the pirfenidone granulation is encapsulated using a suitable encapsulator into two-piece, size 1, gelatin capsules to yield a desired pirfenidone dose of 100-400 mg. The dose of 200-300 mg is yielded in a preferred embodiment. To conclude the capsule manufacturing process, finished capsules may be packaged in secured, double polybags and stored at controlled room temperature. Those skilled in drug research and drug making will appreciate that certain of the aforementioned steps may be modified or omitted, and additional steps may be included, without materially altering the outcome of the manufacturing.

An exemplary composition of the pirfenidone/excipient formulation-containing capsules that was prepared and tested is provided in FIG. **6**. A representative batch of the pirfenidone/excipient formulation was prepared using routine wet formulation methods to combine the components listed in FIG. **7**.

Pharmacokinetic studies were performed on the pirfenidone capsules of the present disclosure. A first study depicted in FIG. **4** shows average changes in serum concentrations over time in four groups of subjects to whom were administered a single dose of the 267 mg pirfenidone capsule formulation of FIG. **6**. The four lines of this graph, A, B, C, and D, represent four different groups of subjects: A, fasted subjects; B, fasted subjected with antacid administered; C, fed subjects; and D, fed subjects with antacid administered.

In another pharmacokinetic study, two groups of human subjects on normal diet were included, each having 13 subjects. One group (Group I) received no antacid, while the other group (Group II) received antacid. The 267 mg pirfenidone capsule formulation of FIG. **6** was given to each subject. FIG. **5** is a table summarizing the resulting PK values for both groups (Capsule Groups I and II), compared to the PK values reported in the one additional pharmacokinetic study of a capsule of pirfenidone only. As demonstrated in FIG. **5**, T_{max} is significantly longer (an approximately two-fold increase in each of Groups I and II) for these excipient-containing capsules than what was reported in the one additional pharmacokinetic study of a capsule of pirfenidone only. AUC is also significantly higher for these excipient-containing capsules than what was reported in the one additional pharmacokinetic study of a capsule of pirfenidone only. AUC values are computed over a time period of zero to infinity. The values of C_{max} and $T_{1/2}$ are also higher than or comparable with those reported in the one additional pharmacokinetic study of a capsule of pirfenidone only.

These resulting PK values, especially the increased T_{max} and AUC, indicate a prolonged absorption phase for the pirfenidone capsules with excipients according to the present disclosure. Consequently, these capsules are capable of sustaining prolonged therapeutic actions in a patient. Therefore, compared to the capsules without excipients, as what were used in Schmidt 1974, the capsule formulation with the excipients may be advantageously administered to a patient in need, thereby eliciting desirable pharmacokinetic responses in the patient. Whilst such desirable PK responses are surprising results, it is conceivable that binders such as microcrystalline cellulose or povidone favorably interact with the amide carbonyl group of pirfenidone forming a transient complex which may then dissociate, resulting in a slow build-up in the plasma concentration of pirfenidone, or a slow decline or clearance in the plasma concentration.

In addition to the therapeutic advantages of the pirfenidone/excipient formulations provided herein, these capsules and the formulations also show good stability under various storage conditions over time. In some embodiments, under various storage conditions the capsules and pirfenidone/excipient formulations provided herein can be stable for at least, or at least about, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 36 months, or 48 months. For example, under storage conditions of 25° C. and 60% relative humidity, the capsules and pirfenidone/excipient formulations provided herein can be stable for at least, or at least about, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 36 months, or 48 months. In another example, under storage conditions of 30° C. and 65% relative humidity, the capsules and pirfenidone/excipient formulations provided herein can be stable for at least, or at least about, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 24 months, 36 months, or 48 months. In another example, under storage conditions of 40° C. and 75% relative humidity, the capsules and pirfenidone/excipient formulations provided herein can be stable for at least, or at least about, 3 months, 6 months, 9 months, or 12 months.

In some embodiments, the stability of the capsules and pirfenidone/excipient formulations provided herein is determined by measuring the dissolution rate of the stored capsule and/or pirfenidone/excipient formulations. Any of a variety of dissolution methods provided herein or otherwise known in the art can be performed to determine the stability of capsules and pirfenidone/excipient formulations. Dissolution measurements are in vitro methods known in the art to be representative of in vivo T_{max} and AUC values. Accordingly, the stability of the capsules and pirfenidone/excipient formulations as measured by dissolution methods will be representative of the in vivo T_{max} and AUC values of a subject when the capsules and pirfenidone/excipient formulations after storage, for example, under the above-exemplified conditions for the indicated amount of time. Typically, a dissolution level indicative of an acceptable level of stability is a dissolution of at least, or at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, of the pirfenidone in the capsules provided herein. Any of a variety of dissolution methods provided herein or otherwise known in the art can be performed to determine the stability of capsules and pirfenidone/excipient formulations. For example, dissolution can be determined according to the pharmacopoeial dissolution method specified in USP29.

The stability of the capsules and pirfenidone/excipient formulations provided herein is demonstrated in the results presented in FIG. **8**. The 267 mg pirfenidone capsule formulation of FIG. **6** was stored for 18 months under three different storage conditions: 25° C. and 60% relative humidity, 30° C. and 65% relative humidity, and 40° C. and 75% relative humidity. FIG. **8** shows that the dissolution of the capsule and pirfenidone/excipient formuations at 25° C. and 60% relative humidity, 30° C. and 65% relative humidity did not appreciably change over the duration of the 18 month period. The dissolution of the capsule and pirfenidone/excipient formuations at 40° C. and 75% relative humidity did not appreciably change over the initial 12 month period. The dissolution analysis was performed according to the pharmacopoeial dissolution method specified in USP29 using Apparatus **2** (paddles) with water as a solvent and a specification of $Q \geqq 70\%$ of label claim in 30 minutes. Also shown in FIG. **8**, the level of impurities in each formulation, as determined by HPLC, was less than 0.05% over the duration of the 18 month period. In addition, the moisture content, as determined by the Karl Fischer method, of all but one time point (40° C., 75% RH at 18 months) remained below 2%, and the moisture content of all samples remained below 2.5% over the duration of the 18 month period. Finally, the percent of pirfenidone in

each sample, as determined by HPLC, showed no appreciable degradation over the 18 month period.

In addition to the specific formulation provided herein in FIG. **6**, further formulations contemplated herein are provided in FIGS. **9***a* and **9***b*.

Therapeutic Indications

One embodiment of this disclosure provides methods for treating fibrotic conditions and other cytokine-mediated disorders. These methods comprise administering the excipients-containing pirfenidone capsules of this disclosure to a patient suffering from a fibrotic condition or a cytokine-mediated disorder. The dosing may be twice or three times daily, with one or more capsules per intake. According to a particularly embodiment, the total daily intake is at least 1200 mg pirfenidone. The total daily intake amount may vary, depending on the patient profile, including among other things the patient's demographic characteristics, physiological and genetic conditions, and disease prognosis. For example, a child or a senior person may be given a lower amount daily than that given to an ordinary adult.

The anti-fibrotic activity of pirfenidone is demonstrated in in vivo animal fibrosis models, as well as in vitro cell culture studies with human or animal lung fibroblasts, dermal fibroblasts, and fibroblast-like cells. Those data indicates that pirfenidone may be an effective agent for preventing and treating post-surgical adhesions, myocardial fibrosis, renal fibrosis, liver cirrhosis, atherosclerosis, and other fibrotic disorders. In vitro cell cultures with human mesenchymal-like cells (including lung fibroblasts, skin fibroblasts, prostate stromal cells, and renal mesangial cells, etc) have shown pharmacologic inhibition by pirfenidone of excessive cell proliferation induced by cytokine growth factors (TGF-β1, bFGF, PDGF, and EGF). In cell culture media, graded concentrations of pirfenidone were effective at levels which were ten to twenty times lower than those exerting any pharmacologically toxic effects on the cells.

At the site of injury, otherwise normal resident cells (e.g., fibroblasts, pericytes, mesangial cells, astrocytes, microglia, and oligodendrocytes) manufacture and discharge high concentrations of growth factors into adjacent tissue spaces. These resident sources of pathologically high levels of growth factors are directly responsible for the persistently excessive levels of growth factors. They cause excessive and harmful formation of collagen or amyloid matrix as well as damage to adjacent cells, the associated organ dysfunction, and frequently, organ malformation.

TGF-β1 is a potent growth-related peptide whose effects may be observed at femtomolar concentrations. It appears to be ubiquitous, and is a bifunctional regulator of cell proliferation in vitro. It acts either as a mitogen or a growth inhibitor depending on tissue concentration and the state of cell confluence (L. J. Striker et al., Lab. Invest. 64:446-456, 1991). In skin incisions, after attracting macrophages and fibroblasts, TGF-β1 enhances extracellular matrix formation by increasing transcription of genes for collagen and fibronectin, decreasing secretion of proteases, increasing secretion of protease inhibitors, and increasing transcription of cellular receptors for matrix proteins.

The anti-fibrotic activities of pirfenidone have been demonstrated in vivo in laboratory animals with fibrotic lesions, in vitro with human lung fibroblast (WI38) cell cultures, and observed through pilot open trials in patients with severe pulmonary fibrosis, benign prostate hypertrophy, or keloids. Pirfenidone may selectively arrest scar enlargement, and remodels or removes scar tissue or fibrosis. The dysfunction caused by fibrotic lesions may be ameliorated by the reduction or removal of the fibrotic lesion following pirfenidone treatment. Apparently organ and tissue function can be restored, even after the presence of fibrosis for several years. When given immediately after an insult, such as trauma, infection, or allergy, to a tissue, pirfenidone also may prevent formation of excessive scar tissue, or fibrotic lesions, and thus help retain normal function and appearance of the tissue.

Pirfenidone may cause removal of excessive collagenous fibrotic tissue by a phagocytic action of local fibroblasts. This has been observed by examination of histological sections of lung tissue under the light microscope from dogs, mice, rats, and hamsters with pulmonary fibrosis treated with pirfenidone, and also through the electron micrographs of histological sections of lung tissue taken from hamsters with experimentally-induced asbestosis that were treated with pirfenidone. No infiltration of inflammation-inducing neutrophils, PMN cells, monocytes, lymphocytes occurred.

The enhanced proliferation of WI38 fibroblasts upon in vitro exposure to PDGF or bFGF may be blocked by pirfenidone added to cell growth media. Pirfenidone may also inhibit the TGF-β1 induced rise in collagen output in lung and dermal fibroblast cultures.

The human clinical findings after treatment with pirfenidone have been consistent with the anti-fibrotic effects observed in the laboratory animals. Pilot open clinical trials with oral pirfenidone have been undertaken with patients afflicted with pulmonary asbestosis, bleomycin-induced pulmonary fibrosis, idiopathic pulmonary fibrosis, scleroderma with pulmonary fibrosis, and Hermansky-Pudlak Syndrome characterized by pulmonary fibrosis.

The clinical criteria for beneficial response during the first months on pirfenidone included reduction in incidence of coughs, reduction in supplemental oxygen requirements, increased exercise tolerance, reduced dyspnea during exercise, amelioration of cor pulmonale, resumption of normal daily tasks, body weight gain, and survival. During the early months, pulmonary function as gauged by chest x-ray, spirometry, or CO diffusion (DLCO) showed little, if any, change. However, after 4 to 6 months on pirfenidone, inhibition or blocking of further deterioration in lung function was evidenced by pulmonary function tests, vital capacity (VC), in the diffusing capacity of the lung for carbon monoxide (DLCO). These overall observations compare favorably with those described by Van Barneveld et al. (Amer. Rev. Respr. Dis., vol. 135, 48-51, 1987), during the spontaneous recovery by patients from bleomycin-induced pulmonary pneumonitis (early stage fibrosis).

Martinet et al. (NE Jour. Med., vol 317, 202-209, 1987) have described an exaggerated release of PDGF by alveolar macrophages in patients with idiopathic pulmonary fibrosis. The in vitro demonstration of inhibition by pirfenidone of the mitogenesis and enhanced formation of collagen caused by growth factors (bFGF, PDGF, and TGF-β1) may partly explain the beneficial in vivo anti-fibrotic action of pirfenidone.

In an open pilot trial of pirfenidone in older men with clinically advanced benign prostate hypertrophy (BPH, noncancerous fibrous enlargement of the male prostate gland), the patients experienced functional improvement based on objective criteria. After taking oral pirfenidone the frequent urinary bladder urgency was ameliorated, and nocturia rarely recurred. In another pilot open trial, topical applications of pirfenidone ointment to surgical sites immediately after keloid resection has prevented recurrence of the keloids as observed in two-year follow-ups in the patients. Each of those patients had a prior history of repeated early keloid re-growths after such surgery. Pirfenidone may induce a remodeling of skin fibrotic lesions to reduce or remove kel-

oids, reduce or remove dermal scars, and remove or lessen the contractures of hypertrophic (post burn injury) scars. In a similar condition, pirfenidone also acts to inhibit post-operative surgical adhesions.

Thus, clinical investigations under both controlled protocol designs and open label trials have demonstrated that pirfenidone exerts anti-fibrotic and cytoprotective actions. The observed side effects after oral administration were relatively mild (drowsiness, gastric nausea or photosensitivity rash). No serious adverse reactions have been reported.

In summary, based on the TNF-α inhibitor (cytoprotective) activity of pirfenidone, the capsule formulation of the present disclosure may be administered according to certain embodiments of this disclosure to treat patients suffering from the following disorders:

1) Central Nervous System syndromes: relapsing-remitting multiple sclerosis, primary and secondary multiple sclerosis, spinal multiple sclerosis, cerebral malaria, viral or bacterial infections of the CNS, bacterial meningitis, "autoimmune" disorders of the central nervous system (CNS), CNS stroke and infarction, brain edema, Parkinson's syndrome, Alzheimer's disease, amylotrophic lateral sclerosis (ALS), and brain concussion or contusion;

2) Musculo-skeletal syndromes: rheumatoid arthritis, trauma-induced arthritis, arthritis caused by a microbial infection, or by a parasite, tendonitis, and, arthritis induced by medical products or drugs (including small synthetic molecules as well as purified natural or synthesized peptides or proteins);

3) Pulmonary syndromes: acute adult respiratory distress syndrome, asthma, allergic rhinitis, allergic conjunctivitis, chronic obstructive pulmonary disease (COPD), and lung sarcoidosis;

4) Systemic immunologic, inflammatory or toxic syndromes: endotoxemia shock syndrome, septic shock, graft-host disease, allograft vasculopathy, hemorrhagic shock, reperfusion injury of the brain or myocardium, thermal burns, radiation injury, general or dermal traumatic or contusion injuries, eosinophilic granuloma, diabetic mellitus (type II), or systemic lupus erythromatosus;

5) Gastro-intestinal syndromes: Crohn's disease, ulcerative colitis, and liver inflammatory disorders; and

6) Congestive heart failure.

Further, based on the anti-fibrotic activity of pirfenidone, the capsule formulation of the present disclosure may be administered according to other embodiments to treat patients suffering from the following disorders: pulmonary fibrosis, radiation and drug-induced lung fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, post-surgical adhesions, benign prostate hypertrophy in humans, arteriosclerosis, dermal fibrosis, and coronary restenosis.

It is to be understood that the description, specific examples and data, while indicating exemplary embodiments, are given by way of illustration and are not intended to limit the various embodiments of the present disclosure. All references cited herein for any reason, are specifically and entirely incorporated by reference. Various changes and modifications within the present disclosure will become apparent to the skilled artisan from the description and data contained herein, and thus are considered part of the various embodiments of this disclosure.

What is claimed is:

1. A granulate formulation of 5-methyl-1-phenyl-2-(1H)-pyridone, wherein said granulate formulation comprises 5-methyl-1-phenyl-2-(1H)-pyridone and pharmaceutically acceptable excipients, said excipients comprising an effective amount of binder to increase the AUC of the 5-methyl-1-phenyl-2-(1H)-pyridone at least 45% upon oral administration, as compared to pirfenidone without excipients orally administered in a capsule shell.

2. The granulate formulation of claim **1**, wherein said excipients further comprise one or more selected from the group consisting of a disintegrator, a filler, a lubricant, and combinations thereof.

3. The granulate formulation of claim **2**, wherein said disintegrator comprises one or more selected from the group consisting of agar-agar, algins, calcium carbonate, carboxymethylcellulose, cellulose, clays, colloidal silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesium aluminium silicate, methylcellulose, polacrilin potassium, sodium alginate, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone hydroxypropylcellulose, sodium starch glycolate, and starch.

4. The granulate formulation of claim **1**, wherein said binder comprises one or more selected from the group consisting of microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, and polyvinylpyrrolidone.

5. The granulate formulation of claim **2**, wherein said filler comprises one or more selected from the group consisting of calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrates, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol.

6. The granulate formulation of claim **2**, wherein said lubricant comprises one or more selected from the group consisting of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, and zinc stearate.

7. The granulate formulation of claim **2**, wherein said disintegrator is 2-10%, said binder is 2-30%, said filler is 2-30%, and said lubricant is 0.3-0.8% by weight of the granulate formulation.

8. The granulate formulation of claim **2**, wherein said binder comprises povidone.

9. The granulate formulation of claim **8**, wherein said povidone is 1-4% by weight of the granulate formulation.

10. The granulate formulation of claim **9**, comprising 100-400 mg 5-methyl-1-phenyl-2-(1H)-pyridone.

11. A method for treating a fibrotic condition or inhibiting actions of cytokines, comprising administering the granulate formulation of claim **1** to a patient suffering from said fibrotic condition or suffering from a disorder mediated by said cytokines.

12. The method of claim **11**, wherein said fibrotic condition is one selected form the group consisting of pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, keloid, dermal fibrosis, coronary restenosis, and post-surgical adhesions.

13. The method of claim **12**, wherein said pulmonary fibrosis is one selected from the group consisting of idiopathic pulmonary fibrosis and Hermansky-Pudlak Syndrome.

14. The method of claim **11**, wherein said cytokines comprise one or more selected from the group consisting of TNF-α, TGF-β1, bFGF, PDGF, and EGF.

15. The method of claim **14**, wherein said disorder is one selected from the group consisting of multiple sclerosis, arthritis, asthma, chronic rhinitis, and edema.

16. The method of claim **11**, comprising administering said granulate formulation to said patient one or more times a day, wherein the total intake of 5-methyl-1-phenyl-2-(1H)-pyridone is at least 1200 mg a day.

17. The method of claim **16**, wherein said granulate formulation is administered to the patient twice a day or three times a day.

18. The method of claim **11**, wherein said fibrotic condition is a pulmonary fibrotic condition.

19. The granulate formulation of claim **1**, wherein the granulate formulation comprises a wet-granulated mixture comprising the 5-methyl-1-phenyl-2-(1H)-pyridone and the effective amount of binder and further comprises a filler and a disintegrator.

20. The granulate formulation of claim **8**, wherein said povidone comprises at least about 1% by weight of the formulation.

21. The granulate formulation of claim **8**, wherein said povidone comprises at least about 1.85% by weight of the formulation.

22. The granulate formulation of claim **9**, wherein the binder further comprises microcrystalline cellulose.

23. The granulate formulation of claim **1**, wherein the total amount of binder is 2-30% by weight of the formulation.

24. The granulate formulation of claim **1**, wherein said effective amount of binder increases the AUC of 5-methyl-1-phenyl-2-(1H)-pyridone at least 50% upon oral administration, as compared to pirfenidone without excipients orally administered in a capsule shell.

25. The granulate formulation of claim **1**, wherein said effective amount of binder increases the AUC of 5-methyl-1-phenyl-2-(1H)-pyridone at least 55% upon oral administration, as compared to pirfenidone without excipients orally administered in a capsule shell.

26. The granulate formulation of claim **1**, wherein said effective amount of binder increases the AUC of 5-methyl-1-phenyl-2-(1H)-pyridone at least 60% upon oral administration, as compared pirfenidone without excipients orally administered in a capsule shell.

27. The method of claim **11**, wherein the fibrotic condition is idiopathic pulmonary fibrosis.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,383,150 B2
APPLICATION NO. : 13/162048
DATED : February 26, 2013
INVENTOR(S) : Radhakrishnan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Column 12, Line 52, in Claim 12, delete "form the" and insert -- from the --, therefor.

In Column 14, Line 14, in Claim 26, after "compared" insert -- to --.

Signed and Sealed this
Seventeenth Day of March, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

EXHIBIT 10

US008420674B2

(12) **United States Patent**
Bradford

(10) **Patent No.: US 8,420,674 B2**
(45) **Date of Patent: *Apr. 16, 2013**

(54) **METHOD OF PROVIDING PIRFENIDONE THERAPY TO A PATIENT**

(75) Inventor: **Williamson Z. Bradford**, Ross, CA (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 320 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/831,944**

(22) Filed: **Jul. 7, 2010**

(65) **Prior Publication Data**

US 2010/0324097 A1 Dec. 23, 2010

Related U.S. Application Data

(63) Continuation of application No. 11/959,338, filed on Dec. 18, 2007, now Pat. No. 7,767, 700.

(60) Provisional application No. 60/870,593, filed on Dec. 18, 2006.

(51) **Int. Cl.**
A61K 31/445 (2006.01)
A61K 31/44 (2006.01)

(52) **U.S. Cl.**
USPC **514/327**; 514/345; 514/350

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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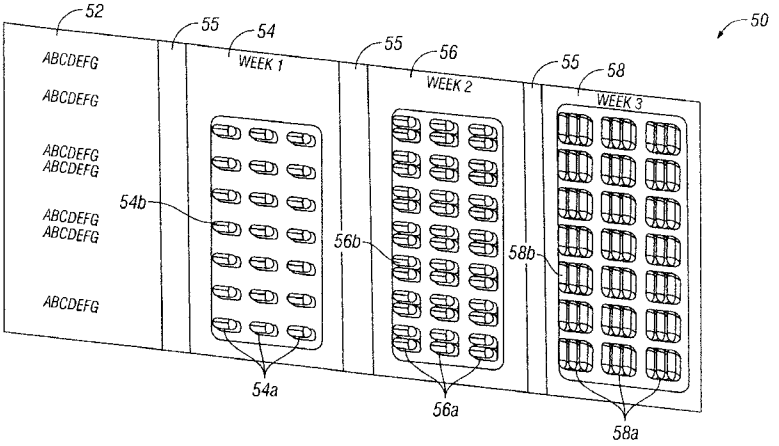
Primary Examiner — Bong-Sook Baek
(74) *Attorney, Agent, or Firm* — Marshall, Gerstein & Borun LLP; John A. Bendrick

(57) **ABSTRACT**

The invention relates to methods for decreasing adverse events associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy. The invention discloses an optimized dose escalation scheme that results in the patient having increased tolerance to adverse events associated with the administration of pirfenidone. The invention also discloses a starter pack that may be used in conjunction with the dose escalation scheme.

12 Claims, 7 Drawing Sheets



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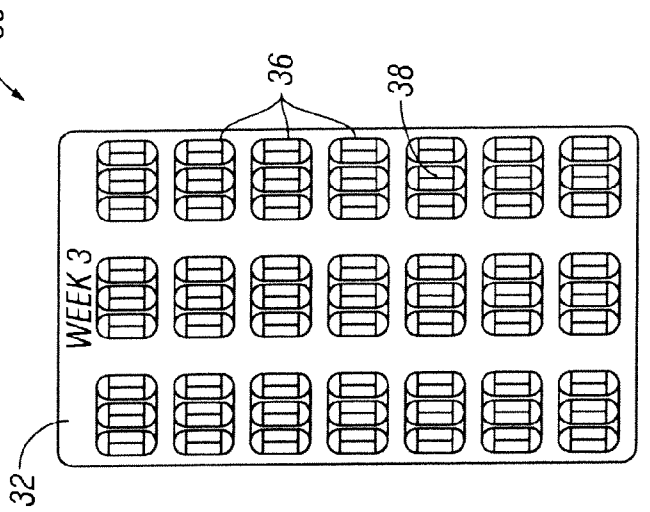


FIG. 3

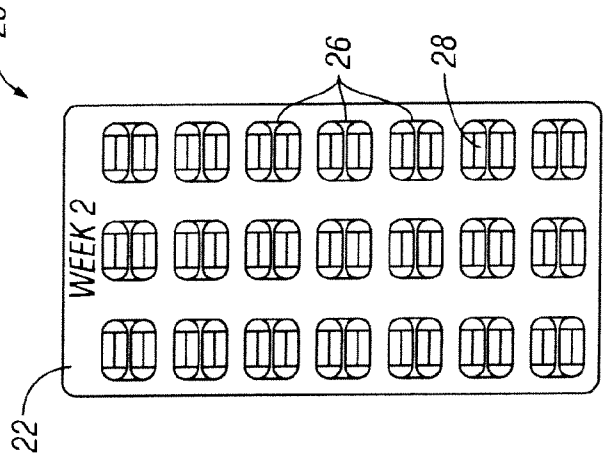


FIG. 2

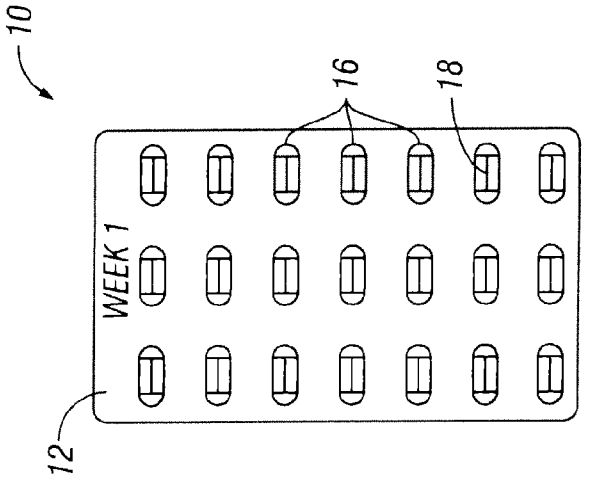
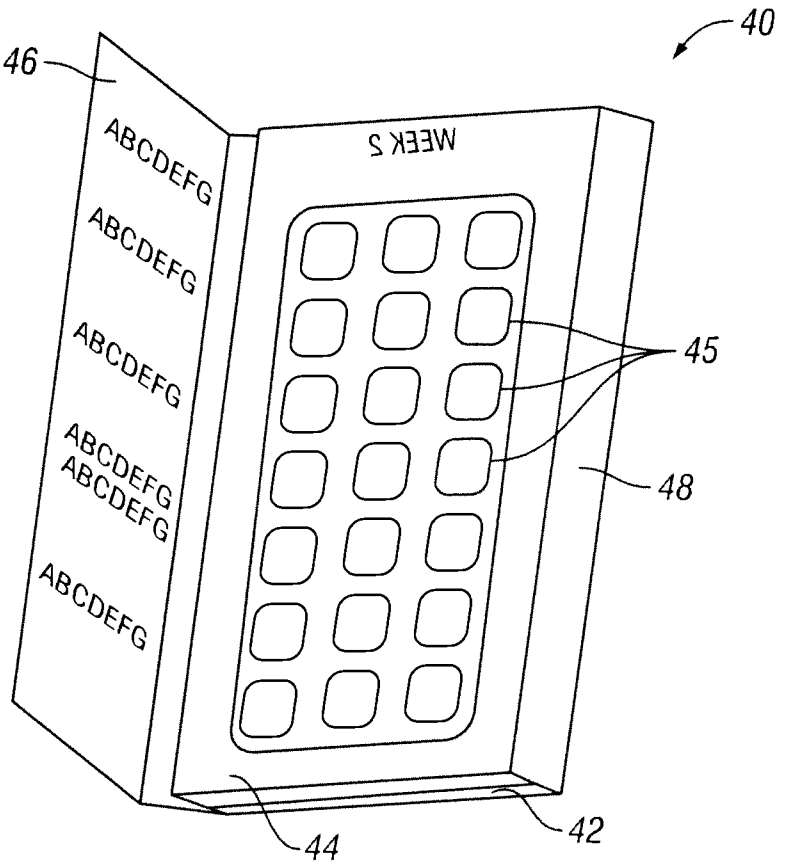


FIG. 1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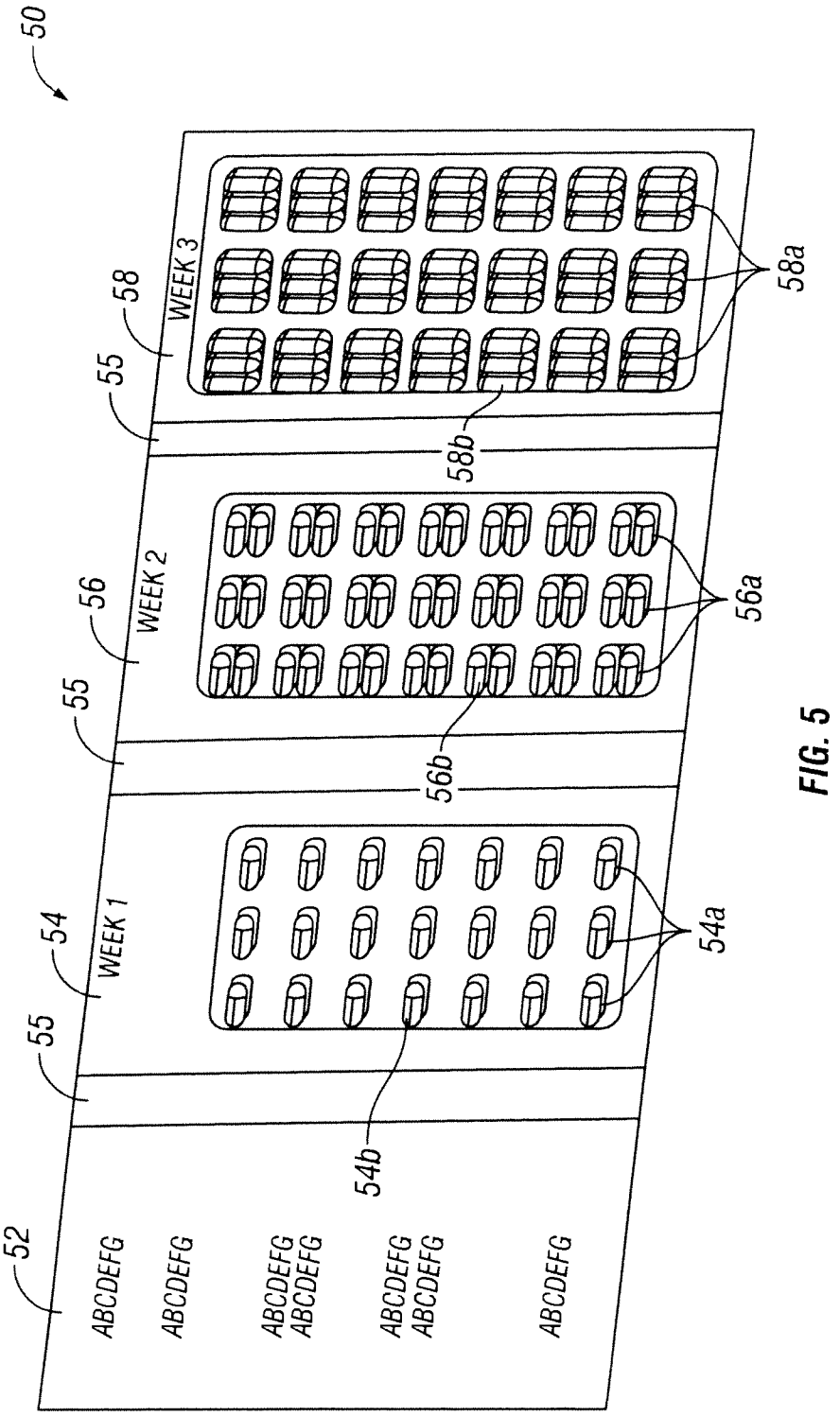
46
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
WEEK 5
45
48
44
42

FIG. 4


50
WEEK 3
58
58a
55
58b
WEEK 2
56
56a
55
56b
WEEK 1
54
54a
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54b
52
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ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG

FIG. 5

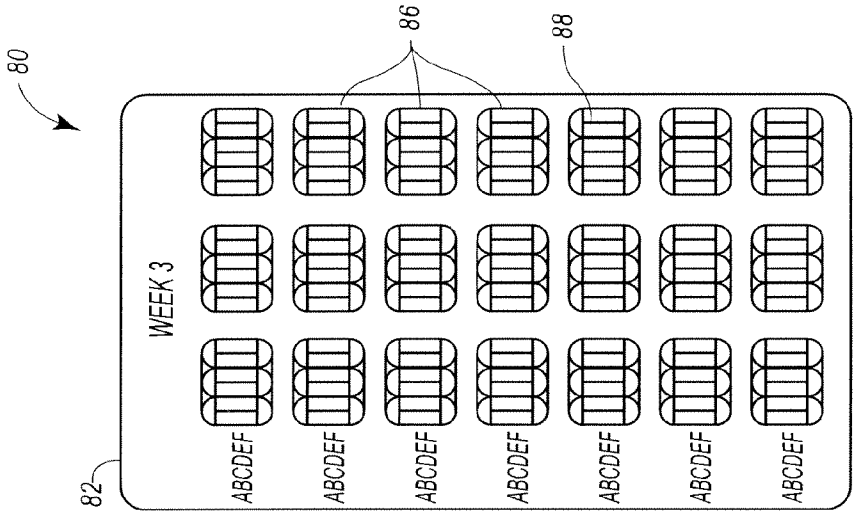


FIG. 8

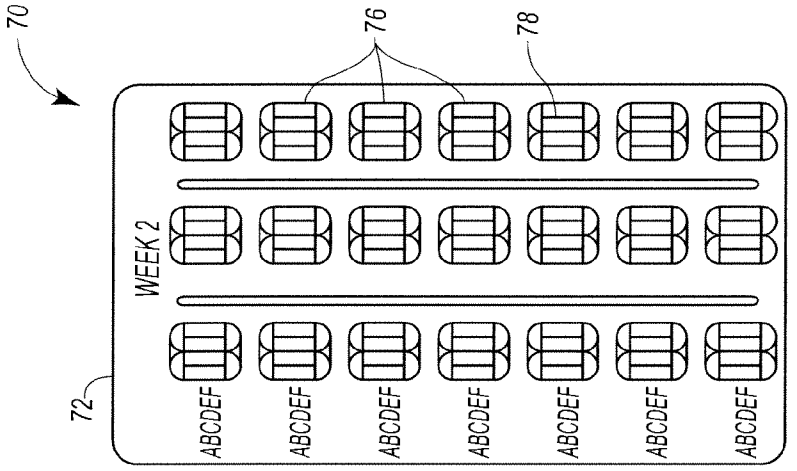


FIG. 7

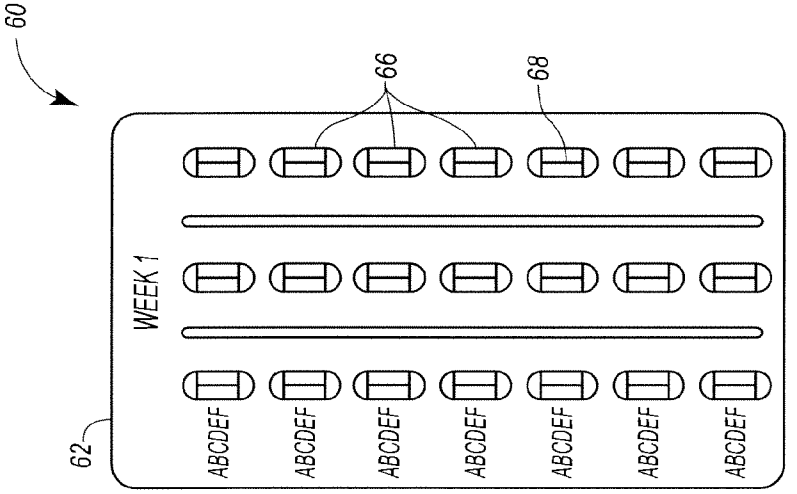


FIG. 6

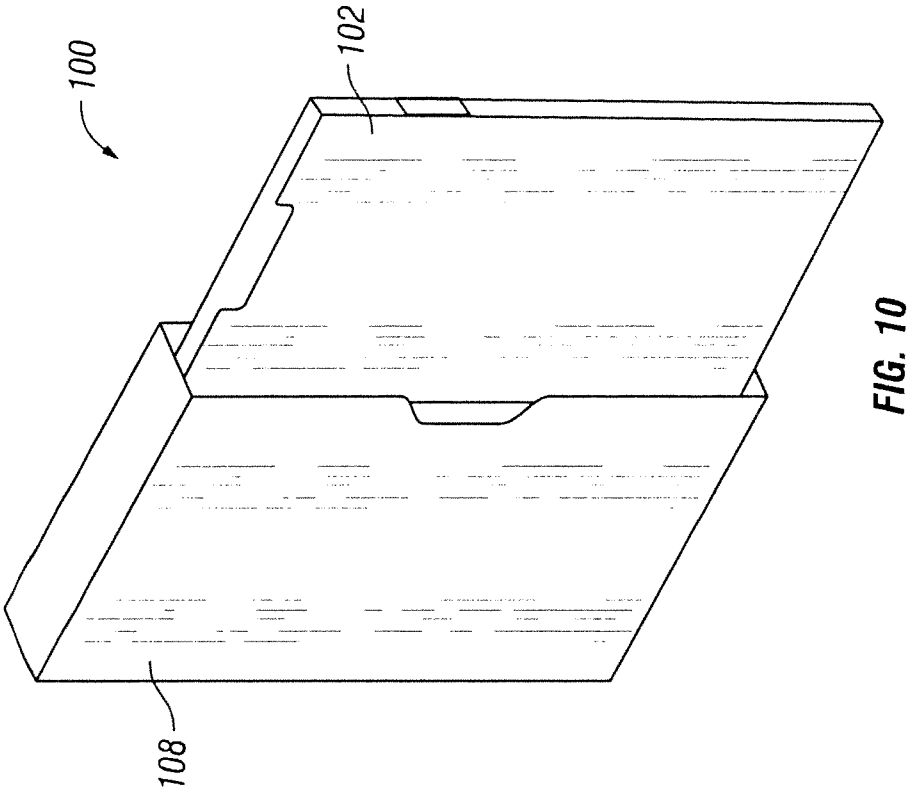


FIG. 10

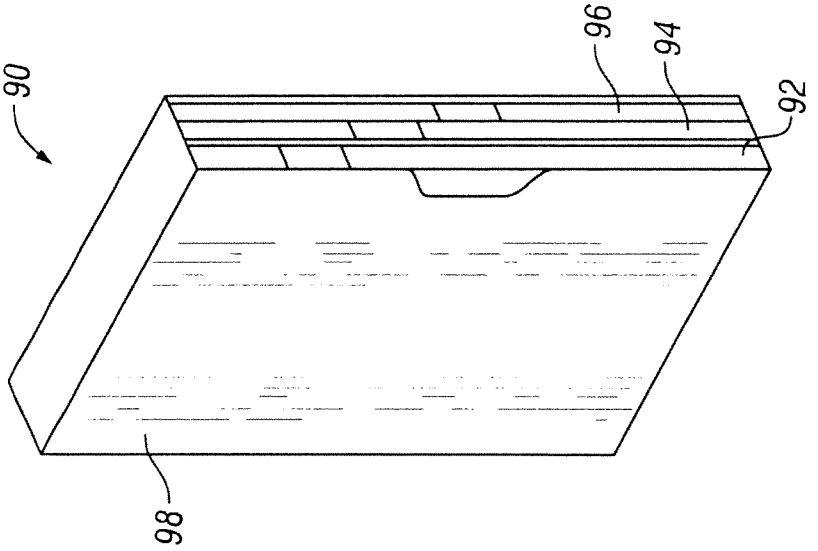
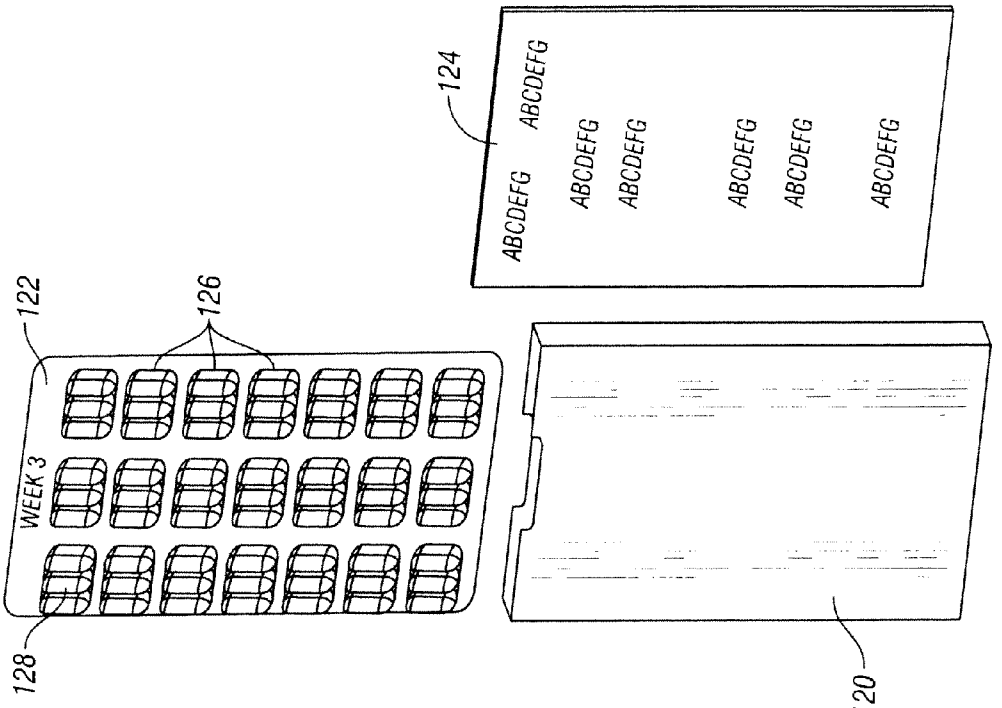


FIG. 9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ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
ABCDEFG
122
126
WEEK 3
128
120

FIG. 12

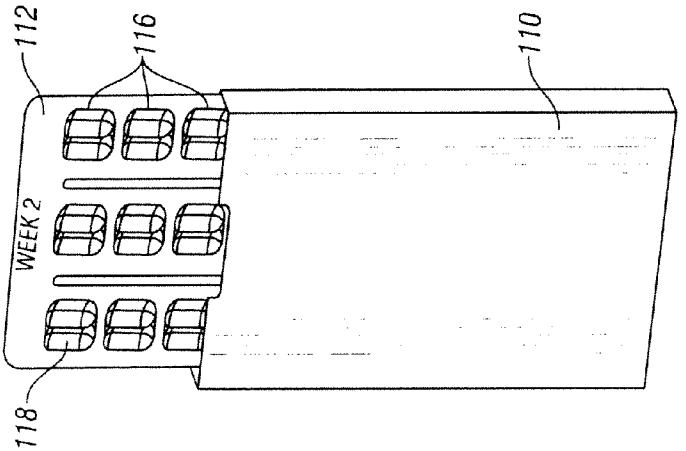
112
116
110
WEEK 2
118

FIG. 11

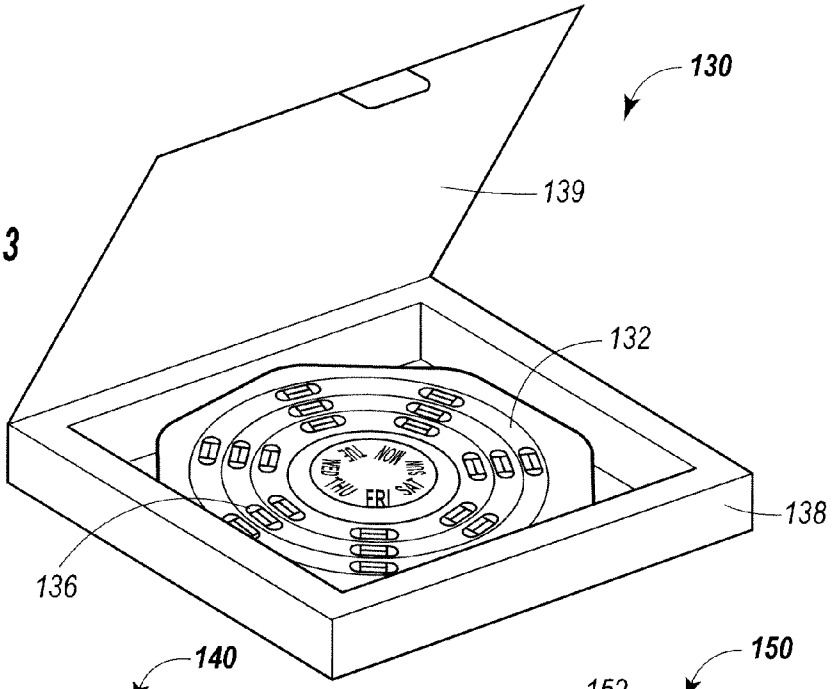

FIG. 13

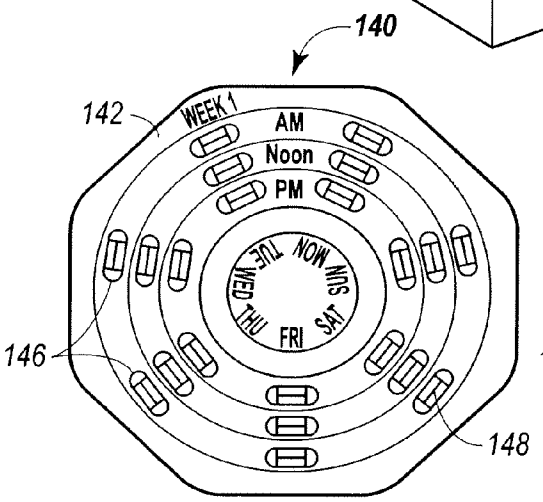

FIG. 14

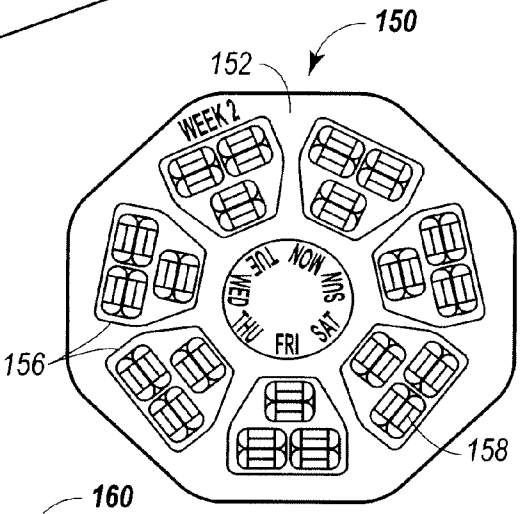

FIG. 15

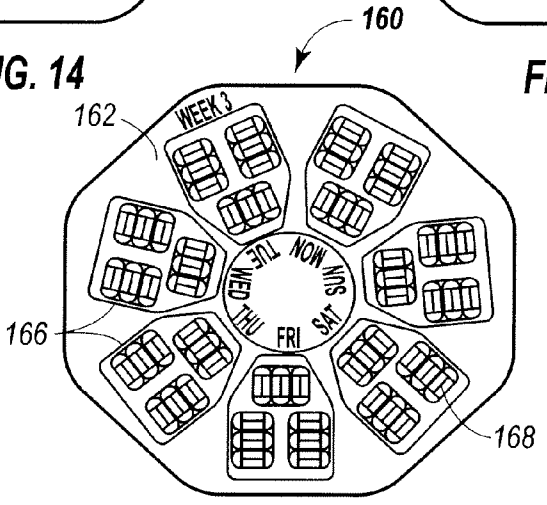

FIG. 16

METHOD OF PROVIDING PIRFENIDONE THERAPY TO A PATIENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 11/959,338, filed Dec. 18, 2007, now U.S. Pat. No. 7,767,700, which claims the benefit of U.S. Provisional Application Ser. No. 60/870,593, filed Dec. 18, 2006, the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

1. Field of the Invention

The invention relates to methods for decreasing adverse events associated with pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) therapy.

2. Description of the Related Art

Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 Daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Several pirfenidone Investigational New Drug Applications (INDs) are currently on file with the U.S. Food and Drug Administration. Phase II human investigations are ongoing or have recently been completed for pulmonary fibrosis, renal glomerulosclerosis, and liver cirrhosis. There have been other Phase II studies that used pirfenidone to treat benign prostate hypertrophy, hypertrophic scarring (keloids), and rheumatoid arthritis.

Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

It is understood that one mechanism by which pirfenidone exerts its therapeutic effects is modulating cytokine actions. Pirfenidone is a potent inhibitor of fibrogenic cytokines and TNF-α. It is well documented that pirfenidone inhibits excessive biosynthesis or release of various fibrogenic cytokines such as TGF-β1, bFGF, PDGF, and EGF. Zhang S et al., *Australian and New England J Ophthalmology* 26:S74-S76 (1998). Experimental reports also show that pirfenidone blocks the synthesis and release of excessive amounts of TNF-α from macrophages and other cells. Cain et al., *Int'l J Immunopharmacology* 20:685-695 (1998).

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy include gastrointestinal upset, nausea, fatigue, somnolence, dizziness, headache, and photosensitivity rash. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related.

The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at these higher doses.

Currently, adverse events following administration of pirfenidone are alleviated by dose reduction or discontinuation of pirfenidone. In a recent study, for adverse events rated Grade 2 or worse, the dosage was reduced in a stepwise manner: from 9 tablets having 200 mg of pirfenidone per day to 6 tablets having 200 mg of pirfenidone per day and 6 tablets having 200 mg of pirfenidone per day to 3 tablets having 200 mg of pirfenidone per day. Azuma, A. et al., *Am J Respir Crit Care Med* 171:1040-47 (2005) ("Azuma study"). More specifically, if, after a period of 14 days of observation with reduced dosage, the adverse event persisted or increased, the dosage was further reduced by one more step—from 6 tablets per day to 3 tablets per day. If the adverse event persisted or increased despite reducing the dosage to 3 tablets per day, the study medication was discontinued.

The Azuma study discloses a dose-titration schedule for all patients wherein patients received a 200-mg dose of pirfenidone three times a day for the first two days; then a 400-mg dose of pirfenidone three times a day for the following two days; and then a maximum 600-mg dose of pirfenidone three times a day for the remainder of treatment. Thus, the maximum dose obtained by the Azuma study was only 1,800 mg/day of pirfenidone. Additionally, the dose-titration schedule of the Azuma study reaches the full maximum dosage of pirfenidone after only four days of treatment. There is significant reason to believe that the Azuma dose escalation does not optimally match the rate of dose escalation with the rate at which a patient develops sufficient tolerance to reduce the incidence of adverse events. Thus, there remains an unmet clinical need for a method of administering higher doses of pirfenidone to a patient in a manner that eliminates or minimizes adverse events, such as nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, somnolence, and other undesirable side effects.

SUMMARY

The present invention overcomes the unmet clinical need by providing an improved, optimized dose escalation scheme for the administration of pirfenidone. The dose escalation scheme of the present invention provides pirfenidone in an amount such that the full maximum dosage is not reached for at least one week. In a preferred embodiment, the full maximum dosage of pirfenidone is not reached until about Day 15 of treatment. The method of the present invention allows for a maximum dosage of 2,403 mg of pirfenidone per day to be administered to a patient and also reduces the incidence of adverse events associated with the administration of pirfenidone by more accurately matching dose escalation with tolerance development in the patient. Indeed, it has been observed that even as the dosage escalates using the dosing escalation scheme described herein, adverse events, such as somnolence, decrease.

The present invention discloses a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in a first amount for the duration of a first period of time; providing a second daily dosage of pirfenidone to the patient in a second amount for a second period of time; and providing a final daily dosage of pirfenidone to the patient in a final amount for a final period of time, wherein the first and second periods of time together total at least about 7 days, more preferably about 8, 9, 10, 11 or 12 days, and most preferably about 13 or

14 days. In some embodiments, the first and second periods can together total up to about 15 or about 20 or 21 days.

In one embodiment, the first amount is about 801 mg/day; the second amount is about 1,602 mg/day; and the third amount is about 2,403 mg/day. In another embodiment, the first period of time is about 7 days; the second period of time is about 7 days; and the third period of time is in the range of about 1 day up to an unlimited number of days. In specific embodiments, the third period of time lasts at least about 1 month, at least about 2 months, at least about 3 months, at least about a year, at least about 18 months, at least about 2 years, or more than 2 years, at least about 3 years, at least about 4 years, at least about 5 years, or as long as therapy with pirfenidone is needed.

The present invention also discloses a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. Advantageously, the compartments can be arranged in columns and in rows, although other arrangements are also contemplated.

In one exemplary embodiment, the starter pack comprises rows designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. In one embodiment, the starter pack may comprise separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day. In one embodiment, each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone. In another embodiment, each week of treatment may be designated on a separate panel. In another embodiment, each panel contained within the starter pack may be approximately the same size. In another embodiment, the starter pack has compartments arranged such that a user of the starter pack may administer the pirfenidone in accordance with the dose escalation method taught by the present invention.

Also contemplated is use of pirfenidone in preparation of a medicament for the treatment of a fibrosis condition comprising administration of pirfenidone according to a dosing regimen as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a structure of a portion of a starter pack for the first week of treatment.

FIG. **2** shows a structure of a portion of a starter pack for the second week of treatment.

FIG. **3** shows a structure of a portion of a starter pack for the third week of treatment.

FIG. **4** shows a starter pack having multiple panels that are folded.

FIG. **5** shows a starter pack having multiple panels in an unfolded position.

FIG. **6** shows another structure of a portion of a starter pack for the first week of treatment.

FIG. **7** shows another structure of a portion of a starter pack for the second week of treatment.

FIG. **8** shows another structure of a portion of a starter pack for the third week of treatment.

FIG. **9** shows a starter pack having a casing material holding three different containers in such a manner that a user can easily slide a container out of the casing material.

FIG. **10** shows a starter pack wherein a container is partially pulled out from the casing material.

FIG. **11** shows a container comprising a panel having a plurality of compartments for containing a dosage amount of pirfenidone.

FIG. **12** shows a container wherein the panel has been pulled outside of the container.

FIG. **13** shows a starter pack having a casing material holding at least one circular panel containing pirfenidone.

FIG. **14** shows another structure of a portion of a circular starter pack for the first week of treatment.

FIG. **15** shows another structure of a portion of a circular starter pack for the second week of treatment.

FIG. **16** shows another structure of a portion of a circular starter pack for the third week of treatment.

DETAILED DESCRIPTION

The present invention discloses a method of providing pirfenidone therapy to a patient with an escalating dosage regimen that mitigates adverse events associated with the use of pirfenidone and, it is believed, better matches the development of tolerance to potentially adverse effects of the drug with increases in the dosage. In one embodiment of the present invention is a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in a first amount for the duration of a first period of time; providing a second daily dosage of pirfenidone to the patient in a second amount for a second period of time; and providing a final daily dosage of pirfenidone to the patient in a final amount for a final period of time. The sum of the first and second periods of time is preferably at least about 7 days, more preferably about 8, 9, 10, 11, or 12 days, and most preferably about 13 or 14 days. In some embodiments, the first and second periods can together total up to about 15 or about 20 or 21 days. Although it is also contemplated that the first and second periods together can total more than 21 days, and can (for example) be 22, 24, 26, or 30 days, it is believed that the longer dose escalation periods are less than optimal, due to the decrease in therapeutic benefit to the patient resulting from the delay in administering the full therapeutic dosage.

Although the present disclosure exemplifies dose escalation regimens having three steps, it is also possible to have more steps in the same amount of time, so that the dosage escalates in smaller steps. Indeed, if desired, each dose can be incrementally larger than the previous dose, or the dose can escalate every day, every two days, or every three or four days, for example. Regardless of the dose escalation step size, the use of an initial dose and an ending dose in the amounts discussed below is particularly preferred.

In one embodiment, the first amount is in the range of about 400 mg/day to about 1,200 g/day. In another embodiment, the first amount is in the range of about 700 mg/day to about 900 mg/day. In another embodiment, the first amount is in the range of about 780 mg/day to about 820 mg/day. In another embodiment, the first amount is about 801 mg/day.

In one embodiment, the second amount is in the range of about 1,200 mg/day to about 2,000 mg/day. In another embodiment, the second amount is in the range of about 1,500 mg/day to about 1,700 mg/day. In another embodiment, the second amount is in the range of about 1,580 mg/day to about 1,620 mg/day. In another embodiment, the second amount is about 1,602 g/day.

In one embodiment, the third amount is in the range of about 2,000 mg/day to about 3,000 mg/day. In another embodiment, the third amount is in the range of about 2,300 mg/day to about 2,400 mg/day. In another embodiment, the

third amount is in the range of about 2,380 mg/day to about 2,420 mg/day. In another embodiment, the third amount is about 2,403 mg/day.

In one embodiment, the first period of time is in the range of about 3 days to about 10 days. In another embodiment, the first period of time is about 6 to about 8 days. In another embodiment, the first period of time is about 7 days.

In one embodiment, the second period of time is in the range of about 3 days to about 10 days. In another embodiment, the second period of time is about 6 to about 8 days. In another embodiment, the second period of time is about 7 days.

In one embodiment, the final period of time is in the range of about 1 day to an unlimited number of days. Preferably, the final period of time will be however long the duration of treatment with pirfenidone should last.

In one embodiment of the present invention is a method of providing pirfenidone therapy to a patient comprising providing an initial daily dosage of pirfenidone to the patient in an amount of 801 mg/day over the course of Day 1 to Day 7; providing a second daily dosage of pirfenidone to the patient in an amount of 1602 mg/day over the course of Day 8 to Day 14; and providing a final daily dosage of pirfenidone to the patient in an amount of 2403 mg/day on the beginning of Day 15 and continuing with the 2403 mg/day dosage on each day following Day 15.

In one embodiment, the patient is administered one capsule (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day over the course of Day 1 to Day 7, to provide a daily dosage of 801 mg pirfenidone; then the patient is administered two capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day over the course of Day 8 to Day 14, to provide a daily dosage of 1602 mg pirfenidone; and then the patient is administered three capsules (a sub-daily dosage) comprising 267-mg of pirfenidone three times a day on Day 15 and each day thereafter, to provide a daily dosage of 2403 mg pirfenidone where the therapy continues after Day 15.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In another embodiment of the present invention, there is provided a starter pack comprising pirfenidone. Starter packs are a relatively easy method for singulating, transporting, storing and finally dispensing oral solid drugs. Such packs include, for instance, a planar transparent piece of plastic provided with "blisters" or convex protrusions configured in rows and columns. Each of the blisters or convex protrusions is sized to receive a singulated dosage amount of the particular oral solid drug being dispensed.

Typically, at least one backing layer is fastened to a solid receiving side of the blister pack. This layer is a low strength retaining barrier. This low strength retaining layer stretches across the backs of the blisters and retains the singulated oral dosage amounts individually sealed within each of the blisters.

Dispensing of drugs from such blister packs is easy to understand. The consumer presses down on a blister from the convex side of the blister. Such pressure bears directly against the singulated oral dosage amount contained in the blister. The singulated oral solid drug is then forced through the low strength retaining barrier. This low strength retaining barrier at least partially tears and breaks away. During this partial breaking and tearing away, the singulated oral dosage amount is partially—but typically not totally—ejected from its individual blister. Preferably, it is during this partial ejection that the oral solid drug is grasped by the user and consumed as directed. The result is a safe, sterile dispensing of the drug in desired single dosage amounts from the blister pack.

The starter pack of the present invention may comprise various dosage amounts of pirfenidone designated within blisters or other individual compartments so that the patient will take the proper dosage amount of the drug each day. The starter pack may comprise many different forms. One embodiment of the starter pack is shown in FIGS. **1-3**. FIG. **1** shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**10**) for the first week of treatment may comprise a panel (**12**) having a plurality of compartments (**16**) for containing a dosage amount (**18**) of pirfenidone. The compartments (**16**) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. In an embodiment where the starter pack comprises columns and rows, each daily dosage may be represented in a singular row or a singular column.

FIG. **2** shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**20**) for the second week of treatment may comprise a panel (**22**) having a plurality of compartments (**26**) for containing a dosage amount (**28**) of pirfenidone. The compartments (**26**) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**16**) for the first week of treatment. The dosage amount (**28**) of pirfenidone for the second week may be greater than the dosage amount (**18**) of the first week.

FIG. **3** shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (**30**) for the third week of treatment may comprise a panel (**32**) having a plurality of compartments (**36**) for containing a dosage amount (**38**) of pirfenidone. The compartments (**36**) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**26**) for the second week of treatment. The dosage amount (**38**) of pirfenidone for the third week may be greater than the dosage amount (**28**) of the second week.

Although FIGS. **1-3** show a starter pack wherein a panel represents one week of dosages, it is contemplated that a panel may be constructed to comprise more or less compartments. For instance, a panel may be constructed to hold dosage amounts for three days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for six days of treatment. In another embodiment, a panel may be constructed to hold dosage amounts for ten days of treatment. Any number of days and dosages in a single panel are contemplated by the inventors. Preferably, the starter pack may be designed so that the user administers pirfenidone according to the dose escalation scheme of the present invention.

In one embodiment, the starter pack comprises panels giving dosage amounts of pirfenidone for the first week of treatment and the second week of treatment. In another embodiment, the starter pack further comprises a panel giving dosage amounts of pirfenidone for the third week of treatment. In another embodiment, the starter pack comprises a panel or an insert that gives instructions to a patient for administering the proper dosage amount of pirfenidone.

In one embodiment, the starter pack may comprise only dosage amounts for the first week of treatment and the second week of treatment. Preferably, such a starter pack may also comprise instructions to the patient for administering the pirfenidone from a bottle for therapy after dose escalation is

completed. It is contemplated that the user of the starter pack will continue therapy with pirfenidone pills from a bottle after dose escalation is completed.

The size of the starter pack and the panels that comprise the starter pack may be typical of similar starter packs already known. In a preferred embodiment, each panel within a starter pack is approximately of similar size dimensions as the other panels of the starter pack.

In some embodiments, the starter pack comprises a unitary structure, wherein the unitary structure comprises more than one panel and each panel may comprise dosage amounts for one week of treatment. In some embodiments, the starter pack comprises a panel that has printed instructions thereon. FIG. **4** shows a starter pack (**40**) having multiple panels (**42**, **44**, **46**) that are folded. The starter pack has at least one region (**48**) capable of folding so that the separate panels (**42**, **44**, **46**) can be stacked upon one another while the starter pack (**40**) maintains its unitary structure. In some embodiments, the starter pack may comprise panels (**42**, **44**) having compartments for containing dosages of pirfenidone. The dosages may be pushed through the low strength retaining barrier at points (**45**) opposite the location of the blisters.

FIG. **5** shows a fully unfolded starter pack (**50**) comprising four panels (**52**, **54**, **56**, **58**). The Week 1 panel (**54**) may have compartments (**54***a*) that comprise a dosage amount (**54***b*) of pirfenidone related to the first week of treatment. The Week 2 panel (**56**) may have compartments (**56***a*) that comprise a dosage amount (**56***b*) of pirfenidone related to the second week of treatment. Optionally, a panel for the dosage amounts of Week 3 may be included. The Week 3 panel (**58**) may have compartments (**58***a*) that comprise a dosage amount (**58***b*) of pirfenidone related to the third week of usage. The other panel (**52**) may be left blank or provided with instructions or any other type of indicia. In some embodiments, the starter pack (**50**) may comprise an adhesive seal or a sticker that holds the starter pack in folded form until the adhesive seal or sticker is broken by a user. The starter pack may comprise regions (**55**) capable of folding so that the separate panels (**52**, **54**, **56**, **58**) can be stacked upon one another while the starter pack (**50**) maintains its unitary structure.

In one embodiment, one panel (**54**) may comprise compartments (**54***a*) giving the dosage amount (**54***b*) for Days 1-7 of the dose escalation scheme and the second panel (**56**) may comprise compartments (**56***a*) giving the dosage amount (**56***b*) for Days 8-14 of the dose escalation scheme. In another embodiment, an optional third panel (**58**) may be further provided to comprise compartments (**58***a*) giving the dosage amount (**58***b*) for Days 15-21 of the dose escalation scheme.

FIG. **6** shows a portion of another starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**60**) for the first week of treatment may comprise a panel (**62**) having a plurality of compartments (**66**) for containing a dosage amount (**68**) of pirfenidone. The compartments (**66**) may be arranged in column and row fashion as illustrated, although other arrangements are also contemplated, including having all of the compartments arranged in a line, or having them arranged in a circular fashion. Additionally, instructions may be provided on the starter pack (**60**) indicating the proper day and time the dosage amount (**68**) should be administered.

FIG. **7** shows a portion of another starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**70**) for the second week of treatment may comprise a panel (**72**) having a plurality of compartments (**76**) for containing a dosage amount (**78**) of pirfenidone. The compartments (**76**) for the second week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**66**) for the first week of treatment. The dosage amount (**78**) of pirfenidone for the second week may be greater than the dosage amount (**68**) of the first week. Additionally, instructions may be provided on the starter pack (**70**) indicating the proper day and time the dosage amount (**78**) should be administered.

FIG. **8** shows a portion of another starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The starter pack (**80**) for the third week of treatment may comprise a panel (**82**) having a plurality of compartments (**86**) for containing a dosage amount (**88**) of pirfenidone. The compartments (**86**) for the third week of treatment may be fashioned to hold a greater amount of pirfenidone than the compartments (**76**) for the second week of treatment. The dosage amount (**88**) of pirfenidone for the third week may be greater than the dosage amount (**78**) of the second week. Additionally, instructions may be provided on the starter pack (**80**) indicating the proper day and time the dosage amount (**88**) should be administered.

In some embodiments, the starter pack may comprise a casing material that holds separate panels, wherein at least one panel comprises a plurality of compartments for containing a dosage amount of pirfenidone. In some embodiments, the panel may be located within a container having flat outer surfaces so that the container may easily be slid in and out of the casing material. FIG. **9** shows a starter pack (**90**) having a casing material (**98**) holding three different containers (**92**, **94**, **96**) in such a manner that a user can easily slide a container out of the casing material (**98**). In one embodiment, each container may comprise a panel that comprises a plurality of compartments that hold a dosage amount of pirfenidone. In some embodiments, the panels may further comprise instructions or indicia so that a user can administer pirfenidone according to the dose escalation scheme. In some embodiments, a panel may be provided separately for providing indicia or instructions on using the drug. In some embodiments, indicia or instructions may be provided on one or more of the containers (**92**, **94**, **96**).

FIG. **10** shows a starter pack (**100**) comprising a casing material (**108**) and at least one container (**102**). The container (**102**) is partially pulled out from the casing material (**108**) and may comprise a panel having a plurality of compartments for containing a dosage amount of pirfenidone. For example, the container (**102**) may comprise any of the panels shown in FIGS. **1-3** and FIGS. **6-8**. Preferably, each panel will be approximately the same size for easy and compact insertion into the casing material (**108**).

FIG. **11** shows a container (**110**) comprising a panel (**112**) having a plurality of compartments (**116**) for containing a dosage amount (**118**) of pirfenidone. The panel (**112**) is partially pulled out from the container (**110**) and can be slid in and out for easy use. FIG. **12** shows a container (**120**) wherein the panel (**122**) having a plurality of compartments (**126**) for containing a dosage amount (**128**) of pirfenidone has been completely pulled from the container (**120**). Instructions may be provided on a separate sheet (**124**) within the container (**120**) in addition to the panel (**122**). Alternatively, instructions or other indicia may be printed directly on the container (**120**) or the panel (**122**).

One embodiment of the present invention is a starter pack comprising dosage amounts of pirfenidone and compartments that separate the dosage amounts according to a daily dosage of pirfenidone. In one embodiment, the starter pack comprises a row designating Day numbers and separate columns for the number of times a dosage of pirfenidone is taken each day. In one embodiment, the starter pack may comprise separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13,

and 14 with three separate columns for three dosage amounts to be taken each day. In one embodiment, each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone. In another embodiment, each week of treatment may be designated on a separate panel. In another embodiment, each panel contained within the starter pack may be approximately the same size. In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention.

In one embodiment, the starter pack further comprises additional rows for Days 15, 16, 17, 18, 19, 20, and 21. In another embodiment, each of the three compartments corresponding to Days 15, 16, 17, 18, 19, 20, and 21 separately contain three pills of 267-mg pirfenidone. The addition of the rows for Days 15, 16, 17, 18, 19, 20, and 21 is for the purpose of training the patient as to the correct amount of dosage that will be needed after the starter pack is finished and the patient begins taking pills from another source, such as a pill bottle. By providing the starter pack with a third week at the full dosage of pirfenidone, the patient will be better accustomed to taking the 2,403 mg/day dosage from Day 15 and each Day thereafter as required by the pirfenidone therapy method of the present invention.

In another embodiment, the starter pack comprises a circular form. FIG. **13** shows a container (**130**) comprising a base (**138**) that holds at least one panel (**132**) having a plurality of compartments (**136**) for containing a dosage amount of pirfenidone. The panel (**132**) is circular in shape with compartments (**136**) extending in a radial pattern from the center and wherein each radius designates its own Day for treatment with pirfenidone. The dosages for AM, noon, and PM may be separated in a manner shown in FIG. **13**. The container (**130**) also comprises a lid (**139**) so that at least one panel (**132**) containing pirfenidone can be stored within the container (**130**) and sealed.

FIG. **14** shows a portion of a starter pack comprising dosage amounts for the first week of therapy using pirfenidone. The starter pack (**140**) for the first week of treatment may comprise a circular panel (**142**) having a plurality of compartments (**146**) for containing a dosage amount (**148**) of pirfenidone. The compartments (**146**) may be arranged so that they extend radially from the center of the pane (**142**). The panel (**142**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

FIG. **15** shows a portion of a starter pack comprising dosage amounts for the second week of therapy using pirfenidone. The starter pack (**150**) for the second week of treatment may comprise a circular panel (**152**) having a plurality of compartments (**156**) for containing a dosage amount (**158**) of pirfenidone. The compartments (**156**) may be arranged so that they extend radially from the center or so that they fit within a panel. The panel (**152**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

FIG. **16** shows a portion of a starter pack comprising dosage amounts for the third week of therapy using pirfenidone. The panel for the third week of therapy is optionally provided. The starter pack (**160**) for the third week of treatment may comprise a circular panel (**162**) having a plurality of compartments (**166**) for containing a dosage amount (**168**) of pirfenidone. The compartments (**146**) may be arranged so that they extend radially from the center of the pane (**162**). The panel (**162**) may comprise indicia informing the patient which dosage to administer at the appropriate time.

In another embodiment, the starter pack has compartments arranged such that a user of the starter pack will administer the pirfenidone in accordance with the dose escalation method taught by the present invention. Of course, as an alternative to blister packs, the doses can be contained in any other type of compartment, such as plastic bags or other containers fastened together in book form; plastic containers with snap-open lids arranged in a row or other geometric pattern, or any of a wide variety of other dosage-containing packages.

In one embodiment, a method for administering pirfenidone therapy to a patient comprises initially administering a predetermined starting dosage of pirfenidone to the patient and escalating the dosage administered to the patient over a predetermined time to a predetermined full dosage of pirfenidone. In some embodiments, the predetermined time is measured from the initial starting dosage and is between about 7 and 20 days. In some embodiments, the predetermined wined time is 13 or 14 days. In some embodiments, the starting dosage is about 801 mg/day. In some embodiments, the full dosage is about 2,403 mg/day. In some embodiments, the dosages are split into three daily oral administrations.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions indicates the exclusion of equivalents of the features shown and described or portions thereof. It is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

What is claimed is:

1. A starter pack for use in an initial dose escalation regimen which provides pirfenidone to a patient at a first oral daily dosage of 801 mg for days one to seven of the dose escalation regimen; provides a second oral daily dosage of 1602 mg pirfenidone for days eight to fourteen of the dose escalation regimen; and provides a third oral daily dosage of 2403 mg pirfenidone for at least day fifteen of the dose escalation regimen,

the starter pack comprising a plurality of compartments for containing a dosage amount of pirfenidone arranged within rows and columns,

wherein the starter pack comprises separate rows for Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 with three separate columns for three dosage amounts to be taken each day; and

wherein each of the three compartments for Days 1, 2, 3, 4, 5, 6, and 7 separately contain one pill of 267-mg pirfenidone and each of the three compartments for Days 8, 9, 10, 11, 12, 13, and 14 separately contain two pills of 267-mg pirfenidone; and

wherein the starter pack optionally further comprises at least one additional set of compartments for Days 15, 16, 17, 18, 19, 20 and 21 in separate rows and each compartment in the additional set of compartments separately contain three pills of 267-mg pirfenidone.

2. The starter pack of claim **1**, further comprising a first panel comprising the compartments for days 1, 2, 3, 4, 5, 6 and 7 and an additional panel for the compartments for days 8, 9, 10, 11, 12, 13, and 14.

3. The starter pack according to claim 1, wherein the compartments comprise blisters.

4. The starter pack according to claim 1, wherein the starter pack comprises at least two panels and at least one fold separating the two panels.

5. The starter pack of claim 1, further comprising a casing for holding several containers wherein each container comprises a panel bearing a set of compartments for Days 1, 2, 3, 4, 5, 6, and 7 or Days 8, 9, 10, 11, 12, 13, and 14, or one of the at least one additional set of compartments.

6. An initial dose escalation regimen method for providing pirfenidone therapy to a patient in need thereof, comprising:

administering pirfenidone to a patient at a first oral daily dosage of 801 mg for days one to seven of the dose escalation regimen;

administering a second oral daily dosage of 1602 mg pirfenidone for days eight to fourteen of the dose escalation regimen; and

administering a third oral daily dosage of 2403 mg pirfenidone for at least day fifteen of the dose escalation regimen, wherein the pirfenidone therapy is provided for a patient with a fibrosis condition.

7. The method of claim 6, wherein the fibrosis condition is selected from the group consisting of Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF).

8. The method of claim 6, further comprising instructing the patient to administer the dosage with food.

9. The method of claim 6, wherein each daily dosage is provided as a plurality of dosage forms comprising sub-daily dosages.

10. The method of claim 6, wherein each daily dosage is split into three divided doses provided three times a day.

11. The method of claim 6, wherein each oral daily dosage is provided in capsule form.

12. The method of claim 11, wherein each capsule comprises 267 mg of pirfenidone.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,420,674 B2
APPLICATION NO. : 12/831944
DATED : April 16, 2013
INVENTOR(S) : Williamson Z. Bradford

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification:

Column 9, line 65, "pane" should be -- panel --.

Column 10, lines 18-19, "predetermined wined time" should be -- predetermined time --.

Signed and Sealed this
Third Day of December, 2013

Margaret A. Focarino

Commissioner for Patents of the United States Patent and Trademark Office

EXHIBIT 11

US008592462B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,592,462 B2**
(45) **Date of Patent: *Nov. 26, 2013**

(54) **PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 118 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/312,746**

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Related U.S. Application Data

(63) Continuation of application No. 13/128,569, filed as application No. PCT/US2009/063702 on Nov. 9, 2009, which is a continuation of application No. 12/553,292, filed on Sep. 3, 2009, now Pat. No. 7,635,707, which is a continuation-in-part of application No. 12/488,228, filed on Jun. 19, 2009, now abandoned, which is a continuation of application No. 12/428,393, filed on Apr. 22, 2009, now Pat. No. 7,566,729.

(60) Provisional application No. 61/113,107, filed on Nov. 10, 2008, provisional application No. 61/228,943, filed on Jul. 27, 2009.

(51) **Int. Cl.**
A01N 43/40 (2006.01)
A61K 31/44 (2006.01)

(52) **U.S. Cl.**
USPC **514/345**; 514/350; 546/261; 546/262

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods are provided for administering pirfenidone to a patient that has exhibited abnormal biomarkers of liver function in response to pirfenidone administration. The methods include administering to a patient pirfenidone at doses lower than the full target dosage for a time period, followed by administering to the patient pirfenidone at the full target dosage. The methods also include administering pirfenidone at the full target dose with no reduction and administering permanently reduced doses of pirfenidone.

30 Claims, No Drawings

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PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 13/128,569, filed Jul. 13, 2011, which is the national phase of International Application No. PCT/US2009/063702, filed Nov. 9, 2009, which claims priority to U.S. Provisional Application Nos. 61/113,107 filed Nov. 10, 2008, and 61/228,943, filed Jul. 27, 2009, and is a continuation of U.S. patent application Ser. No. 12/553,292, filed Sep. 3, 2009 (now U.S. Pat. No. 7,635,707 granted Dec. 22, 2009), which claims priority to U.S. Provisional Application No. 61/228,943, filed Jul. 27, 2009, and is a continuation-in-part of U.S. patent application Ser. No. 12/488,228, filed Jun. 19, 2009, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/428,393, filed Apr. 22, 2009 (now U.S. Pat. No. 7,566,729 granted Jul. 28, 2009), which claims priority to U.S. Provisional Application No. 61/113,107, filed Nov. 10, 2008, the disclosures of which are incorporated herein by reference in their entirety.

BACKGROUND

1. Field of the Disclosure

The disclosure relates generally to methods for reducing adverse effects associated with the treatment of diseases and disorders. More particularly, the disclosure relates to methods for reducing abnormal liver function associated with 5-methyl-1-phenyl-2-(1H)-pyridone ("pirfenidone") therapy.

2. Brief Description of Related Technology

U.S. Pat. Nos. 3,974,281, 4,042,699, and 4,052,509 generally relate to pirfenidone administration. U.S. Pat. Nos. 5,310,562, 5,518,729, and 5,716,632, all to Margolin and incorporated by reference herein, relate to pirfenidone administration.

Pulmonary fibrosis can be caused by a number of different conditions, including sarcoidosis, hypersensitivity pneumonitis, collagen vascular disease, and inhalant exposure. Idiopathic pulmonary fibrosis (IPF) is a distinct entity, characterized by breathing difficulty, radiographic abnormalities, and progressive loss of lung function. It is invariably progressive, and carries a grave prognosis with a median life expectancy of 2-3 years.

Pirfenidone has been administered to IPF patients. In a compassionate-use study, Raghu et al. ("Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study." Am J Respir Crit Care Med 159:1061-1069, 1999) reported administration of pirfenidone. No adverse events in hematology or blood chemistry were noted.

Nagai et al. conducted an uncontrolled, open-label study of pirfenidone in patients ("Open label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis." Internal Medicine 41:1118-1123, 2002). During treatment, no liver dysfunctions, hematologic abnormalities, or allergic or shock reactions were reported.

Moises et al. "A double-blind, multicenter study comparing pirfenidone and prednisone for moderate-to-severe pulmonary fibrosis." Chest 124:116S, 2003 reported administration of pirfenidone.

Azuma et al. "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." Am J Respir Crit Care Med 171:1040-1047, 2005) describes administration of pirfenidone to a maximum of 1800 mg/day

of pirfenidone, and reports a protocol for stepwise reduction and rechallenge with drug after an adverse event.

Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See *FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation,* October 2007.

SUMMARY

One aspect of the invention provides methods for administering a therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal biomarkers of liver function after pirfenidone administration for the treatment of fibrosis, e.g. idiopathic pulmonary fibrosis (IPF). In some embodiments, a patient is identified who exhibits a significantly abnormal level of one, two, three or more biomarkers of liver function, e.g. the level of a Grade 2 abnormality, after administration of an original full target dose of pirfenidone, e.g. about 2400 mg/day or 2403 mg/day. In such patients, the dose of pirfenidone is reduced or discontinued until levels of the abnormal biomarkers approach or are within normal range, after which patients are administered increasing doses of pirfenidone, up to the original full target dose. Alternatively, the dose of pirfenidone is not reduced at all, but liver biomarkers continue to be monitored. In another embodiment, after an optional temporary dose reduction or discontinuation, patients are administered pirfenidone at a permanently reduced dose of 1602 mg/day. As used herein, "original full target dose" means the therapeutically effective dose approved by the U.S. Food and Drug Administration or a similar agency in a foreign country, optionally other than Japan. In some embodiments, the original full target dose is about 2400 mg/day or 2403 mg/day pirfenidone, or about 34 mg/kg/day (e.g. 33-35 mg/kg/day), or from 2200 to 2600 mg/day pirfenidone, or from 31 mg/kg/day to 37 mg/kg/day. The total daily dose is administered one, two or three times per day.

Thus, the invention provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 2 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

The invention also provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 1 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about a week, or until biomarkers of liver function are within normal limits, and (b) administering about

1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In any of the embodiments described herein, any of the reduced doses of pirfenidone may be administered for a time period of 2 days, 3 days, 4 days, 5 days, 6 days, one week, about two weeks, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits.

In any of the embodiments described herein, the patient can have fibrotic lesional tissue. Such a patient is a patient who would benefit from pirfenidone administration. In one embodiment, the patient is suffering from pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions. In one embodiment, the patient is suffering from lymph node fibrosis associated with HIV. In one embodiment, the patient is suffering from pulmonary fibrosis, or idiopathic pulmonary fibrosis. In another embodiment, the patient is a person who would benefit from pirfenidone administration, optionally with the proviso that the patient is not suffering from idiopathic pulmonary fibrosis.

In some embodiments, the biomarker of liver function is alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase. Elevated gamma-glutamyl transferase has been observed in some patients receiving pirfenidone, without clinical liver impairment, and thus elevated gamma-glutamyl transferase alone is not necessarily a sign of liver impairment. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase. In another embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5-fold increased compared to the upper limit of normal (ULN). In a related embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5- to about 5-fold increased compared to the upper limit of normal (ULN), i.e. a "liver function Grade 2 abnormality". In some embodiments, the abnormal level of bilirubin is greater than about 1.5- to about 3-fold increased compared to the upper limit of normal (ULN), i.e., a "liver function Grade 2 abnormality".

In some embodiments the abnormal biomarkers of liver function, e.g. elevated alanine transaminase and/or aspartate transaminase and/or elevated bilirubin, are accompanied by clinical signs of impaired liver function such as jaundice.

Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the examples. While the method is susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

The invention provides methods for administering a full therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal levels of biomarkers of liver function after the patient has been treated with pirfenidone. Because liver function abnormalities can be indicative of drug-induced liver injury (hepatotoxicity), it is important to determine whether the abnormalities reflect liver injury or merely indicate limited toxicity that will resolve over time while continuing to take the drug. According to the present invention, even patients that exhibit abnormal liver function may continue taking pirfenidone at the original full target dose, optionally after a short time period of discontinuing pirfenidone or taking the pirfenidone at reduced doses. This administration regimen has the advantage of maximizing the time on the full target dose of drug and therefore the potential for a beneficial therapeutic effect.

The patient may be suffering from any disease for which pirfenidone therapy may be useful in ameliorating symptoms. Such a patient is a patient who would benefit from pirfenidone administration. These diseases include, but are not limited to: chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis (IPF), rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric

cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as Multiple Sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

The methods of the invention optionally include identifying abnormal liver function in a patient receiving pirfenidone, and monitoring biomarkers of liver function in a patient receiving a reduced dose of pirfenidone. In any of the methods described herein, AST and/or ALT may be elevated, e.g. to a Grade 2 or Grade 3 level. In some embodiments, the elevation is to a Grade 1 level. Alternatively, AST and bilirubin may be elevated, or AST or ALP may be elevated, or AST and GGT may be elevated, or ALT and bilirubin may be elevated, or ALT and ALP may be elevated, or ALT and GGT may be elevated, or bilirubin and ALP may be elevated, or bilirubin and GGT may be elevated, e.g., to a Grade 1, Grade 2, or Grade 3 level. Alternatively, three biomarkers of liver function may be elevated, e.g., ALT and AST and bilirubin, or ALT and AST and ALP, to a Grade 1, Grade 2, or Grade 3 level. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality after pirfenidone administration as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period. In some embodiments, step (a) is followed by (b) administering the original full target dose. In other embodiments, the original full target dose is continued without a temporary reduction or discontinuation of the dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 1600

mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (b) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

Pirfenidone can be provided in tablet or capsule forms or any other oral dosage form, and typically is formulated for oral administration. Exemplary capsule formulations are described in WO 2007/038315 (Int'l Appl. No. PCT/US2006/037057).

Pirfenidone therapy can be associated with adverse effects including photosensitivity rash, anorexia (decreased appetite), stomach discomfort, nausea, heartburn, drowsiness (somnolence), fatigue, upper respiratory tract infection, fever, positive urinary occult blood, elevation of C-reactive protein (CRP), decreased weight, headache, constipation, and malaise. Abnormal liver function also can occur as an adverse effect (AE) in patients receiving pirfenidone. Prior to receiving pirfenidone, the baseline liver function of the patient can be, and typically is, normal. Liver function can be assessed by various means known in the art, such as blood chemistry tests measuring biomarkers of liver function. Examples of biomarkers of liver function include, but are not limited to, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Alanine transaminase (ALT), also called serum glutamic pyruvate transaminase (SGPT) or alanine aminotransferase (ALAT), catalyzes the transfer of an amino group from alanine to α-ketoglutarate to produce pyruvate and glutamate. When the liver is damaged, levels of ALT in the blood can rise due to the leaking of ALT into the blood from damaged or necrosed hepatocytes.

Aspartate transaminase (AST) also called serum glutamic oxaloacetic transaminase (SGOT or GOT) or aspartate aminotransferase (ASAT), catalyzes the transfer of an amino group from aspartate to α-ketoglutarate to produce oxaloacetate and glutamate. AST can increase in response to liver damage. Elevated AST also can result from damage to other sources, including red blood cells, cardiac muscle, skeletal muscle, kidney tissue, and brain tissue. The ratio of AST to ALT can be used as a biomarker of liver damage.

Bilirubin is a catabolite of heme that is cleared from the body by the liver. Conjugation of bilirubin to glucuronic acid by hepatocytes produces direct bilirubin, a water-soluble product that is readily cleared from the body. Indirect bilirubin is unconjugated, and the sum of direct and indirect bilirubin constitutes total bilirubin. Elevated total bilirubin can be indicative of liver impairment.

Alkaline phosphatase (ALP) hydrolyzes phosphate groups from various molecules and is present in the cells lining the biliary ducts of the liver. ALP levels in plasma can rise in response to liver damage, and are higher in growing children and elderly patients with Paget's disease. However, elevated ALP levels usually reflect biliary tree disease.

Adverse effect Grades for abnormal liver function are defined herein by the modified Common Toxicity Criteria (CTC) provided in Table 1. See the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published Aug. 9, 2006 by the National Cancer Institute, incorporated herein by reference in its entirety.

TABLE 1

Modified Common Toxicity Criteria					
	Grade				
Toxicity	0	1	2	3	4
ALT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
AST	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
Bilirubin	WNL	>ULN-1.5 × ULN	>1.5-3 × ULN	>3-10 × ULN	>10 × ULN
ALP	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
GGT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN

(WNL = within normal limits; ULN = upper limit of normal)

The ULN for various indicators of liver function depends on the assay used, the patient population, and each laboratory's normal range of values for the specified biomarker, but can readily be determined by the skilled practitioner. Exemplary values for normal ranges for a healthy adult population are set forth in Table 2 below. See Cecil Textbook of Medicine, pp. 2317-2341, W.B. Saunders & Co. (1985).

TABLE 2

ALT	8-20 U/L
AST	8-20 U/L
Bilirubin	0.2-1.0 mg/dL
	3.4-17.1 μmol/L
ALP	20-70 U/L
GGT	Men: 9-50 U/L
	Women: 8-40 U/L

Grade 0 levels are characterized by biomarker levels within normal limits (WNL). "Normal" liver function, as used herein, refers to Grade 0 adverse effects. "Abnormal" liver function, as used herein, refers to Grade 1 and above adverse effects.

"Grade 1 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than the ULN and less than or equal to 2.5-times the ULN. Grade 1 liver function abnormalities also include elevations of bilirubin levels greater than the ULN and less than or equal to 1.5-times the ULN.

"Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver function abnormalities also include elevations of bilirubin levels greater than 1.5-times and less than or equal to 3-times the ULN.

"Grade 3 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 5-times and less than or equal to 20-times the ULN. Grade 3 liver function abnormalities also include elevations of bilirubin levels greater than 3-times and less than or equal to 10-times the ULN.

"Grade 4 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 20-times the ULN. Grade 4 liver function abnormalities also include elevations of bilirubin levels greater than 10 the ULN.

The present disclosure provides methods for treating a patient having idiopathic pulmonary fibrosis and receiving a full target dose of pirfenidone, wherein the full target dose is 2400 or 2403 mg pirfenidone per day. In accordance with the methods, a patient with abnormal liver function is administered a second dose of pirfenidone, wherein the second dose is 1600 or 1602 mg pirfenidone per day until liver function is within normal limits, followed by administering the patient the full target dose of 2400 or 2403 mg pirfenidone per day.

The present disclosure also provides methods for treatment of patients that exhibit Grade 1 abnormality in one or more biomarkers of liver function after pirfenidone administration. The method includes administering to the patient pirfenidone at doses of 2400 mg/day or 2403 mg/day or administering to the patient pirfenidone at doses of 1600 mg/day or 1602 mg/day. Preferably, the patient may be receiving pirfenidone for treatment of idiopathic pulmonary fibrosis. Alternatively, the patient may be suffering from a condition for which pirfenidone administration may be beneficial. Optionally, patients may receive reduced doses or discontinue treatment for a time period, and then resume administration of pirfenidone.

The methods disclosed herein are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described herein (including those described in the examples), unless stated otherwise.

Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

It will be appreciated that the invention provides pirfenidone as a medicament wherein the administration pattern of the medicament comprises administering according to any of the treatment methods described herein.

It will be appreciated that the invention provides pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to any of the treatment regimes as described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration. Pirfenidone is packaged and presented for use in a treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to such treatment regimes. Pirfenidone is administered to the patient in accordance with the treatment regimes as described above. The patient is one

who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration.

In particular, the invention includes pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Optionally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

It will be appreciated that the invention provides the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to any of the treatment regimes as described above with respect to any of the methods. The medicaments manufactured according to this aspect of the invention are for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration in accordance with such treatment regimes. The medicament so manufactured is administered to the patient in accordance with the treatment regimes as described above. The patient is one who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration.

In particular, the invention includes the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Optionally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

In respect of the aspects of the invention relating to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, the preferences expressed with respect to the preferred embodiments of the aspect of the invention relating to a method for administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis apply in the same way. Similarly, the examples relate to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, as well as to a method for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis.

EXAMPLES

The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1

Pirfenidone Dosing Regimen

Patients begin pirfenidone treatment by receiving escalating doses of pirfenidone over a period of 15 days until the full maintenance dose is reached. Specifically, from days 1 to 7, patients are administered one capsule of 267 mg pirfenidone three times per day. During days 8 to 14, patients receive two capsules of 267 mg pirfenidone three times per day. From day 15 onward, patients are treated with three capsules of 267 mg pirfenidone three times per day. Pirfenidone is administered orally, and each dose should be taken with food. If the patient is unable to eat, then the pirfenidone dose should be taken with milk or juice (excluding grapefruit juice).

Pirfenidone is known to cause photosensitivity reactions; therefore, throughout the treatment period, patients should use sun block that protects against at least UV-A with a sun protective factor (SPF) of 50. In addition, patients should wear appropriate clothing to minimize sun exposure, and if possible, avoid other medications known to cause photosensitivity reactions.

Once the full maintenance dose is reached, pirfenidone is administered orally to patients three times per day to provide a daily dose of 2403 mg pirfenidone. Each of the three doses of 801 mg pirfenidone includes three capsules of 267 mg pirfenidone each. The contents of the pirfenidone 267 mg capsules are pirfenidone (82.15%); croscarmellose sodium (8.15%); microcrystalline cellulose (7.39%); povidine, USP, EP (1.85%); and magnesium stearate (0.46%).

Patients are treated with pirfenidone for up to 72 weeks. Some patients are treated longer than 72 weeks. At weeks 2, 4, 6, 12, and every 12 weeks (±2 weeks) thereafter during the treatment period, with the exception of week 72 and the treatment completion visit, patients are examined and histories are collected as detailed in the steps below.

1. Patient history is collected to include review of adverse effects (AEs) and severe adverse effects (SAEs), use of concomitant medications, use of oxygen, hospitalizations, IPF exacerbations or acute respiratory decompensation, and dosing.

2. Patients receive a physical examination, and vital signs and weight are measured.

3. Pulmonary function is assessed by spirometry before and after administration of bronchodilators. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) are measured.

4. Clinical laboratory tests are performed, including hematology, serum chemistries, pregnancy tests for women of childbearing capacity, and urinalysis with microscopic examination.

5. Questionnaires are administered, including the University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ), St. George's Hospital Respiratory Questionnaire (SGRQ), and the World Health Organization Quality of Life (WHO QOL) questionnaire. After week 72, only the UCSD SOBQ and SGRQ are obtained at the scheduled 12 week visits.

Additionally, every 24 weeks starting with Week 12 (for example, weeks 12, 36, and 60), electrocardiogram (ECG) measurements are obtained. ECG data is obtained before administering bronchodilators for the pulmonary function test (PFT) measurements. At the week 36 visit, pharmacokinetic (PK) data is obtained for selected patients.

If a patient experiences a Grade 1 or greater elevation in alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin at baseline or after the start of pirfenidone dosing

up to and including week 6, an additional safety chemistry blood test must be obtained between weeks 8 and 10.

Example 2

Modification of Pirfenidone Dosing Regimen in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to one capsule of 267 mg pirfenidone three times per day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

At any time after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 capsules per day. After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose also can be re-escalated in a manner consistent with the initial dose escalation, up to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly or every 2 weeks, or every 3 weeks, or every month to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 3

Temporary Discontinuation of Pirfenidone Dosing in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is discontinued. Following discontinuation of the pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. Pirfenidone dosing is discontinued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The pirfenidone dose can be discontinued for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, if the patient has been off drug for 14 days or more, the pirfenidone dose is re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 or 9 capsules per day, i.e. 1602 mg/day or 2403 mg/day. Alternatively, after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose is re-instituted at a dose of 6 capsules per day, i.e. 1602 mg/day, and re-escalated after 1 week to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly, or every 2 weeks, or every month, to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 4

Modification of Pirfenidone Dosing Regimen to 2 Capsules Three Times Per Day in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to two capsules of 267 mg pirfenidone three times per day, i.e. 1602 mg/day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After 1 week of treatment at 1602 mg/day, if AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated to the maximum of 9 capsules per day, i.e. 2403 mg.

Example 5

No Modification of Pirfenidone Dosing Regime in Response to a Grade 1 or Grade 2 Liver Function Test (LFT) Elevations

Patients were treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, some patients exhibited abnormal liver function test results. As described in Example 1, serum chemistry tests were performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphate (ALP), and gamma-glutamyl transferase (GGT).

If a patient exhibited a Grade 1 or Grade 2 increase in any one of AST, ALT, or bilirubin, the pirfenidone dose was not reduced for some patients. The patient continued to receive the full target dose of 2403 mg/day. While receiving the full target dose, the patient was monitored for AST, ALT, and bilirubin levels.

Example 6

Incidence of Liver Function Abnormality and Dosing Regimen Response

Grade 1 Abnormalities in Liver Function

In a study of 345 patients with idiopathic pulmonary fibrosis receiving pirfenidone three times per day for a total daily dose of 2403 mg/day, 49 patients without a baseline liver function abnormality exhibited a Grade 1 elevation in AST or ALT levels after pirfenidone administration. Of the 49 patients, three patients with a Grade 1 liver function test elevation had a treatment emergent adverse event of increased AST or ALT. In one patient, study drug dose was reduced to 1602 mg/day for the remainder of study participation (from Day 51 to Day 602), and the Grade 1 AST or ALT abnormality returned to Grade 0. For the second patient, study drug dose was reduced to 1602 mg/day and then increased to 2403 mg/day for remainder of study participation, and ALT returned to Grade 0. The third patient had study drug dose reduced to 801 mg/day, ultimately completing study at 1602 mg/day, at which time ALT returned to Grade 0. The remaining patients (46 patients) received no dose modification.

Grade 2 Abnormalities in Liver Function

Fifteen patients developed a Grade 2 liver function test abnormality in AST and/or ALT levels after pirfenidone administration of 2403 mg/day. Of the fifteen patients, 12 had reported treatment emergent adverse events of increased AST or ALT or hepatitis. The liver function test elevations for the remaining three patients were not documented as an adverse event (discussed below).

Of the twelve patients, two patients received continued administration of pirfenidone at the full daily dose of 2403 mg/day. The liver function test of one patient resolved to a Grade 0. The other patient had a history of steatosis and a Grade 1 abnormality prior to pirfenidone treatment and underwent a dose reduction for unrelated reasons (rash and diarrhea), not for abnormal liver function tests, and ended the study with a Grade 1 elevation.

Two patients had a temporary dose reduction or a temporary discontinuation of pirfenidone, and were rechallenged and escalated back to full dose. They completed the study at the full dose of 2403 mg/day with normal liver enzymes.

Seven patients underwent a permanent dose reduction of pirfenidone, in some cases after a temporary discontinuation of drug; by completion of the study, 3 patients were receiving 801 mg/day and 4 patients were receiving 1602 mg/day. With the exception of one patient, rechallenge with a higher dose was not attempted with these patients. The patient that was rechallenged received the full dose of 2403 mg/day, but the dose was later reduced due to a recurrence of Grade 2 elevation in ALT levels. All seven patients completed the study with resolution of transaminases, except for one patient that had a Grade 1 elevation at study completion.

One patient discontinued treatment due to abnormal liver function tests in AST and/or ALT levels. The dose for this patient was initially decreased to 1602 mg/day, then discontinued, and then resumed at 1602 mg/day. For this patient, however, treatment was permanently discontinued because a Grade 2 elevation of AST coincided with a Grade 3 ALT elevation in liver function tests.

Of the three patients whose liver function test elevations were not documented as an adverse event, one had Grade 1 AST and ALT elevation at baseline, and experienced a Grade 1 elevation of AST at the last documented assessment. This patient received no dose modification after a Grade 2 elevation in AST and/or ALT levels. A second patient with a Grade 2 transaminase elevation had treatment temporarily discontinued for acute cerebral artery occlusion. Transaminase levels returned to normal once the dose was escalated back to 2403 mg/day, and the patient completed the study on full dose with normal transaminases. The third patient had no liver function test abnormalities while on treatment until Day 422, then the patient experienced a Grade 2 AST and Grade 1 ALT elevation with respiratory failure due to IPF. Study drug was discontinued the same day for respiratory failure. The patient was hospitalized on Day 434 and died on Day 439 due to respiratory failure.

Grade 3 Abnormalities in Liver Function

Four patients developed Grade 3 liver function abnormality in AST and/or ALT levels after pirfenidone administration, all of who had a treatment emergent adverse event of either increased AST and/or ALT. Two of the four patients discontinued study drug for elevated liver function tests. In both instances, the abnormalities had not resolved, with Grade 2 and Grade 3 abnormalities last documented. The two other patients had Grade 1 abnormalities at screening and/or baseline. One patient discontinued for lung transplant at which time the last documented values showed a Grade 1 abnormality. The other patient interrupted study drug (investigator decision), and subsequently discontinued study drug (sponsor decision). The AST and ALT elevations had normalized at the last documented value.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art. Although methods have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used.

All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

What is claimed is:

1. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited an increase of about 2.5-fold to about 5-fold, compared to the upper limit of normal, in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

2. The method of claim **1** wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 1600 mg/day for about a week, or until biomarkers of liver function are within normal limits.

3. The method of claim **1**, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 2400 mg/day or 2403 mg/day.

4. The method of claim 3 wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 2400 mg/day.

5. The method of claim 1, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 1800 mg/day.

6. The method of claim 5 wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses of 1600 mg/day or lower for about a week, or until biomarkers of liver function are within normal limits.

7. The method of claim 5 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

8. The method of claim 1 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

9. The method of claim 1 wherein the second administration of pirfenidone further comprises, prior to step (a), administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

10. The method of claim 3 wherein the second administration of pirfenidone further comprises, prior to step (a), administering about 1600 mg/day or 1602 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

11. The method of claim 1, wherein the pirfenidone is administered three times per day with food.

12. The method of claim 3 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

13. The method of claim 3 wherein the second administration of pirfenidone further comprises, prior to step (a), administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

14. The method of claim 13 wherein the second administration of pirfenidone further comprises, prior to step (a), administering about 1600 mg/day or 1602 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

15. The method of claim 3, wherein the pirfenidone is administered three times per day with food.

16. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited an increase of about 2.5-fold to about 5-fold, compared to the upper limit of normal, in one or more biomarkers of liver function after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

17. The method of claim 16 wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 1600 mg/day for about a week, or until biomarkers of liver function are within normal limits.

18. The method of claim 16 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

19. The method of claim 16, wherein the pirfenidone is administered three times per day with food.

20. The method of claim 16, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 1800 mg/day.

21. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a Grade 2 abnormality in one or more biomarkers of liver function after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

22. The method of claim 21 wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 1600 mg/day for about a week, or until biomarkers of liver function are within normal limits.

23. The method of claim 21 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits.

24. The method of claim 21, wherein the pirfenidone is administered three times per day with food.

25. The method of claim 21, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 1800 mg/day.

26. A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a Grade 2 abnormality in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

27. The method of claim 26 wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 1600 mg/day for about a week, or until biomarkers of liver function are within normal limits.

28. The method of claim 26 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

29. The method of claim 26, wherein the pirfenidone is administered three times per day with food.

30. The method of claim 26, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 1800 mg/day.

* * * * *

EXHIBIT 12

US008609701B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,609,701 B2**
(45) **Date of Patent: *Dec. 17, 2013**

(54) **PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 122 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 12/553,292, filed on Sep. 3, 2009, now Pat. No. 7,635,707, which is a continuation-in-part of application No. 12/488,228, filed on Jun. 19, 2009, now abandoned, which is a continuation of application No. 12/428,393, filed on Apr. 22, 2009, now Pat. No. 7,566,729.

(60) Provisional application No. 61/113,107, filed on Nov. 10, 2008, provisional application No. 61/228,943, filed on Jul. 27, 2009.

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A61K 31/44 (2006.01)

(52) **U.S. Cl.**
USPC **514/345**; 514/350; 546/261; 546/262

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

Methods are provided for administering pirfenidone to a patient that has exhibited abnormal biomarkers of liver function in response to pirfenidone administration. The methods include administering to a patient pirfenidone at doses lower than the full target dosage for a time period, followed by administering to the patient pirfenidone at the full target dosage. The methods also include administering pirfenidone at the full target dose with no reduction and administering permanently reduced doses of pirfenidone.

19 Claims, No Drawings

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PIRFENIDONE TREATMENT FOR PATIENTS WITH ATYPICAL LIVER FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This is the national phase of International Application No. PCT/US2009/063702, filed Nov. 9, 2009, which claims priority to U.S. Provisional Application Nos. 61/113,107, filed Nov. 10, 2008, and 61/228,943, filed Jul. 27, 2009, and is a continuation of U.S. patent application Ser. No. 12/553,292, filed Sep. 3, 2009 (now U.S. Pat. No. 7,635,707 granted Dec. 22, 2009), which claims priority to U.S. Provisional Application No. 61/228,943, filed Jul. 27, 2009, and is a continuation-in part of U.S. patent application Ser. No. 12/488,228, filed Jun. 19, 2009, now abandoned, which is a continuation of U.S. patent application Ser. No. 12/428,393, filed Apr. 22, 2009 (now U.S. Pat. No. 7,566,729, granted Jul. 28, 2009), which claims priority to U.S. Provisional Application Ser. No. 61/113,107, filed Nov. 10, 2008, the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

1. Field of the Disclosure

The disclosure relates generally to methods for reducing adverse effects associated with the treatment of diseases and disorders. More particularly, the disclosure relates to methods for reducing abnormal liver function associated with 5-methyl-1-phenyl-2-(1H)-pyridone ("pirfenidone") therapy.

2. Brief Description of Related Technology

U.S. Pat. Nos. 3,974,281, 4,042,699, and 4,052,509 generally relate to pirfenidone administration. U.S. Pat. Nos. 5,310,562, 5,518,729, and 5,716,632, all to Margolin and incorporated by reference herein, relate to pirfenidone administration.

Pulmonary fibrosis can be caused by a number of different conditions, including sarcoidosis, hypersensitivity pneumonitis, collagen vascular disease, and inhalant exposure. Idiopathic pulmonary fibrosis (IPF) is a distinct entity, characterized by breathing difficulty, radiographic abnormalities, and progressive loss of lung function. It is invariably progressive, and carries a grave prognosis with a median life expectancy of 2-3 years.

Pirfenidone has been administered to IPF patients. In a compassionate-use study, Raghu et al. ("Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study." Am J Respir Crit Care Med 159:1061-1069, 1999) reported administration of pirfenidone. No adverse events in hematology or blood chemistry were noted.

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Azuma et al. "Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis." Am J Respir Crit Care Med 171:1040-1047, 2005) describes administration of pirfenidone to a maximum of 1800 mg/day of pirfenidone, and reports a protocol for stepwise reduction and rechallenge with drug after an adverse event.

Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See *FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, October 2007.

SUMMARY

One aspect of the invention provides methods for administering a therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal biomarkers of liver function after pirfenidone administration for the treatment of fibrosis, e.g. idiopathic pulmonary fibrosis (IPF). In some embodiments, a patient is identified who exhibits a significantly abnormal level of one, two, three or more biomarkers of liver function, e.g. the level of a Grade 2 abnormality, after administration of an original full target dose of pirfenidone, e.g. about 2400 mg/day or 2403 mg/day. In such patients, the dose of pirfenidone is reduced or discontinued until levels of the abnormal biomarkers approach or are within normal range, after which patients are administered increasing doses of pirfenidone, up to the original full target dose. Alternatively, the dose of pirfenidone is not reduced at all, but liver biomarkers continue to be monitored. In another embodiment, after an optional temporary dose reduction or discontinuation, patients are administered pirfenidone at a permanently reduced dose of 1602 mg/day. As used herein, "original full target dose" means the therapeutically effective dose approved by the U.S. Food and Drug Administration or a similar agency in a foreign country, optionally other than Japan. In some embodiments, the original full target dose is about 2400 mg/day or 2403 mg/day pirfenidone, or about 34 mg/kg/day (e.g. 33-35 mg/kg/day), or from 2200 to 2600 mg/day pirfenidone, or from 31 mg/kg/day to 37 mg/kg/day. The total daily dose is administered one, two or three times per day.

Thus, the invention provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 2 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day

or 801 mg/day pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for about one week, or until the liver function biomarkers return to Grade 0 or Grade 1, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

The invention also provides methods of administering pirfenidone to a patient at doses of 2400 mg/day or 2403 mg/day after identifying that the patient has exhibited a liver function Grade 1 abnormality after pirfenidone administration. In some embodiments, the methods involve continuing the full target dose, e.g. of 2400 mg/day or 2403 mg/day, without temporarily discontinuing or reducing the dose. The patient's biomarkers of liver function may continue to be monitored. In some embodiments, the method involves (a) administering a dose lower than 2400 mg/day for a time period, e.g., one week, two weeks, three weeks, four weeks, one month, six weeks, or two months, followed by (b) administering a dose of 2400 mg/day or 2403 mg/day. In specific embodiments, the pirfenidone is temporarily discontinued before step (a).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering the original full target dose for at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (c) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about one week, (c) administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period, optionally about one week, and (d) administering the original full target dose for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. Preferably, the total daily dose is administered three times per day, with food.

Alternatively, pirfenidone is administered at a permanently reduced dose, e.g. 800 or 801 mg/day, or 1600 or 1602 mg/day. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: administering about 1600 mg/day or 1602 mg/day pirfenidone for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In some embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering about 800 mg/day or 801 mg/day pirfenidone for a time period, optionally about a week, or until biomarkers of liver function are within normal limits, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four

weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, (b) administering about 800 mg/day or 801 mg/day pirfenidone for about a week, or until biomarkers of liver function are within normal limits, and (c) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years. In still other embodiments, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, optionally about one week, or until the liver function biomarkers return to Grade 0, and (b) administering about 1600 mg/day or 1602 mg/day pirfenidone to the patient for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years.

In any of the embodiments described herein, any of the reduced doses of pirfenidone may be administered for a time period of 2 days, 3 days, 4 days, 5 days, 6 days, one week, about two weeks, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits.

In any of the embodiments described herein, the patient can have fibrotic lesional tissue. Such a patient is a patient who would benefit from pirfenidone administration. In one embodiment, the patient is suffering from pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions. In one embodiment, the patient is suffering from lymph node fibrosis associated with HIV. In one embodiment, the patient is suffering from pulmonary fibrosis, or idiopathic pulmonary fibrosis. In another embodiment, the patient is a person who would benefit from pirfenidone administration, optionally with the proviso that the patient is not suffering from idiopathic pulmonary fibrosis.

In some embodiments, the biomarker of liver function is alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase. Elevated gamma-glutamyl transferase has been observed in some patients receiving pirfenidone, without clinical liver impairment, and thus elevated gamma-glutamyl transferase alone is not necessarily a sign of liver impairment. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase. In another embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5-fold increased compared to the upper limit of normal (ULN). In a related embodiment, the abnormal level of alanine transaminase, aspartate transaminase, or alkaline phosphatase is greater than about 2.5- to about 5-fold increased compared to the upper limit of normal (ULN), i.e. a "liver function Grade 2 abnormality". In some embodiments, the abnormal level of bilirubin is greater than about 1.5- to about 3-fold increased compared to the upper limit of normal (ULN), i.e., a "liver function Grade 2 abnormality".

In some embodiments the abnormal biomarkers of liver function, e.g. elevated alanine transaminase and/or aspartate transaminase and/or elevated bilirubin, are accompanied by clinical signs of impaired liver function such as jaundice.

Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the examples. While the method is susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

The invention provides methods for administering a full therapeutically effective dose of pirfenidone to a patient that has exhibited abnormal levels of biomarkers of liver function after the patient has been treated with pirfenidone. Because liver function abnormalities can be indicative of drug-induced liver injury (hepatotoxicity), it is important to determine whether the abnormalities reflect liver injury or merely indicate limited toxicity that will resolve over time while continuing to take the drug. According to the present invention, even patients that exhibit abnormal liver function may continue taking pirfenidone at the original full target dose, optionally after a short time period of discontinuing pirfenidone or taking the pirfenidone at reduced doses. This administration regimen has the advantage of maximizing the time on the full target dose of drug and therefore the potential for a beneficial therapeutic effect.

The patient may be suffering from any disease for which pirfenidone therapy may be useful in ameliorating symptoms. Such a patient is a patient who would benefit from pirfenidone administration. These diseases include, but are not limited to: chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis (IPF), rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as Multiple Scle-

rosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

The methods of the invention optionally include identifying abnormal liver function in a patient receiving pirfenidone, and monitoring biomarkers of liver function in a patient receiving a reduced dose of pirfenidone. In any of the methods described herein, AST and/or ALT may be elevated, e.g. to a Grade 2 or Grade 3 level. In some embodiments, the elevation is to a Grade 1 level. Alternatively, AST and bilirubin may be elevated, or AST or ALP may be elevated, or AST and GGT may be elevated, or ALT and bilirubin may be elevated, or ALT and ALP may be elevated, or ALT and GGT may be elevated, or bilirubin and ALP may be elevated, or bilirubin and GGT may be elevated, e.g., to a Grade 1, Grade 2, or Grade 3 level. Alternatively, three biomarkers of liver function may be elevated, e.g., ALT and AST and bilirubin, or ALT and AST and ALP, to a Grade 1, Grade 2, or Grade 3 level. In any of the embodiments described herein, biomarkers of liver function can exclude gamma-glutamyl transferase.

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality after pirfenidone administration as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period. In some embodiments, step (a) is followed by (b) administering the original full target dose. In other embodiments, the original full target dose is continued without a temporary reduction or discontinuation of the dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 2 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfeni-

done, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (b) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or until all biomarkers or liver function has returned to within normal limits. In some embodiments, step (b) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (b) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (c) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (c) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c).

In some embodiments of the methods, pirfenidone is administered to a patient exhibiting a liver function Grade 1 abnormality as follows: (a) discontinuing pirfenidone for a time period, (b) administering at least about 800 mg/day or 801 mg/day pirfenidone, or about 11 mg/kg/day (e.g. 10-12 mg/kg/day), or from 600-1000 mg/day, or from 700-900 mg/day, or from 8 mg/kg/day to 15 mg/kg/day, for a time period, (c) administering at least about 1600 mg/day or 1602 mg/day pirfenidone, or about 23 mg/kg/day (e.g. 22-24 mg/kg/day), or from 1400-1800 mg/day pirfenidone, or from 20 mg/kg/day to 26 mg/kg/day, for a time period, and (d) administering the original full target dose. In some embodiments, the time period of step (a) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (b) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, the time period of step (c) is 2 days, 3 days, 4 days, 5 days, 6 days, about one week, about two weeks, about three weeks, about four weeks, about 1 month, or until the level of at least one biomarker of liver function has returned to within normal limits, or to Grade 1, or until all biomarkers or liver function has returned to within normal limits, or to Grade 1. In some embodiments, step (d) is carried out for a time period of at least one week, two weeks, three weeks, four weeks or a month, two months, or three months, or one year, or two years, or three years, or four years, or five years, or seven years, or ten years, or more. Optionally the method includes measuring one or more biomarkers of liver function during step (a) and/or step (b) and/or step (c) and/or step (d).

Pirfenidone can be provided in tablet or capsule forms or any other oral dosage form, and typically is formulated for oral administration. Exemplary capsule formulations are described in WO 2007/038315 (Int'l Appl. No. PCT/US2006/037057).

Pirfenidone therapy can be associated with adverse effects including photosensitivity rash, anorexia (decreased appetite), stomach discomfort, nausea, heartburn, drowsiness (somnolence), fatigue, upper respiratory tract infection, fever, positive urinary occult blood, elevation of C-reactive protein (CRP), decreased weight, headache, constipation, and malaise. Abnormal liver function also can occur as an adverse effect (AE) in patients receiving pirfenidone. Prior to receiving pirfenidone, the baseline liver function of the patient can be, and typically is, normal. Liver function can be assessed by various means known in the art, such as blood chemistry tests measuring biomarkers of liver function. Examples of biomarkers of liver function include, but are not limited to, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Alanine transaminase (ALT), also called serum glutamic pyruvate transaminase (SGPT) or alanine aminotransferase (ALAT), catalyzes the transfer of an amino group from alanine to α-ketoglutarate to produce pyruvate and glutamate. When the liver is damaged, levels of ALT in the blood can rise due to the leaking of ALT into the blood from damaged or necrosed hepatocytes.

Aspartate transaminase (AST) also called serum glutamic oxaloacetic transaminase (SGOT or GOT) or aspartate aminotransferase (ASAT), catalyzes the transfer of an amino group from aspartate to α-ketoglutarate to produce oxaloacetate and glutamate. AST can increase in response to liver damage. Elevated AST also can result from damage to other sources, including red blood cells, cardiac muscle, skeletal muscle, kidney tissue, and brain tissue. The ratio of AST to ALT can be used as a biomarker of liver damage.

Bilirubin is a catabolite of heme that is cleared from the body by the liver. Conjugation of bilirubin to glucuronic acid by hepatocytes produces direct bilirubin, a water-soluble product that is readily cleared from the body. Indirect bilirubin is unconjugated, and the sum of direct and indirect bilirubin constitutes total bilirubin. Elevated total bilirubin can be indicative of liver impairment.

Alkaline phosphatase (ALP) hydrolyzes phosphate groups from various molecules and is present in the cells lining the biliary ducts of the liver. ALP levels in plasma can rise in response to liver damage, and are higher in growing children and elderly patients with Paget's disease. However, elevated ALP levels usually reflect biliary tree disease.

Adverse effect Grades for abnormal liver function are defined herein by the modified Common Toxicity Criteria (CTC) provided in Table 1. See the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) published Aug. 9, 2006 by the National Cancer Institute, incorporated herein by reference in its entirety.

TABLE 1

Modified Common Toxicity Criteria

	Grade				
Toxicity	0	1	2	3	4
ALT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
AST	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
Bilirubin	WNL	>ULN-1.5 × ULN	>1.5-3 × ULN	>3-10 × ULN	>10 × ULN
ALP	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN
GGT	WNL	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-20 × ULN	>20 × ULN

(WNL = within normal limits; ULN = upper limit of normal)

The ULN for various indicators of liver function depends on the assay used, the patient population, and each laboratory's normal range of values for the specified biomarker, but can readily be determined by the skilled practitioner. Exemplary values for normal ranges for a healthy adult population are set forth in Table 2 below. See Cecil Textbook of Medicine, pp. 2317-2341, W.B. Saunders & Co. (1985).

TABLE 2

ALT	8-20 U/L
AST	8-20 U/L
Bilirubin	0.2-1.0 mg/dL
	3.4-17.1 μmol/L
ALP	20-70 U/L
GGT	Men: 9-50 U/L
	Women: 8-40 U/L

Grade 0 levels are characterized by biomarker levels within normal limits (WNL). "Normal" liver function, as used herein, refers to Grade 0 adverse effects. "Abnormal" liver function, as used herein, refers to Grade 1 and above adverse effects.

"Grade 1 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than the ULN and less than or equal to 2.5-times the ULN. Grade 1 liver function abnormalities also include elevations of bilirubin levels greater than the ULN and less than or equal to 1.5-times the ULN.

"Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver function abnormalities also include elevations of bilirubin levels greater than 1.5-times and less than or equal to 3-times the ULN.

"Grade 3 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 5-times and less than or equal to 20-times the ULN. Grade 3 liver function abnormalities also include elevations of bilirubin levels greater than 3-times and less than or equal to 10-times the ULN.

"Grade 4 liver function abnormalities" include elevations in ALT, AST, ALP, or GGT greater than 20-times the ULN. Grade 4 liver function abnormalities also include elevations of bilirubin levels greater than 10 the ULN.

The present disclosure provides methods for treating a patient having idiopathic pulmonary fibrosis and receiving a full target dose of pirfenidone, wherein the full target dose is 2400 or 2403 mg pirfenidone per day. In accordance with the methods, a patient with abnormal liver function is administered a second dose of pirfenidone, wherein the second dose is 1600 or 1602 mg pirfenidone per day until liver function is within normal limits, followed by administering the patient the full target dose of 2400 or 2403 mg pirfenidone per day.

The present disclosure also provides methods for treatment of patients that exhibit Grade 1 abnormality in one or more biomarkers of liver function after pirfenidone administration. The method includes administering to the patient pirfenidone at doses of 2400 mg/day or 2403 mg/day or administering to the patient pirfenidone at doses of 1600 mg/day or 1602 mg/day. Preferably, the patient may be receiving pirfenidone for treatment of idiopathic pulmonary fibrosis. Alternatively, the patient may be suffering from a condition for which pirfenidone administration may be beneficial. Optionally, patients may receive reduced doses or discontinue treatment for a time period, and then resume administration of pirfenidone.

The methods disclosed herein are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described herein (including those described in the examples), unless stated otherwise.

Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

It will be appreciated that the invention provides pirfenidone as a medicament wherein the administration pattern of the medicament comprises administering according to any of the treatment methods described herein.

It will be appreciated that the invention provides pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to any of the treatment regimes as described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration. Pirfenidone is packaged and presented for use in a treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to such treatment regimes. Pirfenidone is administered to the patient in accordance with the treatment regimes as described above. The patient is one who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or to a patient who would benefit from pirfenidone administration.

In particular, the invention includes pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Option-

ally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

It will be appreciated that the invention provides the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration according to any of the treatment regimes as described above with respect to any of the methods. The medicaments manufactured according to this aspect of the invention are for use in treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration in accordance with such treatment regimes. The medicament so manufactured is administered to the patient in accordance with the treatment regimes as described above. The patient is one who has exhibited abnormal biomarkers of liver function after pirfenidone administration as is described above with respect to the methods of the invention for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration.

In particular, the invention includes the use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis or a patient who would benefit from pirfenidone administration, said patient having exhibited a Grade 1 or Grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, wherein said patient is administered pirfenidone at doses of 2400 mg/day or 2403 mg/day. Optionally, prior to administration of pirfenidone at doses of 2400 mg/day or 2403 mg/day, said patient is administered pirfenidone at doses lower than 2400 mg/day for a time period.

In respect of the aspects of the invention relating to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, the preferences expressed with respect to the preferred embodiments of the aspect of the invention relating to a method for administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis apply in the same way. Similarly, the examples relate to pirfenidone for use in treating a patient with idiopathic pulmonary fibrosis, and to use of pirfenidone in the manufacture of a medicament for treating a patient with idiopathic pulmonary fibrosis, as well as to a method for administering pirfenidone to a patient for treating idiopathic pulmonary fibrosis.

EXAMPLES

The following examples are provided for illustration and are not intended to limit the scope of the invention.

Example 1

Pirfenidone Dosing Regimen

Patients begin pirfenidone treatment by receiving escalating doses of pirfenidone over a period of 15 days until the full maintenance dose is reached. Specifically, from days 1 to 7, patients are administered one capsule of 267 mg pirfenidone three times per day. During days 8 to 14, patients receive two capsules of 267 mg pirfenidone three times per day. From day 15 onward, patients are treated with three capsules of 267 mg pirfenidone three times per day. Pirfenidone is administered orally, and each dose should be taken with food. If the patient is unable to eat, then the pirfenidone dose should be taken with milk or juice (excluding grapefruit juice).

Pirfenidone is known to cause photosensitivity reactions; therefore, throughout the treatment period, patients should use sun block that protects against at least UV-A with a sun protective factor (SPF) of 50. In addition, patients should wear appropriate clothing to minimize sun exposure, and if possible, avoid other medications known to cause photosensitivity reactions.

Once the full maintenance dose is reached, pirfenidone is administered orally to patients three times per day to provide a daily dose of 2403 mg pirfenidone. Each of the three doses of 801 mg pirfenidone includes three capsules of 267 mg pirfenidone each. The contents of the pirfenidone 267 mg capsules are pirfenidone (82.15%); croscarmellose sodium (8.15%); microcrystalline cellulose (7.39%); povidine, USP, EP (1.85%); and magnesium stearate (0.46%).

Patients are treated with pirfenidone for up to 72 weeks. Some patients are treated longer than 72 weeks. At weeks 2, 4, 6, 12, and every 12 weeks (±2 weeks) thereafter during the treatment period, with the exception of week 72 and the treatment completion visit, patients are examined and histories are collected as detailed in the steps below.

1. Patient history is collected to include review of adverse effects (AEs) and severe adverse effects (SAEs), use of concomitant medications, use of oxygen, hospitalizations, IPF exacerbations or acute respiratory decompensation, and dosing.

2. Patients receive a physical examination, and vital signs and weight are measured.

3. Pulmonary function is assessed by spirometry before and after administration of bronchodilators. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) are measured.

4. Clinical laboratory tests are performed, including hematology, serum chemistries, pregnancy tests for women of childbearing capacity, and urinalysis with microscopic examination.

5. Questionnaires are administered, including the University of California at San Diego Shortness of Breath Questionnaire (UCSD SOBQ), St. George's Hospital Respiratory Questionnaire (SGRQ), and the World Health Organization Quality of Life (WHO QOL) questionnaire. After week 72, only the UCSD SOBQ and SGRQ are obtained at the scheduled 12 week visits.

Additionally, every 24 weeks starting with Week 12 (for example, weeks 12, 36, and 60), electrocardiogram (ECG) measurements are obtained. ECG data is obtained before administering bronchodilators for the pulmonary function test (PFT) measurements. At the week 36 visit, pharmacokinetic (PK) data is obtained for selected patients.

If a patient experiences a Grade 1 or greater elevation in alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin at baseline or after the start of pirfenidone dosing up to and including week 6, an additional safety chemistry blood test must be obtained between weeks 8 and 10.

Example 2

Modification of Pirfenidone Dosing Regimen in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters,

including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to one capsule of 267 mg pirfenidone three times per day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

At any time after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 capsules per day. After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose also can be re-escalated in a manner consistent with the initial dose escalation, up to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly or every 2 weeks, or every 3 weeks, or every month to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 3

Temporary Discontinuation of Pirfenidone Dosing in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is discontinued. Following discontinuation of the pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. Pirfenidone dosing is discontinued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The pirfenidone dose can be discontinued for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, if the patient has been off drug for 14 days or more, the pirfenidone dose is re-escalated in a manner consistent with the initial dose escalation, up to a dose of 6 or 9 capsules per day, i.e. 1602 mg/day or 2403 mg/day. Alternatively, after AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose is re-instituted at a dose of 6 capsules per day, i.e. 1602 mg/day, and re-escalated after 1 week to the maximum of 9 capsules per day.

Serum chemistry tests are optionally performed at scheduled intervals during the escalation period, e.g. weekly, or every 2 weeks, or every month, to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

Example 4

Modification of Pirfenidone Dosing Regimen to 2 Capsules Three Times per Day in Response to Grade 2 Liver Function Test (LFT) Elevations

Patients are treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, patients exhibiting abnormal liver function test results are candidates for dose modification. As described in Example 1, serum chemistry tests are performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).

If a patient experiences a Grade 2 increase in any one of AST, ALT or bilirubin, the pirfenidone dose is reduced to two capsules of 267 mg pirfenidone three times per day, i.e. 1602 mg/day. While receiving the reduced pirfenidone dose, the patient undergoes additional monitoring of AST, ALT and bilirubin. The reduced pirfenidone dose is continued at least until AST, ALT and bilirubin are all Grade 1 or within normal limits (Grade 0). The reduced pirfenidone dose can be administered for a period of time after AST, ALT and bilirubin have reached Grade 1 or Grade 0.

After 1 week of treatment at 1602 mg/day, if AST, ALT and bilirubin have resolved to Grade 0 or Grade 1, the pirfenidone dose can be re-escalated to the maximum of 9 capsules per day, i.e. 2403 mg.

Example 5

No Modification of Pirfenidone Dosing Regime in Response to a Grade 1 or Grade 2 Liver Function Test (LFT) Elevations

Patients were treated with pirfenidone in accordance with Example 1. During the course of pirfenidone treatment, some patients exhibited abnormal liver function test results. As described in Example 1, serum chemistry tests were performed at scheduled intervals during the treatment period to monitor various parameters, including biomarkers of liver function such as alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphate (ALP), and gamma-glutamyl transferase (GGT).

If a patient exhibited a Grade 1 or Grade 2 increase in any one of AST, ALT, or bilirubin, the pirfenidone dose was not reduced for some patients. The patient continued to receive the full target dose of 2403 mg/day. While receiving the full target dose, the patient was monitored for AST, ALT, and bilirubin levels.

Example 6

Incidence of Liver Function Abnormality and Dosing Regimen Response

Grade 1 Abnormalities in Liver Function

In a study of 345 patients with idiopathic pulmonary fibrosis receiving pirfenidone three times per day for a total daily dose of 2403 mg/day, 49 patients without a baseline liver function abnormality exhibited a Grade 1 elevation in AST or

ALT levels after pirfenidone administration. Of the 49 patients, three patients with a Grade 1 liver function test elevation had a treatment emergent adverse event of increased AST or ALT. In one patient, study drug dose was reduced to 1602 mg/day for the remainder of study participation (from Day 51 to Day 602), and the Grade 1 AST or ALT abnormality returned to Grade 0. For the second patient, study drug dose was reduced to 1602 mg/day and then increased to 2403 mg/day for remainder of study participation, and ALT returned to Grade 0. The third patient had study drug dose reduced to 801 mg/day, ultimately completing study at 1602 mg/day, at which time ALT returned to Grade 0. The remaining patients (46 patients) received no dose modification.

Grade 2 Abnormalities in Liver Function

Fifteen patients developed a Grade 2 liver function test abnormality in AST and/or ALT levels after pirfenidone administration of 2403 mg/day. Of the fifteen patients, 12 had reported treatment emergent adverse events of increased AST or ALT or hepatitis. The liver function test elevations for the remaining three patients were not documented as an adverse event (discussed below).

Of the twelve patients, two patients received continued administration of pirfenidone at the full daily dose of 2403 mg/day. The liver function test of one patient resolved to a Grade 0. The other patient had a history of steatosis and a Grade 1 abnormality prior to pirfenidone treatment and underwent a dose reduction for unrelated reasons (rash and diarrhea), not for abnormal liver function tests, and ended the study with a Grade 1 elevation.

Two patients had a temporary dose reduction or a temporary discontinuation of pirfenidone, and were rechallenged and escalated back to full dose. They completed the study at the full dose of 2403 mg/day with normal liver enzymes.

Seven patients underwent a permanent dose reduction of pirfenidone, in some cases after a temporary discontinuation of drug; by completion of the study, 3 patients were receiving 801 mg/day and 4 patients were receiving 1602 mg/day. With the exception of one patient, rechallenge with a higher dose was not attempted with these patients. The patient that was rechallenged received the full dose of 2403 mg/day, but the dose was later reduced due to a recurrence of Grade 2 elevation in ALT levels. All seven patients completed the study with resolution of transaminases, except for one patient that had a Grade 1 elevation at study completion.

One patient discontinued treatment due to abnormal liver function tests in AST and/or ALT levels. The dose for this patient was initially decreased to 1602 mg/day, then discontinued, and then resumed at 1602 mg/day. For this patient, however, treatment was permanently discontinued because a Grade 2 elevation of AST coincided with a Grade 3 ALT elevation in liver function tests.

Of the three patients whose liver function test elevations were not documented as an adverse event, one had Grade 1 AST and ALT elevation at baseline, and experienced a Grade 1 elevation of AST at the last documented assessment. This patient received no dose modification after a Grade 2 elevation in AST and/or ALT levels. A second patient with a Grade 2 transaminase elevation had treatment temporarily discontinued for acute cerebral artery occlusion. Transaminase levels returned to normal once the dose was escalated back to 2403 mg/day, and the patient completed the study on full dose with normal transaminases. The third patient had no liver function test abnormalities while on treatment until Day 422, then the patient experienced a Grade 2 AST and Grade 1 ALT elevation with respiratory failure due to IPF. Study drug was discontinued the same day for respiratory failure. The patient was hospitalized on Day 434 and died on Day 439 due to respiratory failure.

Grade 3 Abnormalities in Liver Function

Four patients developed Grade 3 liver function abnormality in AST and/or ALT levels after pirfenidone administration, all of who had a treatment emergent adverse event of either increased AST and/or ALT. Two of the four patients discontinued study drug for elevated liver function tests. In both instances, the abnormalities had not resolved, with Grade 2 and Grade 3 abnormalities last documented. The two other patients had Grade 1 abnormalities at screening and/or baseline. One patient discontinued for lung transplant at which time the last documented values showed a Grade 1 abnormality. The other patient interrupted study drug (investigator decision), and subsequently discontinued study drug (sponsor decision). The AST and ALT elevations had normalized at the last documented value.

The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art. Although methods have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used.

All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

What is claimed is:

1. A method of treating a patient in need of pirfenidone and suffering from a Grade 2 abnormality in a liver function biomarker selected from the group consisting of alanine transaminase (ALT) and aspartate transaminase (AST) and wherein the abnormality occurs after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient at doses of at least 1600 mg/day or 1602 mg/day.

2. The method of claim **1** comprising (a) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day.

3. The method of claim **2** wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 2400 mg/day.

4. The method of claim **1** further comprising, prior to step (a), discontinuing the first administration pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

5. The method of claim **2** wherein the second administration further comprises, prior to step (a), administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

6. The method of claim **2** wherein the second administration further comprises, prior to step (a), administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits, followed by administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

7. The method of claim **2** further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

8. The method of claim **1**, wherein the pirfenidone is administered three times per day with food.

9. The method of claim **1** further comprising the step of measuring one or more of AST and ALT.

10. The method according to claim **1**, wherein the second administration of pirfenidone further comprises, prior to step (a), administering to said patient pirfenidone at doses lower than 1600 mg/day.

11. The method according to claim **10**, wherein the second administration of pirfenidone further comprises, prior to step (a), discontinuation of pirfenidone administration to the patient for about one week or until biomarkers of liver function are within normal limits.

12. The method according to claim **1**, wherein the second administration of pirfenidone further comprises, prior to step (a), about 800 mg/day or 801 mg/day to the patient for about one week, or until biomarkers of liver function are within normal limits.

13. The method according to claim **10**, wherein the pirfenidone is administered three times per day with food.

14. The method according to claim **10** further comprising measuring one or more of ALT and AST during administration of pirfenidone.

15. The method of claim **2** wherein the second administration further comprises, prior to step (a), administering about 800 mg/day or 801 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits, followed by administering about 1600 mg/day or 1602 mg/day pirfenidone for about one week, or until biomarkers of liver function are within normal limits.

16. The method of claim **1**, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 1800 mg/day.

17. The method of claim **1**, wherein the patient suffers from fibrosis.

18. The method of claim **1**, wherein the patient suffers from a condition selected from the group consisting of renal fibrosis, vascular fibrosis and scleroderma.

19. The method of claim **1**, wherein the patient suffers from idiopathic pulmonary fibrosis.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,609,701 B2
APPLICATION NO. : 13/128569
DATED : December 17, 2013
INVENTOR(S) : Williamson Z. Bradford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

In the References Cited:
In Item (56), U.S. Patent Documents, 2nd column, "1,000,828 A1 1/2011 Blatt et al.," should be --2011/0008289 1/2011, Blatt et al.--

Signed and Sealed this
Nineteenth Day of June, 2018

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT 13

US008648098B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,648,098 B2**
(45) **Date of Patent: *Feb. 11, 2014**

(54) **PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450**

(75) Inventors: **Williamson Ziegler Bradford**, Ross, CA (US); **Javier Szwarcberg**, San Francisco, CA (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 16 days.

This patent is subject to a terminal disclaimer.

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USPC **514/350**; 514/354; 514/345

(58) **Field of Classification Search**
USPC 514/350, 354, 345
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with pirfenidone and CYP inducers, such as smoking.

15 Claims, 1 Drawing Sheet

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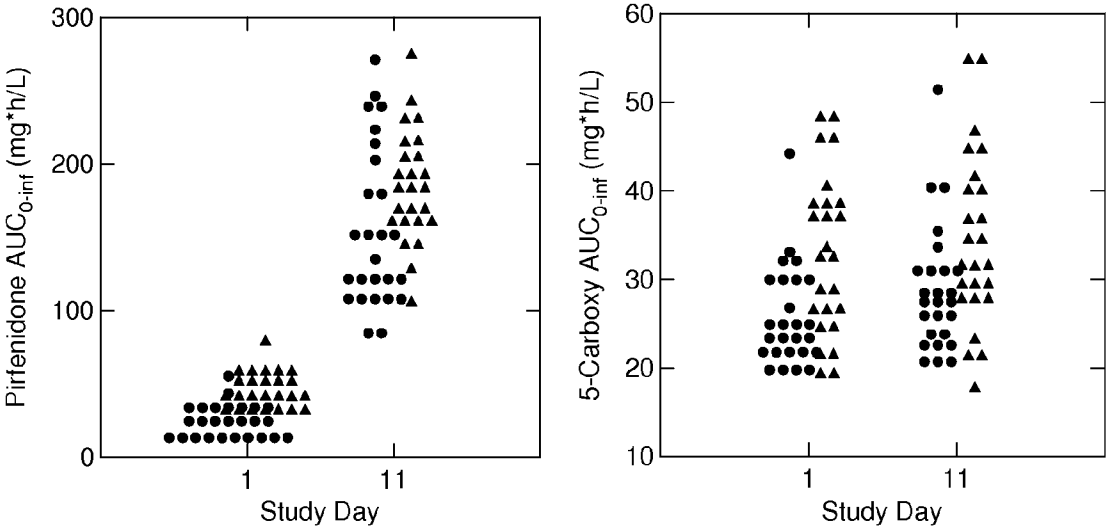
Pirfenidone AUC_{0-inf} (mg*h/L)
300
200
100
0
1
11
Study Day
5-Carboxy AUC_{0-inf} (mg*h/L)
60
50
40
30
20
10
1
11
Study Day

PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450

CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. patent application Ser. No. 12/684,543 filed Jan. 8, 2010, now U.S. Pat. No. 8,084,475, issued Dec. 27, 2011, which in turn claimed the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Ser. No. 61/266,753 filed Dec. 4, 2009. The entire disclosure of each of these applications is hereby incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy, involving increased effectiveness of pirfenidone through the avoidance of inducers of cytochrome P450 (CYP) proteins which metabolize pirfenidone. More specifically, the invention is related to methods of administering pirfenidone therapy involving the avoidance of inducers of CYP1A2.

BACKGROUND

Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Pirfenidone has anti-fibrotic properties via: decreased TGF-β expression, decreased TNF-α expression, decreased PDGF expression, and decreased collagen expression.

Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy (>10%) are nausea, rash, dyspepsia, dizziness, vomiting, and photosensitivity reaction, and anorexia. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related. The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at higher doses. In comparison to studies performed to determine the effects of pirfenidone therapy on patients, relatively little was known about the effects of pirfenidone when used in combination with other therapeutics.

Pirfenidone has been shown to be metabolized by isoforms of the cytochrome P450 (CYP) protein (Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008). Specifically, several CYP isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Activity of CYPs in patients who smoke is significantly increased over their non-smoking counterparts.

SUMMARY

The invention disclosed herein is based upon the discovery of an adverse reaction in patients taking pirfenidone who also smoke.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient can have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered can be a daily dosage of 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage can be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone can be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day can be administered as follows: 800 mg or 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration of an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone ("CYP inducer"). In some cases, the use or administration of the CYP inducer is avoided for at least 2.5 hours after administration of the pirfenidone. In various cases, the CYP inducer that metabolizes pirfenidone is CYP1A2. Induction of CYP1A2 activity has been reported as a consequence of cigarette smoking, dietary factors, several drugs, chronic hepatitis, and exposure to polybrominated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Landi et al. IARC Sci Publ. 1999; (148): 173-95. In addition to, or in the alternative to smoking, the CYP inducers to be discontinued or avoided can be selected from the group consisting of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, and ritonavir. The CYP inducers to be discontinued or avoided can additionally or alternatively be charbroiled foods and/or cruciferous vegetables. The CYP inducers to be discontinued or avoided can additionally or alternatively be selected from the group consisting of phenobarbital, phenytoin, primidone, and St. John's wort.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing use or administration of a CYP inducer that metabolizes pirfenidone to avoid an adverse drug interaction and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient discontinues use or administration of the CYP inducer concurrent with starting administration of pirfenidone. In another embodiment, the use or administration of the CYP inducer is discontinued within at least 3 days to within 4 weeks prior to or after starting pirfenidone therapy. This time period can, for example, permit adequate time for tapering and withdrawal without adverse effects, if such tapering is useful for the CYP inducer. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient

with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of a CYP inducer that metabolizes pirfenidone and administering a therapeutically effective amount of pirfenidone. In some embodiments, when the patient is a smoker (e.g., has not quit smoking), the patient avoids smoking for at least 2.5 hours after administration of pirfenidone.

In some embodiments, the patient is a smoker and discontinues smoking. In various embodiments, the method further comprises administering to the smoker patient a nicotine replacement therapy or other smoking cessation therapy. The nicotine replacement therapy can comprise one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. The method can additionally or alternatively comprise administering buproprion hydrochloride (Zyban®) or varenciline (Chantix®).

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone comprises administering a therapeutically effective amount of pirfenidone to the patient, and any one, two, three, or more of the following:

(a) advising the patient that CYP inducers that metabolize pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

For the patient who smokes, the method can further comprise advising the patient to consider nicotine replacement therapy in place of smoking and/or encouraging the patent to stop smoking before treatment with pirfenidone.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 5 O-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis, irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leu-

kemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

Preferably, a CYP inducer that metabolizes pirfenidone is one that decreases plasma AUC values of pirfenidone by 30% or more. A strong CYP inducer that metabolizes pirfenidone is preferably one that decreases plasma AUC values of pirfenidone by 50% or more.

In some embodiments, the effect of a CYP inducer on metabolism of pirfenidone in an individual patient is normalized based upon the patient's body surface area (BSA). BSA can be calculated using a patient's height and weight. In specific embodiments, the normalized effect of the CYP inducer is an at least 30% or at least 50% decrease in AUC values of pirfenidone.

CYP Inducers

In any of the embodiments described herein, including but not limited to the treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to smoking but also to any other activity or drug that induces a CYP that metabolizes pirfenidone, including CYP1A2. The CYP inducer can be charbroiled meats or cruciferous vegetables. Additionally or alternatively, the CYP inducer can be one or more of phenobarbital, phenytoin, primidone, or St. John's wort. Additionally or alternatively, the CYP inducer can be one or more of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, or ritonavir.

Avoiding or Discontinuing Administration of a CYP Inducer to Avoid Adverse Drug Interactions with Pirfenidone

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration of a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2). In some embodiments, the CYP inducer is smoking (e.g., inhalation of the smoke of burning organic material, particularly tobacco or marijuana), as the result of polycyclic aromatic hydrocarbons which are contained in such smoke.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing administration of a drug that is a CYP1A2 inducer to avoid an adverse drug interaction, and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of a CYP inducer and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the CYP inducer is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the CYP inducer is discontinued within at least 3 days to 4 weeks prior to or after starting pirfenidone therapy. This time period, for example, can permit adequate time for tapering and withdrawal without adverse effects.

In embodiments in which the CYP inducer is discontinued to avoid an adverse drug interaction, the CYP inducer preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP inducer.

In embodiments where the CYP inducer cannot be or is not discontinued prior to pirfenidone therapy, the CYP inducer is preferably discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

In embodiments in which the patient discontinues smoking to avoid an adverse drug interaction, the smoking preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the smoking.

In embodiments in which the patient cannot or does not discontinue smoking prior to pirfenidone therapy, the smoking preferably is discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least

11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

The patient preferably avoids use of the CYP inducer to allow sufficient time for the dose of pirfenidone to be substantially absorbed by the patient's body. Pirfenidone has a serum half life in humans of about 2 to 3 hours. Thus, the patient preferably avoids use of the CYP inducer, for example, for at least 2.5 hours after administration of the pirfenidone. The patient can also avoid use of the CYP inducer for at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone. For example in embodiments where the patient is a smoker, the patient can avoid smoking for at least 2.5 hours, at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone.

Selecting an Alternative Drug or Therapy to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP inducer, such as an inducer of CYP1A2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP inducer.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient who smokes and in need of pirfenidone therapy, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering a stop-smoking therapy, for example nicotine replacement therapy. The nicotine replacement therapy can be any nicotine source and can include a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. Additionally or alternatively, the method can include administration of a drug to assist in smoking cessation. Non-limiting examples of smoking cessation drugs include, but are not limited to, bupropion hydrochloride (Zyban®) or varenicline (Chantix®).

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that administration of pirfenidone and smoking can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In some embodiments, the patient is advised that use of pirfenidone in patients who smoke can alter the therapeutic effect or adverse reaction profile of pirfenidone. In some embodiments, the patient is advised that use of pirfenidone in patients who smoke resulted in a 50% decrease is exposure to pirfenidone.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2) is provided wherein the patient is administered a therapeutically effective amount of the inducer and a dosage of pirfenidone that is increased relative to a patient not taking the inducer. In some aspects, such an increased dosage of pirfenidone is greater than 2400 mg/day. For example, the increased dosage is about 2670 mg per day, 2937 mg per day, 3204 mg per day, 3471 mg per day, or 3738 mg per day (e.g., 10, 11, 12, 13, or 14 capsules per day where each capsule is approximately 267 mg). In some embodiments, the patient is already being administered the CYP inducer. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is increased prior to administration of the CYP inducer.

In embodiments wherein the patient avoids or discontinues use of the CYP inducer, preferably the amount of pirfenidone being administered is 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 2400 mg to about 3800 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2670 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2937 mg, about 2950 mg, about 3000 mg, about 3050 mg, about 3100 mg, about 3150 mg, about 3200 mg, about 3204 mg, about 3250 mg, about 3300 mg, about 3350 mg, about 3400 mg, about 3450 mg, about 3471 mg, about 3500 mg, about 3550 mg, about 3600 mg, about 3650 mg, about 3700 mg, about 3738 mg, about 3750 mg, and about 3800 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP inducer that metabolizes pirfenidone to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is an inducer of CYP1A2 to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is reduced by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 inducer to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day or more.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) advising the patient that strong CYP inducers that metabolize pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism. In some embodiments, the information or recommendation may include that co-administration of pirfenidone with inducers of CYP that metabolize pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that administration of pirfenidone to a patient who smokes can alter the therapeutic effect or adverse reaction profile of pirfenidone. In other embodiments, the information or recommendation may include that co-administration of pirfenidone with CYP1A2 inducers can alter the therapeutic effect or adverse reaction profile of pirfenidone.

In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be avoided. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be discontinued. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be used with caution.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be construed as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

An open-label Phase 1 study was performed to determine the impacts of a strong CYP1A2 inhibitor and a CYP1A2 inducer on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design.

The study was a Phase 1, open-label, parallel-group study designed to investigate the impact of CYP1A2 inhibition and induction on the pharmacokinetics and safety of pirfenidone in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

Days 2-4: fluvoxamine 50 mg at bedtime

Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)

Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9(1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model

was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results.

Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5 carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5 carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. **1**. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5 carboxy pirfenidone AUC_{0-28}.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a]p-value < 0.00001 (paired t-test)

[b]p-value = 0.168 (paired t-test)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5 carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)
Non-smokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; SD = standard deviation.

The relationship between smoking status and exposure to pirfenidone and 5 carboxy pirfenidone were examined using the $AUC_{0-\infty}$ estimates from Day 1. Due to the high degree of correlation between BSA and other demographic variables (sex, creatinine clearance (mL/min) (CLcr), age) and the pharmacologic plausibility of a relationship between exposure and body size, $AUC_{0-\infty}$ was first normalized to body surface area before application of multiple linear regression. Smoking status was the only significant predictor of the variability in pirfenidone $AUC_{0-\infty}$ normalized to BSA. Smoking status had a pronounced effect in that smokers would be predicted to have a ~50% drop in $AUC_{0-\infty}$ after accounting for differences in BSA. For 5 carboxy-pirfenidone $AUC_{0-\infty}$, the only significant predictors were age and CLcr.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition and/or induction on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine. Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

Administration of pirfenidone to patients who smoke resulted in a significant decrease in exposure ($AUC_{0-\infty}$) to pirfenidone, and was, on average, about 50% the exposure of pirfenidone in patients that didn't smoke.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

Examples of Embodiments of the Invention Include

1. A method of administering pirfenidone therapy to a patient in need thereof comprising administering to the patient a therapeutically effective amount of pirfenidone and avoiding use or administration of a strong inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone.

2. The method of paragraph 1, wherein the strong inducer of CYP is avoided for at least 2.5 hours after administration of the pirfenidone.

3. The method of paragraph 2, wherein the patient is a smoker and avoids smoking for at least 2.5 hours after administration of the pirfenidone.

4. A method of administering pirfenidone therapy to a patient in need thereof, wherein the patient is receiving an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone, comprising discontinuing use or administration of the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone to avoid an adverse drug reaction and administering a therapeutically effective amount of pirfenidone.

5. The method of paragraph 4, wherein the inducer of CYP is discontinued prior to administration of pirfenidone.

6. The method of paragraph 5, wherein the inducer of CYP is discontinued within 4 weeks prior to the administration of pirfenidone.

7. The method of paragraph 4, wherein the inducer of CYP is discontinued concurrent to administration of pirfenidone.

8. The method of paragraph 1 or 4, wherein the patient is a smoker, comprising discontinuing smoking.

9. The method of paragraph 8, further comprising administering a nicotine replacement therapy to the patient.

10. The method of paragraph 9, wherein the nicotine replacement therapy comprises one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler.

11. The method of paragraph 8, further comprising administering to the patient bupropion hydrochloride (Zyban) or varenicline (Chantix).

12. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and any one or more of the following:

(a) advising the patient that strong inducers of a cytochrome P450 (CYP) that metabolizes pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with an inducer of CYP that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

13. The method of paragraph 12, wherein the patient is a smoker, and further comprising advising the patient to consider nicotine replacement therapy in place of smoking.

14. The method of any one of paragraphs 12-13, further comprising encouraging patients who smoke to stop smoking before treatment with pirfenidone.

15. The method of any one of paragraphs 1-14, wherein the therapeutically effective amount of pirfenidone is a total daily dose of about 2400 mg.

16. The method of any one of paragraphs 1-15, wherein the pirfenidone is administered three times a day, at a total daily dose of about 2400 mg.

17. The method of any one of paragraphs 1-16, wherein the CYP comprises CYP1A2.

18. The method of any one of paragraphs 1-17, wherein the patient suffers from idiopathic pulmonary fibrosis (IPF).

19. The method of any one of paragraphs 1-18, wherein the pirfenidone is co-administered with food.

20. The method of any one of paragraphs 1-19, wherein the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone is one or more of carbamazepine, charbroiled food, cigarette smoke, cruciferous vegetables, esomeprazole, griseofulvin, insulin, lansprazole, marijuana smoke, moricizine, omeprazole, phenobarbital, phenytoin, primidone rifampin, ritonavir, smoking, and St. John's wort.

What is claimed is:

1. A method of increasing the effectiveness of pirfenidone therapy by avoiding decreased exposure to pirfenidone, in a patient in need of pirfenidone therapy who is a smoker, comprising discontinuing smoking to decrease levels of cytochrome P450 1A2 (CYP1A2) induction and then administering a therapeutically effective amount of pirfenidone.

2. The method of claim **1**, further comprising advising the patient that smoking causes a 50% decrease in pirfenidone exposure compared to patients that do not smoke.

3. The method of claim **1**, wherein the patient has idiopathic pulmonary fibrosis.

4. The method of claim **1**, wherein the therapeutically effective amount of pirfenidone is 2403 mg per day.

5. The method of claim **1**, comprising avoiding smoking during pirfenidone therapy to avoid reduced exposure to pirfenidone.

6. The method of claim **5**, wherein the patient has idiopathic pulmonary fibrosis.

7. The method of claim **5**, wherein the therapeutically effective amount of pirfenidone is 2403 mg per day.

8. The method of claim **5**, further comprising advising the patient that smoking causes a 50% decrease in pirfenidone exposure compared to patients that do not smoke.

9. A method of increasing the effectiveness of pirfenidone therapy by avoiding decreased exposure to pirfenidone, in a patient in need of pirfenidone therapy that is receiving a strong CYP1A2 inducer, comprising discontinuing the strong CYP1A2 inducer to decrease the levels of CYP1A2 induction, and then administering a therapeutically effective amount of pirfenidone.

10. The method of claim **9** wherein the patient has idiopathic pulmonary fibrosis.

11. The method of claim **9** wherein the therapeutically effective amount of pirfenidone is 2403 mg per day.

12. The method of claim **10** wherein the therapeutically effective amount of pirfenidone is 2403 mg per day.

13. The method of claim **9**, wherein the CYP1A2 inducer is discontinued within at least three weeks prior to pirfenidone administration.

14. The method of claim **1**, wherein the smoker discontinues smoking within at least three weeks prior to pirfenidone administration.

15. The method of claim **3**, wherein the therapeutically effective amount of pirfenidone is 2403 mg per day.

* * * * *

EXHIBIT 14

US008754109B2

(12) **United States Patent**
Bradford et al.

(10) **Patent No.: US 8,754,109 B2**
(45) **Date of Patent: *Jun. 17, 2014**

(54) **PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450**

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This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.**
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(58) **Field of Classification Search**
USPC 514/350, 354, 345
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to methods involving avoiding adverse drug interactions with pirfenidone and CYP inducers, such as smoking.

19 Claims, 1 Drawing Sheet

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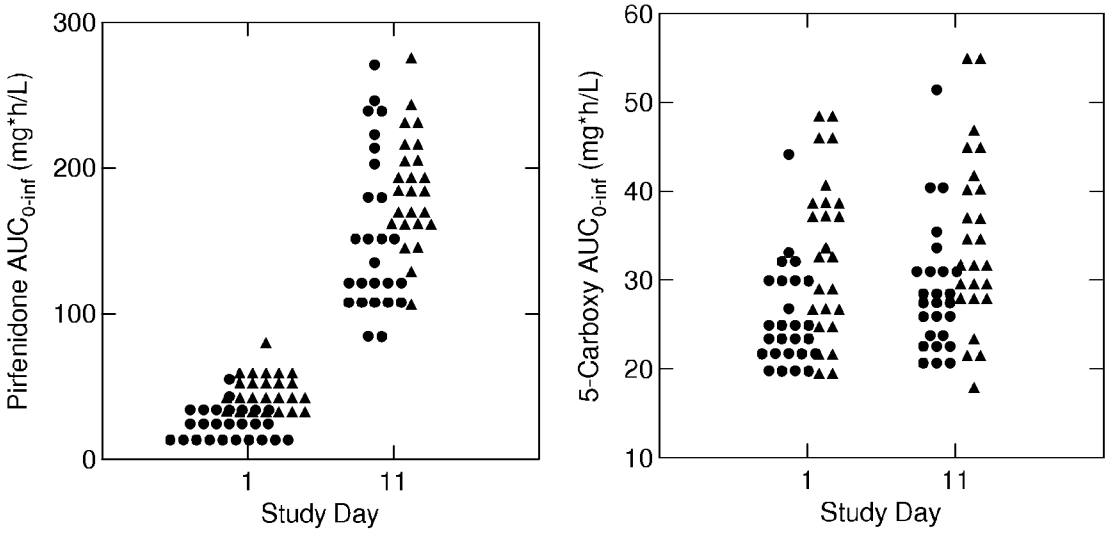
Pirfenidone AUC_{0-inf} (mg*h/L)
300
200
100
0
1
11
Study Day
5-Carboxy AUC_{0-inf} (mg*h/L)
60
50
40
30
20
10
1
11
Study Day

PIRFENIDONE THERAPY AND INDUCERS OF CYTOCHROME P450

FIELD OF THE INVENTION

The invention relates to improved methods of administering pirfenidone therapy, involving increased effectiveness of pirfenidone through the avoidance of inducers of cytochrome P450 (CYP) proteins which metabolize pirfenidone. More specifically, the invention is related to methods of administering pirfenidone therapy involving the avoidance of inducers of CYP1A2.

BACKGROUND

Pirfenidone is small drug molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. It is a non-peptide synthetic molecule with a molecular weight of 185.23 daltons. Its chemical elements are expressed as $C_{12}H_{11}NO$, and its structure and synthesis are known. Pirfenidone is manufactured commercially and being evaluated clinically as a broad-spectrum anti-fibrotic drug. Pirfenidone has anti-fibrotic properties via: decreased TGF-β expression, decreased TNF-α expression, decreased PDGF expression, and decreased collagen expression.

Pirfenidone is being investigated for therapeutic benefits to patients suffering from fibrosis conditions such as Hermansky-Pudlak Syndrome (HPS) associated pulmonary fibrosis and idiopathic pulmonary fibrosis (IPF). Pirfenidone is also being investigated for a pharmacologic ability to prevent or remove excessive scar tissue found in fibrosis associated with injured tissues including that of lungs, skin, joints, kidneys, prostate glands, and livers. Published and unpublished basic and clinical research suggests that pirfenidone may safely slow or inhibit the progressive enlargement of fibrotic lesions, and prevent formation of new fibrotic lesions following tissue injuries.

As an investigational drug, pirfenidone is provided in tablet and capsule forms principally for oral administration. Various formulations have been tested and adopted in clinical trials and other research and experiments. The most common adverse reactions or events associated with pirfenidone therapy (>10%) are nausea, rash, dyspepsia, dizziness, vomiting, and photosensitivity reaction, and anorexia. Many of these effects can interfere with everyday activities and quality of life. These effects appear to be dose related. The adverse reactions associated with pirfenidone therapy are exacerbated when pirfenidone is administered at higher doses. In comparison to studies performed to determine the effects of pirfenidone therapy on patients, relatively little was known about the effects of pirfenidone when used in combination with other therapeutics.

Pirfenidone has been shown to be metabolized by isoforms of the cytochrome P450 (CYP) protein (Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008). Specifically, several CYP isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

Activity of CYPs in patients who smoke is significantly increased over their non-smoking counterparts.

SUMMARY

The invention disclosed herein is based upon the discovery of an adverse reaction (reduced pirfenidone exposure) in patients taking pirfenidone who also smoke.

The invention generally relates to improved methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. In any of the aspects or embodiments, the patient can have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered can be a daily dosage of at least 1800 mg, or 2400 mg or 2403 mg per day. In any of the aspects of the invention, the daily dosage can be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the invention, the pirfenidone can be administered with food. For example, the daily dosage of 2400 mg or 2403 mg pirfenidone per day can be administered as follows: 800 mg or 801 mg taken three times a day, with food.

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration of an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone ("CYP inducer"). In some cases, the use or administration of the CYP inducer is avoided for at least 2.5 hours after administration of the pirfenidone. In various cases, the CYP that metabolizes pirfenidone is cytochrome P450 1A2 (CYP1A2). In some embodiments, the CYP inducer is a strong CYP1A2 inducer. Induction of CYP1A2 activity has been reported as a consequence of cigarette smoking, dietary factors, several drugs, chronic hepatitis, and exposure to polybrominated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Landi et al. IARC Sci Publ. 1999; (148):173-95. In addition to, or in the alternative to smoking, the CYP inducers to be discontinued or avoided can be selected from the group consisting of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, and ritonavir. The CYP inducers to be discontinued or avoided can additionally or alternatively be charbroiled foods and/or cruciferous vegetables. The CYP inducers to be discontinued or avoided can additionally or alternatively be selected from the group consisting of phenobarbital, phenyloin, primidone, and St. John's wort.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, comprising discontinuing use or administration of an inducer of a CYP that metabolizes pirfenidone, e.g. a strong CYP1A2 inducer, to avoid an adverse drug interaction (e.g. or to avoid reduced exposure to pirfenidone) and administering a therapeutically effective amount of pirfenidone. In one embodiment, the patient discontinues use or administration of the CYP inducer concurrent with starting administration of pirfenidone. In another embodiment, the use or administration of the CYP inducer is discontinued within at least 3 days to within 4 weeks prior to or after starting pirfenidone therapy. This time period can, for example, permit adequate time for tapering and withdrawal without adverse effects, if such tapering is useful for the CYP inducer. In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, the invention provides an improvement that comprises avoiding or discontinuing administration of a CYP inducer that metabolizes pirfenidone and administering a therapeutically effective amount of pirfenidone. In some embodiments, when the patient is a smoker (e.g., has not quit smoking), the patient avoids smoking for at least 2.5 hours after administration of pirfenidone.

In some embodiments, the patient is a smoker who is discontinuing smoking. In various embodiments, the method or use further comprises administering to the smoker patient a nicotine replacement therapy or other smoking cessation therapy. The nicotine replacement therapy can comprise one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. The method can additionally or alternatively comprise administering buproprion hydrochloride (Zyban®) or varenciline (Chantix®).

Thus, an aspect of the invention provides pirfenidone for use in treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding, discontinuing, or contraindicating concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2). The concomitant use or co-administration is avoided, discontinued or contraindicated, in order to avoid the reduced (decreased) exposure to pirfenidone, or the potential for reduced exposure to pirfenidone. Administration of pirfenidone in patients that concomitantly smoke results in about 50% decrease in pirfenidone exposure ($AUC_{0-\infty}$), on average, compared to patients that do not smoke. It is understood that any of the aspects or embodiments or examples described herein with respect to methods of treatment apply to this aspect of the invention that provides pirfenidone for use in treating a patient. For example, the patient may be a patient with IPF, and the therapeutically effective amount administered may be at least 1800 mg, or 2400 or 2403 mg per day. As another example, the strong CYP1A2 inducer may be any known in the art or any of the strong CYP1A2 inducers described herein.

Similarly, a further related aspect of the invention provides the use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding, discontinuing, or contraindicating concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone. It is understood that any of the aspects or embodiments or examples described herein with respect to methods of treatment apply to this aspect of the invention that provides for the use of pirfenidone in manufacture of a medicament. For example, the patient may be a patient with IPF, and the therapeutically effective amount administered may be at least 1800 mg, or, more specifically 2400 or 2403 mg per day. As another example, the strong CYP1A2 inducer may be any known in the art or any of the strong CYP1A2 inducers described herein.

As used herein, "concomitant use" is understood to be interchangeable with concurrent administration or co-administration. Thus, the terms are understood to encompass administration simultaneously, or at different times, and by the same route or by different routes, as long as the two agents are given in a manner that allows both agents to be affecting the body at the same time. For example, concomitant use can refer to a medication concomitantly administered, whether prescribed by the same or a different practitioner, or for the same or a different indication.

In some embodiments, the patient is a patient in need of therapy with a CYP1A2 inducer, e.g. a strong CYP1A2 inducer. In some embodiments, the patient is a patient who was or is a smoker. In some embodiments, the patient is a patient who was a smoker immediately prior to starting administration of pirfenidone. In some embodiments, the patient in need of pirfenidone therapy is a patient avoiding concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2). In some embodiments, the patient is a patient who has been or is a smoker, and the patient is avoiding smoking when using pirfenidone. In some embodiments, the patient in need of pirfenidone therapy is a smoker who is discontinuing smoking to avoid reduced exposure to pirfenidone. In exemplary embodiments, the patient discontinues smoking within 4 weeks prior to the administration of pirfenidone, or concurrent with the start of administration of pirfenidone. It is understood that any of the aspects or embodiments or examples described herein with respect to methods of treatment apply to this aspect of the invention that provides for characterization of the patients to be treated with pirfenidone.

In yet other aspects, a method of administering pirfenidone therapy to a patient in need of pirfenidone comprises administering a therapeutically effective amount of pirfenidone to the patient, and any one, two, three, or more of the following:

(a) advising the patient that CYP inducers that metabolize pirfenidone should be avoided or discontinued or that inducers of CYP that metabolize pirfenidone are contraindicated;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

For the patient who smokes, the method can further comprise advising the patient to consider nicotine replacement therapy in place of smoking and/or encouraging the patent to stop smoking before treatment with pirfenidone.

In some embodiments, a method of reducing toxicity of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of improving safety of pirfenidone treatment in a patient is provided comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

In some embodiments, a method of reducing adverse drug interaction with pirfenidone treatment in a patient (e.g., to avoid reduced exposure to pirfenidone) is provided, comprising administering a therapeutically effective amount of pirfenidone to the patient and advising the patient of any of the foregoing advice.

Thus, in some embodiments, the concomitant use or co-administration of strong CYP1A2 inducers is avoided, discontinued, or contraindicated in order to

(a) avoid the potential for the altered therapeutic effect of pirfenidone, and/or

(b) avoid the reduced exposure or potential for reduced exposure, and/or

(c) reduce toxicity of pirfenidone treatment, and/or

(d) improve safety of pirfenidone treatment, and/or

(e) reduce adverse drug interaction associated with pirfenidone treatment.

In some embodiments, smoking is avoided, discontinued, or contraindicated in order to avoid the 50% decrease in pirfenidone exposure compared to patients that do not smoke.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** depicts a symmetrical dot plot of $AUC_{0-\infty}$ estimates by study day—circles indicate smokers, triangles indicate nonsmokers.

DETAILED DESCRIPTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 (approx. 48%) with multiple other CYPs contributing as well (each <13%) (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2). Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 50-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, the term "avoid" and forms thereof are contemplated to have as alternatives the terms abstain, desist, forbear, and refrain, and forms thereof. As used herein, the term "discontinue" and forms thereof are contemplated to have as alternatives the terms cease, stop, suspend, and quit.

Preferably, a CYP inducer that metabolizes pirfenidone or a strong inducer of CYP1A2 is one that decreases plasma AUC values of pirfenidone by 30% or more. A strong CYP inducer that metabolizes pirfenidone, e.g., a strong inducer of CYP1A2, is preferably one that decreases plasma AUC values of pirfenidone by 50% or more.

In some embodiments, the effect of a CYP inducer on metabolism of pirfenidone in an individual patient is normalized based upon the patient's body surface area (BSA). BSA can be calculated using a patient's height and weight. In specific embodiments, the normalized effect of the CYP inducer is an at least 30% or at least 50% decrease in AUC values of pirfenidone.

CYP Inducers

In any of the embodiments described herein, including but not limited to the pirfenidone for use in treating a patient, the use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, treatment methods involving the advice, warnings, discontinuation or dose titration downwards, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the pirfenidone, uses, methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to smoking but also to any other activity or drug that induces a CYP that metabolizes pirfenidone, including CYP1A2. The CYP inducer can be charbroiled meats or cruciferous vegetables. Additionally or alternatively, the CYP inducer can be one or more of phenobarbital, phenyloin, primidone, or St. John's wort. Additionally or alternatively, the CYP inducer can be one or more of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, or ritonavir.

Avoiding, Discontinuing or Contraindicating Administration of a CYP Inducer to Avoid Adverse Drug Interactions with Pirfenidone (E.G., to Avoid Reduced Exposure to Pirfenidone)

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy or pirfenidone for use in treating a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and avoiding use or administration (e.g., concomitant use or co-administration) of a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2). In some embodiments, the CYP inducer is smoking (e.g., inhalation of the smoke of burning organic material, particularly tobacco or marijuana), as the result of polycyclic aromatic hydrocarbons which are contained in such smoke.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy, or pirfenidone for use in treating a patient in need of pirfenidone therapy, comprising discontinuing administration (e.g. co-administration) of a drug that is a CYP1A2 inducer to avoid an adverse drug interaction (e.g., to avoid reduced exposure to pirfenidone), and administering a therapeutically effective amount of pirfenidone.

In one example, in a method of administering a therapeutically effective amount of pirfenidone to a patient with IPF, or pirfenidone for use in treating a patient in need of pirfenidone therapy, the invention provides an improvement that comprises avoiding or discontinuing administration (e.g., concomitant use or co-administration) of a CYP inducer and administering a therapeutically effective amount of pirfenidone.

In some embodiments, the CYP inducer is discontinued concurrent with starting administration of pirfenidone. In other embodiments, the CYP inducer is discontinued within at least 3 days prior to starting pirfenidone therapy. In another embodiment, the CYP inducer can be discontinued within up to 4 weeks prior to starting pirfenidone therapy. In another embodiment, the CYP inducer is discontinued within 3 days after starting pirfenidone therapy, optionally up to 4 weeks after starting pirfenidone therapy. These time periods, for example, can permit adequate time for tapering and withdrawal without adverse effects.

In embodiments in which the CYP inducer is discontinued to avoid an adverse drug interaction (e.g., to avoid reduced exposure to pirfenidone), the CYP inducer preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the CYP inducer.

In embodiments where the CYP inducer cannot be or is not discontinued prior pirfenidone therapy, the CYP inducer is preferably discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the CYP inducer is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the CYP inducer is discontinued no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

In embodiments in which the patient discontinues smoking to avoid an adverse drug interaction (e.g., to avoid reduced exposure to pirfenidone), the smoking preferably is discontinued within at least 3 days prior to starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, prior to starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no earlier than one month, 3 weeks, 2 weeks or 1 week before starting pirfenidone therapy. Preferably, sufficient time is allowed for tapering and/or withdrawal of the smoking.

In embodiments in which the patient cannot or does not discontinue smoking prior to pirfenidone therapy, the smoking preferably is discontinued within at least 3 days after starting pirfenidone therapy. In various embodiments, the patient discontinues smoking within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks), or at least 22 days, or at least 23 days, or at least 24 days, or at least 25 days, or at least 26 days, or at least 27 days, or at least 28 days (or four weeks), or at least 29 days, or at least 30 days, or at least one month, after starting pirfenidone therapy. In some embodiments, the patient discontinues smoking no later than one month, 3 weeks, 2 weeks or 1 week after starting pirfenidone therapy.

The patient preferably avoids use of the CYP inducer to allow sufficient time for the full dose of pirfenidone to be substantially absorbed by the patient's body. Pirfenidone has a serum half life in humans of about 2 to 3 hours. Thus, the patient preferably avoids use of the CYP inducer, for example, for at least 2.5 hours after administration of the pirfenidone. The patient can also avoid use of the CYP inducer for at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone. For example in embodiments where the patient is a smoker, the patient can avoid smoking for at least 2.5 hours, at least 3 hours, at least 3.5 hours, at least 4 hours, at least 4.5 hours, or at least 5 hours after administration of the pirfenidone. Similarly, the patient preferably avoids use of the

CYP inducer for at least 1, 2, 3, or 4 serium half-lives of the CYP inducer prior to use of pirfenidone.

Selecting an Alternative Drug or Therapy to Administer Concurrently with Pirfenidone Therapy

In some aspects, the invention provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy and in need of therapy with a drug that is a CYP inducer, such as an inducer of CYP1A2, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative therapy that is not a CYP inducer.

In other aspects, the invention provides a method of administering pirfenidone therapy to a patient who smokes and in need of pirfenidone therapy, comprising administering a therapeutically effective amount of pirfenidone to the patient, and administering a stop-smoking therapy, for example nicotine replacement therapy. The nicotine replacement therapy can be any nicotine source and can include a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler. Additionally or alternatively, the method can include administration of a drug to assist in smoking cessation. Non-limiting examples of smoking cessation drugs include, but are not limited to, bupropion hydrochloride (Zyban®) or varenicline (Chantix®).

Improving Administration of Pirfenidone by Advising or Cautioning Patient

The administration of a therapeutically effective amount of pirfenidone to a patient in need of pirfenidone therapy can be improved. In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone). In some embodiments, the patient is advised that administration of pirfenidone and smoking can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone).

In some embodiments, the patient is advised that co-administration of pirfenidone with a drug that is a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone). In some embodiments, the patient is advised that co-administration of pirfenidone with a CYP1A2 inducer can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone).

In some embodiments, the patient is advised that use of pirfenidone in patients who smoke can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone). In some embodiments, the patient is advised that use of pirfenidone in patients who smoke resulted in or can result in a 50% decrease in exposure to pirfenidone.

Dosing and Dose Modifications

In various embodiments, a method of administering pirfenidone and a CYP inducer that metabolizes pirfenidone (e.g., CYP1A2) is provided wherein the patient is administered a therapeutically effective amount of the inducer and a dosage of pirfenidone that is increased relative to a patient not taking the inducer. In some aspects, such an increased dosage of pirfenidone is greater than 2400 mg/day. For example, the increased dosage is about 2670 mg per day, 2937 mg per day, 3204 mg per day, 3471 mg per day, or 3738 mg per day (e.g., 10, 11, 12, 13, or 14 capsules per day where each capsule is approximately 267 mg), or higher. In another example, the dosage is increased from about 2400 mg or 2403 mg per day to about 4800 mg or 4806 mg per day. In some embodiments, the patient is already being administered the CYP inducer. In other embodiments, the patient is already being administered pirfenidone. In related embodiments, the dosage of pirfenidone is increased prior to administration of the CYP inducer.

In embodiments wherein the patient avoids or discontinues use of the CYP inducer, preferably the amount of pirfenidone being administered is at least 1800 mg, or 2400 or 2403 mg/day. Pirfenidone can be dosed at a total amount of about 2400 mg to about 3800 mg or 4800 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2670 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2937 mg, about 2950 mg, about 3000 mg, about 3050 mg, about 3100 mg, about 3150 mg, about 3200 mg, about 3204 mg, about 3250 mg, about 3300 mg, about 3350 mg, about 3400 mg, about 3450 mg, about 3471 mg, about 3500 mg, about 3550 mg, about 3600 mg, about 3650 mg, about 3700 mg, about 3738 mg, about 3750 mg, and about 3800 mg.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg. Other specific ranges of doses include about 1 mg/kg to about 35 mg/kg. Specific doses contemplated include about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg.

In one aspect of a use or method described herein, a dosage amount of pirfenidone is taken with food. In another aspect, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP inducer that metabolizes pirfenidone to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day, or about 1650 mg/day, or about 1700 mg/day, or about 1750 mg/day, or about 1800 mg/day, or about 1850 mg/day, or about 1900 mg/day, or about 1950 mg/day, or about 2000 mg/day, or about 2050 mg/day, or about 2100

mg/day, or about 2150 mg/day, or about 2200 mg/day, or about 2250 mg/day, or about 2300 mg/day, or about 2350 mg/day, or about 2400 mg/day or more. For example, the dosage is increased from about 2400 mg or 2403 mg per day to about 4800 mg or 4806 mg per day. As another example, the dosage is increased from about 1800 mg per day to about 3600 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a drug that is an inducer of CYP1A2 to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day, or about 1650 mg/day, or about 1700 mg/day, or about 1750 mg/day, or about 1800 mg/day, or about 1850 mg/day, or about 1900 mg/day, or about 1950 mg/day, or about 2000 mg/day, or about 2050 mg/day, or about 2100 mg/day, or about 2150 mg/day, or about 2200 mg/day, or about 2250 mg/day, or about 2300 mg/day, or about 2350 mg/day, or about 2400 mg/day or more. For example, the dosage is increased from about 2400 mg or 2403 mg per day to about 4800 mg or 4806 mg per day. As another example, the dosage is increased from about 1800 mg per day to about 3600 mg per day.

In some embodiments, a method of optimizing pirfenidone therapy is provided comprising titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, wherein co-administration of a CYP1A2 inducer to the patient does not result in a decreased exposure to pirfenidone. In some embodiments, the dose is increased by about 100 mg/day. In other embodiments, the dose is increased by about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 267 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 450 mg/day, or about 500 mg/day, or about 550 mg/day, or about 600 mg/day, or about 650 mg/day, or about 700 mg/day, or about 750 mg/day, or about 800 mg/day, or about 850 mg/day, or about 900 mg/day, or about 950 mg/day, or about 1000 mg/day, or about 1050 mg/day, or about 1100 mg/day, or about 1150 mg/day, or about 1200 mg/day, or about 1250 mg/day, or about 1300 mg/day, or about 1350 mg/day, or about 1400 mg/day, or about 1450 mg/day, or about 1500 mg/day, or about 1600 mg/day, or about 1650 mg/day, or about 1700 mg/day, or about 1750 mg/day, or about 1800 mg/day, or about 1850 mg/day, or about 1900 mg/day, or about 1950 mg/day, or about 2000 mg/day, or about 2050 mg/day, or about 2100 mg/day, or about 2150 mg/day, or about 2200 mg/day, or about 2250 mg/day, or about 2300 mg/day, or about 2350 mg/day, or about 2400 mg/day or more. For example, the dosage is increased from about 2400 mg or 2403 mg per day to about 4800 mg or 4806 mg per day. As another example, the dosage is increased from about 1800 mg per day to about 3600 mg per day.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including any one, two, three or more of the following information or recommendations:

(a) advising the patient that strong CYP inducers that metabolize pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with a CYP inducer that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism. In some embodiments, the information or recommendation may include that co-administration of pirfenidone with inducers of CYP that metabolize pirfenidone can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone). In other embodiments, the information or recommendation may include that administration of pirfenidone to a patient who smokes can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone). In other embodiments, the information or recommendation may include that co-administration of pirfenidone with CYP1A2 inducers can alter the therapeutic effect or adverse reaction profile of pirfenidone (e.g., can reduce exposure to pirfenidone).

In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be avoided. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be discontinued. It is understood that such avoiding and/or discontinuing by a manufacturer, distributor, or seller of pirfenidone can be a contraindication. In other embodiments, the information or recommendation may include that drugs that are CYP1A2 inducers should be used with caution. In yet other embodiments, the information or recommendation may be any of the regimens for titrating the dosage of pirfenidone administered to a patient upward relative to a previously administered dosage in the patient, as described above.

The package insert, package label, instructions or other labeling may further comprise directions for treating IPF by administering pirfenidone, e.g., at a dosage of at least 1800 mg, or 2400 mg or 2403 mg per day.

In related aspect, the invention provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions including any one, two, three or more of the foregoing information or recommendations.

In some embodiments, a method of treating IPF is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

The invention will be more fully understood by reference to the following examples which detail exemplary embodiments of the invention. They should not, however, be con-

strued as limiting the scope of the invention. All citations throughout the disclosure are hereby expressly incorporated by reference.

EXAMPLES

An open-label Phase 1 study was performed to determine the impacts of a strong CYP1A2 inhibitor and a CYP1A2 inducer on the pharmacokinetics and safety of pirfenidone in healthy subjects.

Study Design.

The study was a Phase 1, open-label, parallel-group study designed to investigate the impact of CYP1A2 inhibition and induction on the pharmacokinetics and safety of pirfenidone in healthy subjects. Fifty-four subjects were to be enrolled in two groups, consisting of 27 subjects who were smokers (Group 1) and 27 subjects who were nonsmokers (Group 2). Each group (smokers and nonsmokers) was to include a minimum of nine females and nine males, and attempts were to be made to enroll equal numbers of each sex in each group. Each subject was to receive a single 801-mg dose of pirfenidone on Days 1 and 11. Fluvoxamine dosing was started on Day 2 and titrated to the final dose according to the following schedule:

- Days 2-4: fluvoxamine 50 mg at bedtime
- Days 5-7: fluvoxamine 50 mg twice a day (in the morning and at bedtime)
- Days 8-11: fluvoxamine 50 mg in the morning and 100 mg at bedtime

All pharmacokinetic (PK) analyses were conducted using population PK methods using Monte-Carlo parametric expectation maximization as implemented in the open-source software program S ADAPT 1.5.6 (Bauer et al., *AAPS Journal* 9 (1):E60-83, 2007). The structural model for the analysis was obtained from a preliminary population PK analysis. This population PK model was fit to the pirfenidone and 5 carboxy-pirfenidone plasma concentration-time data from Days 1 and 11 separately. Once a final population PK model was defined, $AUC_{0-\infty}$ estimates were generated by simulating plasma PK profiles and compared for statistically significant differences between days (to test the effect of fluvoxamine co-administration) and between groups (to test the effect of smoking).

As the primary endpoint of the study, differences in the pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ estimates between Days 1 and 11, and between smokers and nonsmokers were tested for significance. The analysis of the effect of fluvoxamine (i.e., Day 1 versus Day 11) was analyzed using the FDA criteria for bioequivalence for paired data (FDA 2003). The ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1 was used to test for the interaction between smoking status and fluvoxamine coadministration. If other subject characteristics (such as body size or age) were also associated with the ratio of $AUC_{0-\infty}$ on Day 11 to that on Day 1, the significance of these covariates was also tested. The significance of differences in pirfenidone and 5-carboxy-pirfenidone $AUC_{0-\infty}$ estimates on Day 1 in smokers and nonsmokers was tested using multivariable linear regression in order to take into account the effects of other significant covariates.

Pharmacokinetic Results.

Fifty-one of the 54 subjects enrolled in the study were included in the PK analyses. Three subjects were removed from the PK analyses as they did not meet the protocol-specified requirement for adequate compliance with the fluvoxamine dosing regimen. Two subjects discontinued the study early due to adverse events, and one subject only took 73% of the protocol-required fluvoxamine dose. All 51 subjects had the full complement of PK samples available for analysis. Each subject had two profiles on each day: one for pirfenidone and one for 5 carboxy pirfenidone. There were a total of 1224 samples (12 per subject per day); each sample was assayed for pirfenidone and 5 carboxy-pirfenidone for a total of 2448 concentrations.

A robust fit to the data was obtained using the population PK structural model. In general, the fits of the data were excellent: 98% of the individual profiles had r^2 values above 0.9 and there was no systematic bias in the fits.

The summary statistics of $AUC_{0-\infty}$ stratified by study day are provided in Table 1. Symmetrical dot density plots of pirfenidone and 5 carboxy pirfenidone $AUC_{0-\infty}$ values versus study day, identified by smoking status, are provided in FIG. 1. The co-administration of fluvoxamine resulted in a significant increase in the $AUC_{0-\infty}$ of pirfenidone ($p<0.00001$). There was not a statistically significant effect of fluvoxamine co-administration on 5 carboxy pirfenidone $AUC_{0-\infty}$.

TABLE 1

Comparison of $AUC_{0-\infty}$ Between Study Days (n = 51)

		$AUC_{0-\infty}$ (mg · hr/L)	
Study Day	Statistic	Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
1: Pre-Fluvoxamine	Mean (SD)	34.9 (16.9)	29.3 (8.22)
	Median (25^{th}-75^{th})	34.7 (21.4-45.9)	26.9 (22.0-33.7)
11: Post-Fluvoxamine	Mean (SD)	171 (47.7)	31.7 (8.96)
	Median (25^{th}-75^{th})	167 (126-206)	29.4 (25.4-36.5)

[a]p-value <0.00001 (paired t-test)
[b]p-value = 0.168 (paired t-test)
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity;
SD = standard deviation.

There was also a large apparent difference in the C_{max} estimates pre- and post-fluvoxamine; the pirfenidone C_{max} was higher after administration of fluvoxamine while the 5 carboxy pirfenidone C_{max} was lower after administration of fluvoxamine. The mean (95% CI) for the ratio of C_{max} on Day 11 to the C_{max} on Day 1 was 2.09 (1.94-2.25) for pirfenidone and 0.369 (0.349-0.390) for 5-carboxy-pirfenidone.

The summary statistics of the ratio of the $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1, stratified by smoking status, are provided in Table 2. While both smokers and nonsmokers were affected by the coadministration of fluvoxamine, smokers appeared to have a more pronounced increase in exposure to pirfenidone, as evidenced by the higher ratio of Day 11 to Day 1 AUC. Given that there was an imbalance in the demographics between smokers and nonsmokers (smokers were younger, heavier and predominantly male), the impact of these variables on the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1 was tested using multiple linear regression. Using backward elimination (p-value for removal=0.10), smoking status was the only significant predictor of the ratio of the pirfenidone $AUC_{0-\infty}$ on Day 11 to the $AUC_{0-\infty}$ on Day 1; body size, sex, and age were not significant.

TABLE 2

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Smokers	N	26	26
	Mean (SD)	7.32 (2.12)	1.12 (0.0951)
	Median (25^{th}-75^{th})	7.07 (6.12-8.25)	1.13 (1.04-1.19)

TABLE 2-continued

Comparison of Ratio of Day 11 $AUC_{0-\infty}$ to Day 1 $AUC_{0-\infty}$ by Smoking Status

Smoking Status	Statistic	Pirfenidone	5-Carboxy-Pirfenidone
Nonsmokers	N	25	25
	Mean (SD)	4.13 (1.15)	1.05 (0.114)
	Median (25^{th}-75^{th})	3.99 (3.26-4.68)	1.03 (0.978-1.11)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity;
SD = standard deviation.

The relationship between smoking status and exposure to pirfenidone and 5 carboxy pirfenidone were examined using the $AUC_{0-\infty}$ estimates from Day 1. Due to the high degree of correlation between BSA and other demographic variables (sex, creatinine clearance (mL/min) (CLcr), age) and the pharmacologic plausibility of a relationship between exposure and body size, $AUC_{0-\infty}$ was first normalized to body surface area before application of multiple linear regression. Smoking status was the only significant predictor of the variability in pirfenidone $AUC_{0-\infty}$ normalized to BSA. Smoking status had a pronounced effect in that smokers would be predicted to have a ~50% drop in $AUC_{0-\infty}$ after accounting for differences in BSA. For 5 carboxy-pirfenidone $AUC_{0-\infty}$, the only significant predictors were age and CLcr.

In summary, the design and execution of this study allowed for a robust and informative analysis of the effects of CYP1A2 inhibition and/or induction on the pharmacokinetics of pirfenidone. Administration of the potent CYP inhibitor fluvoxamine resulted in a significant drug interaction and markedly increased pirfenidone exposure. Smokers were likely to experience significantly lower pirfenidone exposure (in the absence of the drug interaction) presumably due to the inductive effects of smoking.

The coadministration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after ten days of dosing with fluvoxamine Subjects also experienced, on average, a two-fold increase in C_{max} after administration of fluvoxamine.

Administration of pirfenidone to patients who smoke resulted in a significant decrease in exposure ($AUC_{0-\infty}$) to pirfenidone, and was, on average, about 50% the exposure of pirfenidone in patients that didn't smoke.

While the present invention has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

Examples of Embodiments of the Invention Include

1. A method of administering pirfenidone therapy to a patient in need thereof comprising administering to the patient a therapeutically effective amount of pirfenidone and avoiding use or administration of a strong inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone.

2. The method of paragraph 1, wherein the strong inducer of CYP is avoided for at least 2.5 hours after administration of the pirfenidone.

3. The method of paragraph 2, wherein the patient is a smoker and avoids smoking for at least 2.5 hours after administration of the pirfenidone.

4. A method of administering pirfenidone therapy to a patient in need thereof, wherein the patient is receiving an inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone, comprising discontinuing use or administration of the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone to avoid an adverse drug reaction and administering a therapeutically effective amount of pirfenidone.

5. The method of paragraph 4, wherein the inducer of CYP is discontinued prior to administration of pirfenidone.

6. The method of paragraph 5, wherein the inducer of CYP is discontinued within 4 weeks prior to the administration of pirfenidone.

7. The method of paragraph 4, wherein the inducer of CYP is discontinued concurrent to administration of pirfenidone.

8. The method of paragraph 1 or 4, wherein the patient is a smoker, comprising discontinuing smoking.

9. The method of paragraph 8, further comprising administering a nicotine replacement therapy to the patient.

10. The method of paragraph 9, wherein the nicotine replacement therapy comprises one or more of a nicotine patch, a nicotine gum, a nicotine lozenge, a nicotine nasal spray, and a nicotine inhaler.

11. The method of paragraph 8, further comprising administering to the patient bupropion hydrochloride (Zyban) or varenicline (Chantix).

12. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and any one or more of the following:

(a) advising the patient that strong inducers of a cytochrome P450 (CYP) that metabolizes pirfenidone should be avoided or discontinued;

(b) advising the patient that smoking should be avoided or discontinued;

(c) advising the patient that co-administration of pirfenidone with an inducer of CYP that metabolizes pirfenidone can alter the therapeutic effect of pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

13. The method of paragraph 12, wherein the patient is a smoker, and further comprising advising the patient to consider nicotine replacement therapy in place of smoking.

14. The method of any one of paragraphs 12-13, further comprising encouraging patients who smoke to stop smoking before treatment with pirfenidone.

15. The method of any one of paragraphs 1-14, wherein the therapeutically effective amount of pirfenidone is a total daily dose of about 2400 mg.

16. The method of any one of paragraphs 1-15, wherein the pirfenidone is administered three times a day, at a total daily dose of about 2400 mg.

17. The method of any one of paragraphs 1-16, wherein the CYP comprises CYP1A2.

18. The method of any one of paragraphs 1-17, wherein the patient suffers from idiopathic pulmonary fibrosis (IPF).

19. The method of any one of paragraphs 1-18, wherein the pirfenidone is co-administered with food.

20. The method of any one of paragraphs 1-19, wherein the inducer of a cytochrome P450 (CYP) that metabolizes pirfenidone is one or more of carbamazepine, charbroiled food, cigarette smoke, cruciferous vegetables, esomeprazole, griseofulvin, insulin, lansprazole, marijuana smoke, mori-

cizine, omeprazole, phenobarbital, phenyloin, primidone rifampin, ritonavir, smoking, and St. John's wort.

Other Examples of Embodiments of the Invention Include

1A. A method of administering pirfenidone therapy to a patient in need thereof, wherein the patient is a smoker, comprising discontinuing smoking to avoid an adverse drug reaction and administering a therapeutically effective amount of pirfenidone.

2A. The method of paragraph 1A, wherein the patient discontinues smoking within 4 weeks prior to the administration of pirfenidone.

3A. The method of paragraph 1A, wherein the patient discontinues smoking concurrent to administration of pirfenidone.

4A. The method of paragraph 1A, comprising discontinuing smoking to avoid an adverse drug reaction which is decreased exposure to pirfenidone.

5A. The method of paragraph 1A, further comprising advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke.

6A. The method of paragraph 1A, wherein the patient has idiopathic pulmonary fibrosis.

7A. The method of paragraph 1A, wherein the therapeutically effective amount of pirfenidone is 2400 mg or 2403 mg per day.

8A. A method of administering pirfenidone therapy to a patient in need thereof comprising administering to the patient a therapeutically effective amount of pirfenidone and avoiding use or administration of a strong inducer of a cytochrome P450 1A2 (CYP1A2) to avoid an adverse drug reaction.

9A. The method of paragraph 8A, comprising avoiding use or administration of a strong inducer of CYP1A2 to avoid an adverse drug reaction which is reduced exposure to pirfenidone.

10A. The method of paragraph 8A, wherein the patient is a smoker and avoids smoking when using pirfenidone.

11A. The method of paragraph 8A, wherein the patient has idiopathic pulmonary fibrosis.

12A. The method of paragraph 8A, wherein the therapeutically effective amount of pirfenidone is 2400 mg or 2403 mg per day.

13A. A method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and one or more of the following:

(a) advising the patient that inducers of a cytochrome P450 (CYP) (CYP1A2) should be avoided or discontinued;

(b) advising the patient that smoking should be avoided when using pirfenidone due to the potential for smoking to induce CYP1A2 metabolism resulting in decreased exposure to pirfenidone;

(c) advising the patient that smoking should be discontinued before treatment with pirfenidone;

(d) advising the patient that administration of pirfenidone in patients that smoke results in a 50% decrease in pirfenidone exposure compared to patients that do not smoke; and

(e) advising the patient that smoking may result in decreased pirfenidone exposure due to the potential for smoking to induce CYP1A2 metabolism.

14A. The method of paragraph 13A, further comprising encouraging patients who smoke to stop smoking before treatment with pirfenidone.

15A. The method of paragraph 13A, expedient (a), comprising advising the patient that strong inducers of a CYP1A2 should be avoided or discontinued.

16A. The method of paragraph 13A, wherein the inducer of a CYP1A2 is one or more of carbamazepine, charbroiled food, cigarette smoke, cruciferous vegetables, esomeprazole, griseofulvin, insulin, lansprazole, marijuana smoke, moricizine, omeprazole, phenobarbital, phenyloin, primidone rifampin, ritonavir, smoking, and St. John's wort.

17A. The method of paragraph 16A, wherein the CYP1A2 inducer is selected from the group consisting of carbamazepine, esomeprazole, griseofulvin, insulin, lansprazole, moricizine, omeprazole, rifampin, ritonavir, and smoking.

18A. The method of paragraph 16A, wherein the CYP1A2 inducer is selected from the group consisting of carbamazepine, lansoprazole, omeprazole, phenobarbital, phenyloin, primidone, rifampin, ritonavir, smoking, and St. John's wort.

19A. The method of paragraph 13A, wherein the patient in need of pirfenidone therapy is treated for idiopathic pulmonary fibrosis.

20A. The method of paragraph 13A, wherein the therapeutically effective amount of pirfenidone is 2400 mg or 2403 mg per day.

Still Other Examples of Embodiments of the Invention Include

1B. Pirfenidone for use in treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding or discontinuing concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone.

2B. The use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding or discontinuing concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone.

3B. The pirfenidone or use of any one of paragraphs 1B to 2B characterized in that the treating comprises avoiding concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2).

4B. The pirfenidone or use of any one of paragraphs 1B to 2B wherein the patient is avoiding concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2).

5B. The pirfenidone or use of any one of paragraphs 1B to 2B wherein the patient is a smoker who is discontinuing smoking to avoid reduced exposure to pirfenidone.

6B. The pirfenidone or use of paragraph 5B wherein the patient is discontinuing smoking within 4 weeks prior to the administration of pirfenidone.

7B. The pirfenidone or use of paragraph 5B wherein the patient is discontinuing smoking concurrent with the start of administration of pirfenidone.

8B. The pirfenidone or use of any one of paragraphs 1B to 2B wherein the patient is a smoker and avoids smoking when using pirfenidone.

9B. The pirfenidone or use of any one of paragraphs 1B to 4B wherein the inducer of a CYP1A2 is one or more of carbamazepine, charbroiled food, cigarette smoke, cruciferous vegetables, esomeprazole, griseofulvin, insulin, lansprazole, marijuana smoke, moricizine, omeprazole, phenobarbital, phenyloin, primidone rifampin, ritonavir, smoking, and St. John's wort.

10B. The pirfenidone or use of any one of paragraphs 1B to 9B wherein the patient suffers from a disease selected from pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

11B. The pirfenidone or use of any one of paragraphs 1B to 10B wherein the patient has idiopathic pulmonary fibrosis.

12B. The pirfenidone or use of any one of paragraphs 1B to 11B wherein the pirfenidone is administered at a total daily dosage of 2400 mg or 2403 mg per day.

13B. The pirfenidone or use of any one of paragraphs 1B to 12B, wherein each dose of pirfenidone administered is 801 mg.

14B. Pirfenidone for use in treating a patient in need of pirfenidone therapy, characterized in that the treating comprises administering pirfenidone to the patient and contraindicating, avoiding or discontinuing a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone.

15B. A package or kit comprising (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling comprising contraindicating, avoiding, or discontinuing concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2), and optionally according to any of the embodiments of paragraphs 1B-14B or as described anywhere above.

What is claimed is:

1. A method of increasing the effectiveness of pirfenidone therapy by avoiding decreased exposure to pirfenidone, in a patient in need of pirfenidone therapy and taking a strong inducer of cytochrome P450 1A2 (CYP1A2), comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding the strong inducer of a cytochrome P450 1A2 (CYP1A2).

2. The method of claim **1**, wherein the patient has idiopathic pulmonary fibrosis.

3. The method of claim **1**, wherein the patient suffers from a fibrosis condition.

4. The method of claim **1**, wherein the pirfenidone is administered at a total daily dosage of at least 1800 mg.

5. The method of claim **2**, wherein the pirfenidone is administered at a total daily dosage of at least 1800 mg.

6. The method of claim **1**, wherein the pirfenidone is administered at a total daily dosage of 2400 mg or 2403 mg.

7. The method of claim **2**, wherein the pirfenidone is administered at a total daily dosage of 2400 mg or 2403 mg.

8. The method of claim **1**, wherein each dose of pirfenidone administered is 801 mg.

9. The method of claim **6**, wherein pirfenidone is administered three times a day.

10. The method of claim **9**, wherein pirfenidone is administered with food.

11. The method of claim **1**, wherein the strong CYP1A2 inducer is cigarette smoke.

12. The method of claim **11**, wherein the patient has idiopathic pulmonary fibrosis.

13. The method of claim **11**, wherein the patient suffers from a fibrosis condition.

14. The method of claim **11**, wherein the pirfenidone is administered at a total daily dosage of at least 1800 mg.

15. The method of claim **12**, wherein the pirfenidone is administered at a total daily dosage of at least 1800 mg.

16. The method of claim **11**, wherein the pirfenidone is administered at a total daily dosage of 2400 mg or 2403 mg.

17. The method of claim **12**, wherein the pirfenidone is administered at a total daily dosage of 2400 mg or 2403 mg.

18. The method of claim **16**, wherein pirfenidone is administered three times a day.

19. The method of claim **18**, wherein pirfenidone is administered with food.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,754,109 B2
APPLICATION NO. : 13/513472
DATED : June 17, 2014
INVENTOR(S) : Williamson Z. Bradford et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 1, immediately after the title, add the heading and paragraph as follows:

Cross Reference To Related Applications

This is a national phase of PCT/US10/58936, filed December 3, 2010, which claims priority to European Patent Application 10250378.6 filed March 3, 2010, U.S. Patent Application 61/310,575 filed March 4, 2010, and Canadian Patent application 2710014 filed October 8, 2010, and is a continuation-in-part of U.S. Patent Application 12/684,543 filed January 8, 2010 (now U.S. Patent No. 8,084,475), which claims priority to U.S. Patent Application 61/266,753 filed December 4, 2009.

Signed and Sealed this
Third Day of October, 2017

Joseph Matal

Joseph Matal
Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT 15

US008778947B2

(12) **United States Patent**
Bradford

(10) **Patent No.: US 8,778,947 B2**
(45) **Date of Patent: Jul. 15, 2014**

(54) **METHODS OF ADMINISTERING PIRFENIDONE THERAPY**

(71) Applicant: **Intermune, Inc.**, Brisbane, CA (US)

(72) Inventor: **Williamson Z. Bradford**, Wilson, WY (US)

(73) Assignee: **Intermune, Inc.**, Brisbane, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/015,857**

(22) Filed: **Aug. 30, 2013**

(65) **Prior Publication Data**

US 2014/0066484 A1 Mar. 6, 2014

Related U.S. Application Data

(60) Provisional application No. 61/696,044, filed on Aug. 31, 2012, provisional application No. 61/709,125, filed on Oct. 2, 2012, provisional application No. 61/749,026, filed on Jan. 4, 2013, provisional application No. 61/775,240, filed on Mar. 8, 2013, provisional application No. 61/842,706, filed on Jul. 3, 2013.

(51) **Int. Cl.**
A61K 31/497 (2006.01)
A61K 31/435 (2006.01)

(52) **U.S. Cl.**
USPC **514/253.07**; 514/277

(58) **Field of Classification Search**
USPC 514/253.07, 277
See application file for complete search history.

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(57) **ABSTRACT**

The disclosure relates to improved methods of administering pirfenidone therapy when ciprofloxacin is administered concomitantly.

18 Claims, 1 Drawing Sheet

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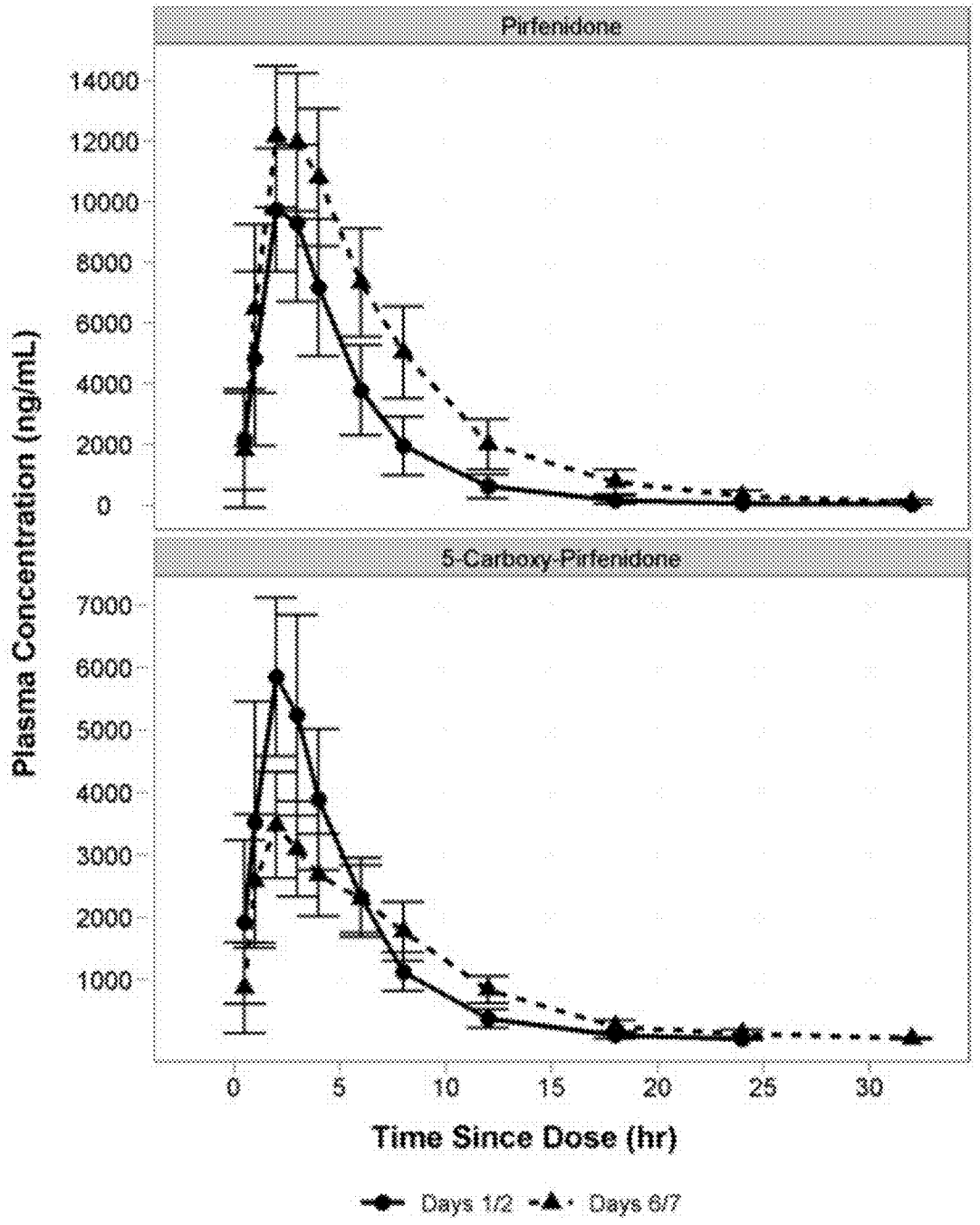

Pirfenidone
5-Carboxy-Pirfenidone
Plasma Concentration (ng/mL)
14000
12000
10000
8000
6000
4000
2000
0
7000
6000
5000
4000
3000
2000
1000
0
5
10
15
20
25
30
Time Since Dose (hr)
Days 1/2
Days 6/7

METHODS OF ADMINISTERING PIRFENIDONE THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority benefit under 35 U.S.C. §119(e) of Provisional U.S. Patent Application No. 61/696,044, filed Aug. 31, 2012; Provisional U.S. Patent Application No. 61/709,125, filed Oct. 2, 2012; Provisional U.S. Patent Application No. 61/749,026, filed Jan. 4, 2013; Provisional U.S. Patent Application No. 61/775,240, filed Mar. 8, 2013; and Provisional U.S. Patent Application No. 61/842,706, filed Jul. 3, 2013, each of which is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

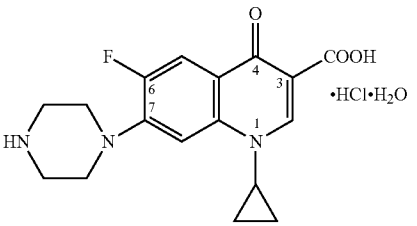
The disclosure relates to improved methods of administering pirfenidone therapy when ciprofloxacin is administered concomitantly and to a novel therapeutic dose of pirfenidone.

BACKGROUND

Pirfenidone is a small molecule with a molecular weight of 185.23 daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved in Japan for treatment of idiopathic pulmonary fibrosis (IPF) under the trade name Pirespa®, and in several European countries under the trade name Esbriet®.

Pirfenidone has been shown to be metabolized by various isoforms of the cytochrome P450 (CYP) protein [See the Report on the Deliberation Results, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health Labour and Welfare, Sep. 16, 2008]. Specifically, several cytochrome P450 (CYP) isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were reported to be involved in the earliest stages of oxidative metabolism of pirfenidone. More recently, it was reported that in vitro experiments showed that pirfenidone metabolism is predominantly carried out by CYP1A2 [U.S. Pat. No. 7,816,383, incorporated by reference herein in its entirety].

Ciprofloxacin is a broad spectrum antimicrobial agent. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It has a molecular weight of 385.8, its empirical formula is $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and its chemical structure is as follows:



Ciprofloxacin was previously classified as a moderate inhibitor of CYP1A2 by the FDA [FDA Draft Guidance for Industry Drug Interaction Studies—Study Design, Data Analysis, and Implications for Dosing and Labeling, September 2006]; this description was recently revised in February 2012 [FDA Draft Guidance for Industry Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, February 2012].

SUMMARY OF THE INVENTION

The disclosure generally relates to improved use of pirfenidone and methods of administering pirfenidone to a patient in need of pirfenidone therapy, and to corresponding methods of preparing or packaging pirfenidone medicaments, containers, packages and kits. The disclosure also relates to pirfenidone for corresponding uses in treating a patient in need of pirfenidone therapy, including use of a novel therapeutic dose.

The present disclosure is based in part on the discovery that concomitant administration of pirfenidone at a dose of 801 mg (e.g., given three times per day for a total daily dose of 2403 mg/day) and ciprofloxacin at a dose of 750 mg (e.g., given twice daily for a total daily dose of 1500 mg/day), produces a modest but significant rise in pirfenidone exposure to about 1.8-fold, on average. Thus, for example, a patient receiving a daily dose of 2403 mg may be exposed to pirfenidone levels equivalent to a dose of about 4325 mg pirfenidone.

In one aspect, therefore, the disclosure relates to the discovery that ciprofloxacin should not be used (e.g., should be avoided) at a high dose of 750 mg or higher with pirfenidone, due to the potential for reduced clearance of pirfenidone and/or the potential for increased exposure to pirfenidone (about 1.8-fold the exposure as measured by area under the curve, AUC). Such improved uses and methods involve avoiding concomitant use of ciprofloxacin at a dose of 750 mg or higher, or 700 mg or higher, during pirfenidone administration (or avoiding concomitant use of pirfenidone during ciprofloxacin administration), as well as discontinuing pirfenidone during the time period of ciprofloxacin use.

In the first aspect, for example, the disclosure provides a method of administering pirfenidone therapy to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding co-administration of ciprofloxacin at a dose of 750 mg or higher, e.g. 750 mg taken twice a day. In any of the aspects or embodiments of the disclosure, a method of administering pirfenidone therapy to a patient in need thereof is provided, comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding co-administration of ciprofloxacin at a dose of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, or higher. In some embodiments, the dose of ciprofloxacin is administered to the patient two times per day (i.e., BID), for a total daily dose of 1500 mg per day.

In embodiments of such methods, for example, pirfenidone at an oral dose of about 800 mg, or about 801 mg, is administered and concomitant dosing of ciprofloxacin at an oral dose of 750 mg or higher, or at a dose of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, is avoided. In one embodiment, the disclosure provides a method wherein a dose of ciprofloxacin lower than 750 mg, or lower than 700 mg, or lower than 650 mg (for example, about 500 mg), is administered to the patient. In another embodiment, an alternative antibiotic therapy that is not ciprofloxacin is administered to the patient. Avoiding concomitant use of pirfenidone and ciprofloxacin at equivalent dosing by other routes is contemplated.

In the first aspect, the disclosure also provides methods of administering pirfenidone therapy to a patient in need thereof,

comprising discontinuing pirfenidone during the time period of ciprofloxacin use at a dose of 750 mg or higher, or at a dose of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, e.g. at doses of 750 mg taken twice a day. For example, in such embodiments, pirfenidone is discontinued before a time period during which ciprofloxacin is administered to the patient, and pirfenidone is restarted after the time period. Discontinuing and/or restarting can occur within, e.g. one day or one week of the time period of concomitant ciprofloxacin use. The time period of ciprofloxacin use can be any appropriate time period, e.g. one week, two weeks, three weeks, or one month. In related embodiments, pirfenidone is discontinued during concomitant administration of ciprofloxacin at equivalent doses by other routes.

The present disclosure is also based in part on the discovery of a novel therapeutic dose of pirfenidone for treatment of patients receiving co-administration of ciprofloxacin.

In a second aspect, the disclosure provides an improved method of administering pirfenidone therapy to a patient in need thereof, comprising reducing the dose of pirfenidone administered to the patient, e.g., by about one-half to about one-third, during concomitant use of ciprofloxacin at a dose of 750 mg, or at a dose of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, e.g. at doses of 750 mg twice per day. For example, if a patient has been receiving about 2400 or 2403 mg/day pirfenidone (e.g., given as 801 mg three times per day) prior to ciprofloxacin administration, then such methods include (a) administering pirfenidone at about 1600 or 1602 mg/day (e.g., given as 534 mg three times per day) and (b) concomitantly administering ciprofloxacin at 750 mg twice per day (i.e. 1500 mg/day). In specific embodiments, where the pirfenidone unit dosage form is a 267 mg capsule, and pirfenidone has been administered as three capsules three times per day, then in step (a) each dose of pirfenidone is reduced to two capsules, three times per day. As another example, if a patient has been receiving 1800 mg/day pirfenidone (e.g., given as 600 mg three times per day), then such methods include (a) administering pirfenidone at 1200 mg/day (e.g., given as 400 mg three times per day), and (b) concomitantly administering ciprofloxacin at 750 mg twice per day.

The disclosure also provides use of pirfenidone at a total daily dose that is reduced e.g., by about one-half to about one-third, during concomitant use of ciprofloxacin at a dose of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, e.g. at a dose of 750 mg twice per day. The invention further contemplates such use of pirfenidone in one or more unit dosage forms. In specific embodiments, where the pirfenidone unit dosage form is a 267 mg capsule, the invention provides use of pirfenidone at a total daily dose of 1602 mg in two unit dosage units three times a day in a patient concurrently receiving 750 mg ciprofloxacin twice per day. The invention therefore also contemplates a pharmaceutical composition comprising pharmaceutically acceptable excipients and 1602 mg/day pirfenidone in one or more unit dosage forms for such use.

Pharmaceutically acceptable excipients refer to substances such as disintegrators, binders, fillers, and lubricants used in formulating pharmaceutical products which are not active pharmaceutical ingredients, as would be well known to those skilled in the art. In embodiments of the pharmaceutical composition of the present invention, the dosage unit may be a capsule, including a capsule containing 267 mg pirfenidone and pharmaceutically acceptable excipients

In related embodiments, the present disclosure involves reduced dosage of pirfenidone, during concomitant ciprofloxacin administration, when the drug(s) are given at equivalent doses by other routes. Intravenous (i.v.) dosing of ciprofloxacin 400 mg i.v. three times per day (every 8 hours) is considered the equivalent of 750 mg orally twice per day.

As used herein, "concomitant use" is understood to be interchangeable with concurrent administration or co-administration. Thus, the terms are understood to encompass administration simultaneously, or at different times, and by the same route or by different routes, as long as the two agents are given in a manner that allows both agents to be affecting the body at the same time. For example, concomitant use can refer to a medication concomitantly administered, whether prescribed by the same or a different practitioner, or for the same or a different indication. With respect to routes of administration, a preferred route of administration by the disclosure is oral administration. Additionally, the drugs may be delivered to a patient using any standard route of administration, including parenterally, such as intravenously, intraperitoneally, intrapulmonary, subcutaneously or intramuscularly, intrathecally, transdermally, rectally, orally, nasally or by inhalation.

In any of the aspects or embodiments, the patient may have idiopathic pulmonary fibrosis (IPF), bronchiolitis obliterans (BO), renal fibrosis or scleroderma and the medicament, use or administration is for treatment of these fibrotic disorders. In any of the aspects or embodiments, the therapeutically effective amount of pirfenidone being administered prior to the need for ciprofloxacin therapy may be a daily dosage of about 2400 mg per day, e.g. 2403 mg per day. In any of the aspects of the disclosure, the daily dosage may be administered in divided doses three times a day, or two times a day, or alternatively is administered in a single dose once a day. In any of the aspects of the disclosure, the pirfenidone may be administered with food. For example, a daily oral dosage of 2400 mg or 2403 mg pirfenidone per day may be administered as follows: 800 mg or 801 mg taken three times a day, with food. Similarly, a daily oral dosage of 1600 mg or 1602 mg pirfenidone per day may be administered as 534 mg taken three times a day, with food. In any of the embodiments, the pirfenidone may be administered in oral unit dosage forms, e.g. capsules or tablets. In any of the embodiments, the amount of pirfenidone in the unit dosage form can be 200 mg or 267 mg.

In any of the aspects or embodiments of the disclosure, it is understood that the patient is in need of therapy with ciprofloxacin.

In some embodiments, ciprofloxacin at a dose of 750 mg, e.g. 750 mg twice per day, is used with caution when administering pirfenidone. In further embodiments, ciprofloxacin at a dose of between about 650 mg to about 850 mg or between about 700 mg to about 800 mg, e.g. twice per day, is used with caution when administering pirfenidone.

A further aspect of the disclosure provides the use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding co-administration of ciprofloxacin at a dose of 750 mg, e.g. given twice per day, or discontinuing pirfenidone during ciprofloxacin use at a dose of 750 mg, or reducing the dose of pirfenidone (e.g., by about one-third) during ciprofloxacin use at a dose of 750 mg. It is understood that this also applies to ciprofloxacin at a dose of between about 650 mg to about 850 mg or between about 700 mg to about 800 mg.

For simplicity of dosing and improved safety, the invention also contemplates that, for patients concurrently being administered ciprofloxacin (e.g. at any dose, 250 mg, 500 mg or 750 mg given twice daily) and pirfenidone, pirfenidone is administered at a dose of about 1602 mg/day, or about 1600

mg/day, or a dose reduced by about one-third (from a reference dose, e.g., 1800 mg/day or 2403 mg/day).

For simplicity of dosing and improved safety, the invention also contemplates that, for patients concurrently being administered ciprofloxacin (e.g. at any dose, 250 mg, 500 mg or 750 mg given twice daily) and pirfenidone, pirfenidone is administered at a dose of about 801 mg/day, or about 800 mg/day, or a dose reduced by about two-thirds (from a reference dose, e.g., 1800 mg/day or 2403 mg/day).

It is also understood that any of the aspects or embodiments or examples described herein with respect to methods of treatment apply equally to "pirfenidone for use" in such methods and to use of pirfenidone for treatment and in manufacture of a medicament for such methods. Such example uses are also further described below. It is further understood that the methods and uses described herein relating to the concurrent administration of ciprofloxacin and pirfenidone apply equally to ciprofloxacin, as well as pirfenidone. Thus, any of the aspects or embodiments or examples described herein with respect to methods of treatment apply equally to "ciprofloxacin for use" in such methods and to use of ciprofloxacin in manufacture of a medicament for such methods. By way of example, any references to "pirfenidone for use" apply equally to "ciprofloxacin for use."

In any of the aspects or embodiments of the disclosure, the patient is in need of pirfenidone therapy. The effect of ciprofloxacin on increasing pirfenidone exposure applies to any patient receiving pirfenidone therapy, and is independent from the disorder for which the patient is in need of pirfenidone. In this case, the inhibition of CYP1A2 by ciprofloxacin that leads to an increase in exposure to pirfenidone in a patient is not a consequence or a result of a particular disorder. As such, it is contemplated that any disorder for which a patient would be receiving pirfenidone, and during which a patient might be receiving the antibiotic ciprofloxacin for any reason including reasons unrelated to pirfenidone administration, is one that would benefit from the disclosure.

For example, the patient suffers from a fibrotic disorder, such as a fibrotic disorder of the lung, kidney, liver, heart, or other organ; an inflammatory disease; an autoimmune disease; or fibrosis accompanying tissue injury from, e.g., infarction, infection, cancer, cirrhosis, and the like. Pirfenidone is known to possess both anti-fibrotic and anti-inflammatory activities. For example, the patient suffers from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases. For example, IPF and scleroderma (or systemic sclerosis) associated interstitial lung disease (SSc-ILD) share overlapping pathologic pathways, most notably the activation and proliferation of fibroblasts, expression of fibrogenic cytokines and growth factors, and progressive interstitial fibrosis (Tzouvelekis et al. 2005; Castro and Jimenez 2010; Collard et al. 2010; Hummers 2010; van den Blink et al. 2010; Richards et al. 2012; Vij and Noth 2012). IPF and SSc-ILD also have biomarkers in common, including CCL 18, SP-A, SP D, KL 6, ICAM-1, VCAM 1, CCL 2, YKL-40, and vWF.

Any of the uses or methods described herein can be carried out for avoiding the potential for reduced clearance of pirfenidone and/or for avoiding the potential for increased exposure to pirfenidone and/or to reduce side effects or toxicity of pirfenidone administration and/or to improve the safety of pirfenidone administration. As detailed in the examples herein, a patient concurrently receiving both pirfenidone and ciprofloxacin at a dose of 750 mg will experience an increased exposure to pirfenidone of about 1.8-fold, due to the reduced clearance of pirfenidone. The uses or methods described herein avoid such increased exposure, thereby reducing dose-dependent side effects or toxicity associated with pirfenidone. For example, reducing a 2403 mg dose by about one-half to about one-third, when concomitantly administering ciprofloxacin at a dose of 750 mg, will result in an effective pirfenidone exposure that is equivalent to a 2403 mg dose when given in the absence of ciprofloxacin. Similarly, reducing a 1800 mg dose by about one-half to about one-third when concomitantly administering ciprofloxacin at a dose of 750

mg, will result in an effective pirfenidone exposure that is equivalent to a 1800 mg dose when given in the absence of ciprofloxacin.

In another aspect, the disclosure provides a package or kit comprising (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling directing or disclosing any of the methods or embodiments disclosed herein.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** depicts the mean (±Standard Deviation (SD)) concentration of pirfenidone and 5-carboxy-pirfenidone versus time since dose of ciprofloxacin.

DETAILED DESCRIPTION OF THE INVENTION

Pirfenidone is an orally active, anti-fibrotic agent. Results of in vitro experiments indicated that pirfenidone is primarily metabolized by CYP1A2 with multiple other CYPs contributing as well (i.e., 1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2) [U.S. Pat. No. 7,816,383, incorporated by reference herein in its entirety]. The data reported herein show that, in vivo, CYP1A2 is responsible for the vast majority of pirfenidone metabolism (70-80%).

Oral administration of pirfenidone results in the formation of four metabolites, 5 hydroxymethyl-pirfenidone, 5 carboxy-pirfenidone, 4'-hydroxy-pirfenidone, and the 5 O-acyl glucuronide metabolite of 5 carboxy-pirfenidone. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities; none of the other metabolites occur in sufficient quantities to allow for PK analysis. There are no unique human metabolites.

Data reported herein show that co-administration of an oral dose of 801 mg pirfenidone with an oral dose of 750 mg ciprofloxacin resulted in an approximate 1.8-fold (~81%) increase in exposure (AUC, or Area Under the Curve) of pirfenidone. Thus, for example, a patient receiving a daily dose of 2403 mg may be exposed to pirfenidone levels equivalent to a dose of about 4325 mg pirfenidone. In contrast, a patient receiving a daily dose that is reduced from 2403 mg by about one-third to about one-half may be exposed to pirfenidone levels equivalent to a dose of about 2403 mg. Computer modeling of the effect of lower doses of ciprofloxacin, e.g. the 500 mg or 250 mg oral doses, suggests less of an effect on pirfenidone levels, e.g. an approximately 1.5-fold or 1.3-fold increase in exposure, respectively.

DEFINITIONS

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

As used herein, a patient "in need of pirfenidone therapy" is a patient who would benefit from administration of pirfenidone. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. Pirfenidone is a known anti-fibrotic agent, so such disorders include fibrotic disorders, such as fibrotic disorders of the lung, kidney, liver, heart, or other organs. Other disorders that would benefit from therapy with pirfenidone include inflammatory disorders or autoimmune disorders. Yet other disorders that would benefit from therapy with pirfenidone include diseases that result in fibrosis, or where accompanying fibrosis is responsible in part for symptoms or complications of the disease, such as infarctions (tissue death), infection, cancer, cirrhosis, and the like. For example, such diseases or conditions include pulmonary fibrosis, idiopathic pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, and/or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute and chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke and ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute and chronic pain; allergies, including allergic rhinitis and allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, and non-small cell lung cancer; graft-versus-host reaction; and auto-immune diseases, such as multiple sclerosis, lupus and fibromyalgia; AIDS and other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) and cytomegalovirus; and diabetes mellitus. In addition, the methods of the embodiments can be used to treat proliferative disorders (including both benign and malignant hyperplasias), including acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases, and the like; pain disorders including neuromus-

cular pain, headache, cancer pain, dental pain, and arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, and infantile hemangioma; conditions associated with the cyclooxygenase and lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, and pain); organ hypoxia; thrombin-induced platelet aggregation; protozoal diseases.

As used herein, a patient in need of "ciprofloxacin therapy" is understood to be a patient in need of "antibiotic therapy" or "fluoroquinolone therapy." Such patients include patients suffering from bacterial infections.

For CYP enzymes, the FDA generally defines a "strong inhibitor" as one that caused a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance of CYP substrates (not limited to sensitive CYP substrate) in clinical evaluations. The FDA generally defines a "moderate inhibitor" as one that caused a >2- but <5-fold increase in the AUC values or 50-80% decrease in clearance of sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations.

Avoiding or Discontinuing Administration of Pirfenidone or Ciprofloxacin

As used herein, the term "avoid" and forms thereof are contemplated to have as alternatives the terms abstain, desist, forbear, and refrain, and forms thereof. In some cases, the alternative terms will be equivalent. For example, "avoiding" means "refraining from." *Merriam-Webster Online Dictionary,* 11th ed., 24 Nov. 2009. As used herein, the term "discontinue" and forms thereof are contemplated to have as alternatives the terms cease, stop, suspend, and quit.

The first aspect of the invention relates to avoiding concomitant use of pirfenidone in a patient with ciprofloxacin at a dose equivalent to 750 mg orally, e.g. 750 mg twice per day (1500 mg/day). It is understood that the patient is in need of pirfenidone therapy and in need of antibiotic therapy. In such methods, pirfenidone is avoided during ciprofloxacin administration, or ciprofloxacin is avoided during pirfenidone administration. In related methods, pirfenidone is discontinued during ciprofloxacin administration or ciprofloxacin is discontinued during pirfenidone administration. Due to the typically short-term nature of ciprofloxacin therapy, it will usually be more convenient to discontinue pirfenidone for the time period of ciprofloxacin administration. The pirfenidone dose that is avoided may be any dose, e.g. ranging from about 1000 to about 4000 mg pirfenidone, or about 1800 mg to about 3600 mg pirfenidone, or about 1800 to about 2500 mg pirfenidone, or about 2200 to about 2600 mg pirfenidone.

In embodiments of such methods, the methods avoid concomitant administration of pirfenidone and ciprofloxacin at equivalent doses by other routes. Intravenous (i.v.) dosing of ciprofloxacin 400 mg i.v. three times per day (every 8 hours) is considered the equivalent of 750 mg orally twice per day.

In some embodiments in which pirfenidone is discontinued during concomitant ciprofloxacin administration at a dose of 750 mg, e.g. 750 mg twice per day, pirfenidone is discontinued and/or restarted within 1, 2, 3, 4, 5, or 6 days or 1 week prior to or after the time period of ciprofloxacin use. In various embodiments, the time period of ciprofloxacin use is, e.g., about 1 week, 2 weeks, 3 weeks, 4 weeks, or 1 month.

In one aspect, concomitant administration of ciprofloxacin at a daily dose of 1500 mg per day (750 mg twice per day) should be avoided during pirfenidone therapy due to the potential for reduced clearance of pirfenidone. The ciprofloxacin dose that is avoided may be within a dosage range (for example and without limitation, between about 650 mg to about 850 mg, optionally given twice per day for a total daily dose of about 1300 mg to about 1700 mg, or between about 700 mg to about 800 mg, optionally given twice per day for a total daily dose of about 1400 mg to about 1600 mg). If ciprofloxacin at a dose of 750 mg cannot be avoided, then the total daily dose of pirfenidone should be reduced during concomitant ciprofloxacin administration.

Selecting an Alternative Drug to Administer Concurrently with Pirfenidone Therapy

In examples of methods involving avoiding ciprofloxacin at 750 mg, the methods comprise administering a therapeutically effective amount of pirfenidone to the patient, and administering an alternative antibiotic therapy that is not ciprofloxacin and preferably is not a strong inhibitor of CYP1A2. In some examples, the alternative drug is another fluoroquinolone. In some examples, the alternative drug is also not a moderate to strong inhibitor of both CYP1A2 and another CYP selected from the group consisting of CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

In some embodiments, the patient is administered ciprofloxacin at an alternative dosage (i.e., lower than 750 mg). Thus, in various embodiments, the patient is administered ciprofloxacin at a dose that is 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg, optionally wherein said dose is given two times per day (i.e., BID).

Improving Administration of Pirfenidone by Advising or Cautioning Patient

In some aspects, the disclosure provides a method of administering pirfenidone therapy to a patient in need of pirfenidone therapy (e.g., a patient with IPF), involving administering to the patient a therapeutically effective amount of pirfenidone, and advising the patient in any one, two, three or more of the following ways:

(a) advising the patient that ciprofloxacin at a dose of 750 mg (or between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg), optionally wherein said dose is given twice per day, should be avoided or discontinued,

(b) advising the patient that co-administration of pirfenidone with ciprofloxacin at a dose of 750 mg (or between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg), optionally wherein said dose is given twice per day, can alter the therapeutic effect or adverse reaction profile of pirfenidone,

(c) advising the patient that the dose of pirfenidone should be reduced in patients being treated with ciprofloxacin at a dose of 750 mg (or between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg), optionally wherein said dose is given twice per day,

(d) advising the patient that co-administration of pirfenidone and ciprofloxacin at 750 mg resulted in an approximate 1.8-fold increase in exposure to pirfenidone, and/or (e) advising the patient that ciprofloxacin at 750 mg (or between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg), optionally wherein said dose is given twice per day, should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance and/or increased pirfenidone exposure.

Dosing and Dose Modifications

In various embodiments of the methods described herein, a method of administering pirfenidone and ciprofloxacin concurrently is provided wherein the patient is administered ciprofloxacin at a dosage equivalent to 750 mg orally, e.g. 750 mg twice daily or the patient is administered ciprofloxacin within a dosage range of between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg, optionally wherein said dose is given twice daily, and the patient is administered a reduced dosage of pirfenidone, given orally or

by other routes (reduced relative to a patient not taking ciprofloxacin, or relative to the previously administered pirfenidone dosage in the patient). Preferably the dosage of pirfenidone is decreased by about one-half to one-third.

Pirfenidone can be dosed at a total amount of about 50 mg to about 4005 mg, or about 1000 to about 4000 mg pirfenidone, or about 1800 mg to about 3600 mg pirfenidone, or about 1800 to about 2500 mg pirfenidone, or about 2200 to about 2600 mg pirfenidone. In some embodiments, the amount of pirfenidone being administered prior to ciprofloxacin administration is 2400 mg/day or 2403 mg/day. The dosage can be divided into two or three doses over the day or given in a single daily dose. In some embodiments, three capsules of pirfenidone, each capsule comprising about 267-mg of pirfenidone, are administered three times per day. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 267 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 534 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1068 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1335 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1602 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1869 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2136 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg and about 2403 mg. A reduction of one-third to one-half can be readily calculated.

Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 30 mg/kg, about 5 mg/kg to about 30 mg/kg, about 10 mg/kg to about 40 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 35 mg/kg. A reduction of one-third to one-half can be readily calculated.

In one embodiment, a dosage amount of pirfenidone is taken with food. In another embodiment, the patient is instructed to administer the dosage of pirfenidone with food.

In some embodiments, the dose is reduced by about one-half to one-third (e.g. 50% to 67%). In specific embodiments, the dose is reduced by about ⅓ relative to the previously administered dose. In further embodiments, the dose is reduced by about 40%, 50%, 60%, 70% or more relative to the previously administered dose, or to a dose ranging from about 40% to about 70%, or about 50% to about 70% of the previously administered dose.

For example, when the patient has been receiving about 2403 mg/day pirfenidone, the pirfenidone dose is reduced to a range of about 1200 mg/day to about 1700 mg/day, or a range of about 1400 mg/day to about 1650 mg/day, during concomitant ciprofloxacin use.

As another example, when the patient has been receiving about 1800 mg/day pirfenidone, the pirfenidone dose is reduced to a range of about 900 mg/day to about 1300 mg/day, or a range of about 1000 mg/day to about 1250 mg/day, during concomitant ciprofloxacin use.

It is understood that, in such embodiments involving dose reduction, upon discontinuation of ciprofloxacin at a dose of 750 mg or higher (or between about 650 mg to about 850 mg, or between about 700 mg to about 800 mg), e.g. twice daily, the dosage of pirfenidone is titrated back up to the maximum recommended dose for the patient. In some embodiments, the dose of pirfenidone is titrated back up to a dose that is not less than 2400 or 2403 mg/day.

As noted above, in any of the embodiments described herein, including but not limited to discontinuation or dose reduction, the packages and kits, and/or the methods of preparing or packaging pirfenidone, the pirfenidone, uses, methods, packages, kits, advice, warnings, discontinuation or dose titration may apply not only to the oral dose of 750 mg ciprofloxacin, e.g. given twice daily, but also to any other equivalent dose given by another route. Intravenous (i.v.) dosing of ciprofloxacin 400 mg i.v. three times per day (every 8 hours) is considered the equivalent of 750 mg orally twice per day.

Packages, Kits, Methods of Packaging, and Methods of Delivering

In another aspect, a package or kit is provided comprising pirfenidone, optionally in a container, and a package insert, package label, instructions or other labeling including instructions or directions for any of the methods disclosed herein.

The package insert, package label, instructions or other labeling may further comprise directions for treating a patient in need of pirfenidone, e.g. with IPF or any other disorder or disease disclosed herein by administering pirfenidone, e.g., at a dosage of 2400 mg or 2403 mg per day.

In a related aspect, the disclosure provides a method of preparing or packaging a pirfenidone medicament comprising packaging pirfenidone, optionally in a container, together with a package insert or package label or instructions for any of the methods disclosed herein.

In some embodiments, a method of treating a patient in need of pirfenidone is disclosed comprising providing, selling or delivering any of the kits of disclosed herein to a hospital, physician or patient.

In some embodiments, a method of treating a patient in need of ciprofloxacin at 750 mg is provided comprising providing or delivering a kit comprising ciprofloxacin together with a package insert or package label or instructions for any of the methods disclosed herein, to a hospital, physician or patient.

The disclosure will be more fully understood by reference to the following examples which detail exemplary embodiments of the disclosure. They should not, however, be construed as limiting the scope of the disclosure. All citations throughout the disclosure are hereby expressly incorporated by reference.

Examples of Aspects and Embodiments of the Invention

1. Pirfenidone for use in treating a patient in need of pirfenidone therapy wherein the dosage of pirfenidone for administration to a patient is reduced by about one-half to about one-third, preferably one-third, during concomitant administration of ciprofloxacin at an oral dose of 750 mg, or at an oral dose of from 650 mg to 850 mg, or at an oral dose of from 700 mg to 800 mg, for example, 750 mg twice daily (1500 mg/day), or at an intravenous (i.v.) dose of 400 mg i.v. three times per day.

2a. Pirfenidone for use in treating a patient in need of pirfenidone therapy wherein the pirfenidone is for administering to the patient at a therapeutically effective amount, and avoiding concomitant administration of ciprofloxacin at an oral dose of 700 mg or higher, or at an oral dose of 750 mg or higher, for example, an oral dose of 750 mg or higher twice

daily (1500 mg or higher per day), or at an intravenous (i.v.) dose of 400 mg or higher i.v. three times per day.

2b. Pirfenidone for use in treating a patient in need of pirfenidone therapy wherein the administration of pirfenidone comprises a time period during which pirfenidone is avoided while ciprofloxacin is administered at an oral dose of 700 mg or higher, or at an oral dose of 750 mg or higher, for example, an oral dose of 750 mg or higher twice daily (1500 mg or higher per day), or at an intravenous dose of 400 mg or higher i.v. three times per day. It is understood that according to this aspect, once ciprofloxacin is discontinued, pirfenidone is restarted.

3. The pirfenidone for use of embodiment 1 wherein the pirfenidone dosage is reduced from about 2403 mg/day to a dosage ranging from about 1400 mg/day to about 1650 mg/day, optionally 1602 mg/day, during ciprofloxacin administration.

4. The pirfenidone for use of embodiment 1 wherein the pirfenidone dosage is reduced from about 1800 mg/day to a dosage ranging from about 1000 mg/day to about 1250 mg/day, optionally 1200 mg/day, during ciprofloxacin administration.

5. The pirfenidone for use of any of embodiments 1-4 wherein the pirfenidone for use is for avoiding the potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

6. The pirfenidone for use of any one of embodiments 1-5 wherein the total daily dose of pirfenidone is administered to the patient in divided doses three times per day, with food.

7. The pirfenidone for use of any of embodiments 1-6 wherein the pirfenidone is administered in unit dosage forms that are capsules or tablets.

8. The pirfenidone for use of embodiment 7 wherein the amount of pirfenidone in the unit dosage form is 200 mg or 267 mg.

9. The pirfenidone for use of embodiment 3 wherein during concomitant ciprofloxacin administration 534 mg of pirfenidone is administered to the patient three times per day, with food.

10. The pirfenidone for use of embodiment 3 wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of 1602 mg.

11. The pirfenidone for use of embodiment 3 wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of about 1600 mg.

12. The pirfenidone for use of any one of embodiments 1-11 wherein the patient has idiopathic pulmonary fibrosis (IPF).

13. The pirfenidone for use of any of embodiments 1-11 wherein the patient has a fibrotic disorder, inflammatory disorder, or autoimmune disorder.

14. The pirfenidone for use of any of embodiments 1-11 wherein the patient suffers from a disease selected from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

15. Ciprofloxacin for use in treating a patient in need of ciprofloxacin therapy, for example, with a bacterial infection, wherein the dosage of ciprofloxacin is an oral dose of 750 mg, or an oral dose of from 650 mg to 850 mg, or an oral dose of from 700 mg to 800 mg, for example, 750 mg twice daily (1500 mg/day), or an intravenous (i.v.) dose of 400 mg i.v. three times per day, during concomitant administration of pirfenidone, wherein the dosage of pirfenidone for administration to the patient is reduced by about one-half to about one-third, preferably one-third.

16. Ciprofloxacin for use in treating a patient in need of ciprofloxacin therapy wherein the ciprofloxacin is for administration at an oral dose of 700 mg or higher, or at an oral dose of 750 mg or higher, for example, an oral dose of 750 mg or higher twice daily (1500 mg or higher per day), or at an intravenous (i.v.) dose of 400 mg or higher i.v. three times per day, wherein (a) pirfenidone is avoided during concomitant administration of ciprofloxacin, or (b) ciprofloxacin is avoided during concomitant administration of pirfenidone.

17. Ciprofloxacin for use in treating a patient in need of ciprofloxacin therapy wherein the administration of ciprof-

loxacin occurs during a time period in which pirfenidone is avoided while ciprofloxacin is administered at an oral dose of 700 mg or higher, or at an oral dose of 750 mg or higher, for example, an oral dose of 750 mg or higher twice daily (1500 mg or higher per day), or at an intravenous dose of 400 mg or higher i.v. three times per day. It is understood that according to this aspect, once ciprofloxacin is discontinued, pirfenidone is restarted.

18. The ciprofloxacin for use of embodiment 15 wherein the pirfenidone dosage is reduced from about 2403 mg/day to a dosage ranging from about 1400 mg/day to about 1650 mg/day, optionally 1602 mg/day, during ciprofloxacin administration.

19. The ciprofloxacin for use of embodiment 15 wherein the pirfenidone dosage is reduced from about 1800 mg/day to a dosage ranging from about 1000 mg/day to about 1250 mg/day, optionally 1200 mg/day, during ciprofloxacin administration.

20. The ciprofloxacin for use of any of embodiments 16-17 wherein the pirfenidone is avoided to avoid the potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

21. The ciprofloxacin for use of embodiment 15 wherein during concomitant ciprofloxacin administration 534 mg of pirfenidone is administered to the patient three times per day, with food.

22. The ciprofloxacin for use of embodiment 15 wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of 1602 mg.

23. The ciprofloxacin for use of embodiment 15 wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of about 1600 mg.

24. The ciprofloxacin for use of any one of embodiments 15-23 wherein the patient has idiopathic pulmonary fibrosis (IPF).

25. The ciprofloxacin for use of any of embodiments 15-23 wherein the patient has a fibrotic disorder, inflammatory disorder, or autoimmune disorder.

26. The ciprofloxacin for use of any of embodiments 15-23 wherein the patient suffers from a disease selected from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

27. Use of pirfenidone at a total daily dose that is reduced by about one-half to about one-third, during concomitant use of ciprofloxacin at a dose of between about 650 mg to about 850 mg twice daily.

28. Pirfenidone for use at a total daily dose that is reduced, by about one-half to about one-third, during concomitant use of ciprofloxacin at a dose of between about 650 mg to about 850 mg twice daily.

29. The use of embodiment 27, or the pirfenidone for use of embodiment 28, where the concomitant use of ciprofloxacin is at a dose of between about 700 mg to about 800 mg twice daily.

30. The use of embodiment 27, or the pirfenidone for use of embodiment 28, where the concomitant use of ciprofloxacin is at a dose of 750 mg twice daily (1500 mg/day).

31. The use or pirfenidone for use of any one of embodiments 27-30 wherein the total daily dose of pirfenidone is reduced from about 2403 mg/day to between about 1400 mg/day to about 1650 mg/day.

32. The use or pirfenidone for use of any one of embodiments 27-30 wherein the total daily dose of pirfenidone is reduced from about 2403 mg/day to about 1602 mg/day.

33. The use or pirfenidone for use of any one of embodiments 27-30 wherein the total daily dose of pirfenidone is reduced from about 1800 mg/day to between about 1000 mg/day to about 1250 mg/day.

34. The use or pirfenidone for use of any one of embodiments 27-30 wherein the total daily dose of pirfenidone is reduced from about 1800 mg/day to about 1200 mg/day.

35. The use or pirfenidone for use of any of embodiments 27-34 for avoiding potential for a reduced clearance of pirfenidone or potential for an increased exposure to pirfenidone.

36. The use or pirfenidone for use of any one of embodiments 27-35 wherein the total daily dose of pirfenidone is for administration in divided doses three times per day, with food.

37. The use or pirfenidone for use of any of embodiments 27-36 wherein the pirfenidone is in one or more unit dosage forms that are capsules or tablets.

38. The use or pirfenidone for use of embodiment 37 wherein the amount of pirfenidone in each of the one or more unit dosage forms is 200 mg or 267 mg.

39. The use or pirfenidone for use of embodiment 37 wherein the pirfenidone is in a 267 mg capsule.

40. The use or pirfenidone for use of any one of embodiments 27-32, 35-39, wherein the amount of pirfenidone is 534 mg, in two unit dosage forms for administration three times per day, with food.

41. The use or pirfenidone for use of any one of embodiments 27-31, 35-40, wherein the total daily dose of pirfenidone is reduced to 1602 mg/day.

42. The use or pirfenidone for use of any one of embodiments 27-31, 35-40, wherein the total daily dose of pirfenidone is reduced to about 1600 mg/day.

43. The use or pirfenidone for use of any one of embodiments 27-42 in a patient that has idiopathic pulmonary fibrosis (IPF).

44. The use or pirfenidone for use of any of embodiments 27-42 in a patient that has a fibrotic disorder, inflammatory disorder, or autoimmune disorder.

45. The use or pirfenidone for use of any of embodiments 27-42 in a patient that suffers from a disease selected from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonehritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal. carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

46. Use of pirfenidone at a total daily dose of 1602 mg/day, for the treatment of a fibrotic disorder in a patient concomitantly receiving ciprofloxacin at a dose of 750 mg three times daily.

47. Pirfenidone for use at a total daily dose of 1602 mg/day for the treatment of a fibrotic disorder in a patient concomitantly receiving ciprofloxacin at a dose of 750 mg three times daily

48. Use of pirfenidone or pirfenidone for use according to embodiments 46 and 47 adapted for administration in one or more unit dosage forms three times daily.

49. Use of pirfenidone or pirfenidone for use according to embodiment 48 wherein the unit dosage form is 267 mg capsule.

50. Use of pirfenidone or pirfenidone for use according to any of embodiments 46-49 wherein the fibrotic disorder is selected from the group consisting of idiopathic pulmonary fibrosis (IPF), bronchiolitis obliterans (BO), renal fibrosis and scleroderma.

51. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and 1602 mg pirfenidone in one or more unit dosage forms for use to treat a fibrotic disorder in a patient concomitantly receiving ciprofloxacin at a dose of 750 mg twice daily.

52. The pharmaceutical composition according to embodiment 51 wherein the fibrotic disorder is selected from the group consisting of idiopathic pulmonary fibrosis (IPF), bronchiolitis obliterans (BO), renal fibrosis and scleroderma.

53. A package or kit comprising (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling for the use or pirfenidone for use according to any of embodiments 27-52.

EXAMPLES

Example 1

An Open-Label Phase 1 Study to Determine the Impact of Ciprofloxacin on the Pharmacokinetics and Safety of Pirfenidone

A Phase 1, open-label crossover study was carried out to investigate the impact of ciprofloxacin administration on the pharmacokinetics and safety of pirfenidone. The study

enrolled 27 healthy subjects. Subjects were enrolled at one Phase 1 clinical center and were screened up to 28 days before dosing. After meeting inclusion/exclusion criteria, subjects were admitted to the clinic on Day −1 in preparation for dosing with a single 801 mg dose of pirfenidone with food on Day 1. Subjects had blood and urine samples collected for pharmacokinetic (PK) analysis of pirfenidone and its major metabolite, 5-carboxy-pirfenidone, before dosing (blood PK only) and at various times during the 32 hours (h) after the pirfenidone dose. Subjects were discharged from the clinic on Day 2 after safety assessments and the final PK sample collection. On Days 2 through 7, subjects received ciprofloxacin, a moderate CYP1A2 inhibitor (self-administered while outside the clinic). On Days 2 through 6, subjects completed diary cards, on which they recorded ciprofloxacin dosing and any adverse events (AEs) experienced. On Day 5, subjects were readmitted to the clinic. On Day 6, each subject received a single 801-mg dose of pirfenidone in addition to the ciprofloxacin. Blood and urine samples were collected for pirfenidone and 5-carboxy-pirfenidone PK analysis, using the same sampling schedule as on Day 1. All subjects were discharged on Day 7 after safety assessments and the final PK sample collection. A follow-up telephone call occurred approximately 24 h after subjects were discharged from the clinic (Day 8).

Ciprofloxacin inhibits CYP1A2 activity [Karjalainen et al., *Basic and Clinical Pharmacology & Toxicology* 103: 157-165 (2008)]. The selected dose of ciprofloxacin (750 mg twice daily [BID]) is higher than the typical prescribed doses of 250-500 mg BID and was chosen to maximize the CYP1A2 inhibition effects of this drug. The duration of ciprofloxacin administration, before concurrent administration of pirfenidone and subsequent PK sampling, was 4 days. Given the short half-life of ciprofloxacin (approximately 3-5 hours), steady-state would be achieved well within the 4 days of dosing.

Inclusion criteria included the following:

- 18 to 55 years old (inclusive) at the time of consent
- Body mass index (BMI) of 18 kg/m^2 to 40 kg/m^2 (inclusive)
- No pregnancy
- Abstaining from alcohol from 48 h before dosing through the final study visit.
- In good health as indicated by medical history, physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory assessments.

Exclusion criteria included the following:

- History of or active cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or neurological disorders capable of altering the absorption, metabolism, or elimination of drugs
- History of clinically significant illness within 30 days before the first dose of study drug
- Previous adverse event (AE), allergic reaction, or sensitivity to ciprofloxacin
- Consumption of grapefruit, grapefruit juice, or any fruit juice within 48 h before the first dose of study drug
- Use of products containing alcohol, caffeine, or xanthine within 48 h before dosing
- Consumption of cruciferous vegetables (i.e., broccoli, brussels sprouts, kale, etc.) or chargrilled meat within 48 h before dosing
- Use of tobacco products within 3 months of first dose of study drug
- Use of concomitant medications (including non-prescription drugs)

Dosing

Pirfenidone

801 mg (given as 3×267-mg capsules) orally with food in the morning on Days 1 and 6.

Ciprofloxacin

750-mg tablets orally, as follows:

Day 2: 750 mg in the evening

Days 3-6: 750 mg twice a day (BID)

Day 7: 750 mg in the morning.

The 750 mg BID dose of ciprofloxacin was chosen as the most likely to result in a moderate and relatively selective inhibition of CYP1A2 activity [Karjalainen et al., *Basic and Clinical Pharmacology & Toxicology* 103: 157-165 (2008)]. This dose is approved for use in severe infections but is higher than the more commonly prescribed dose of 500 mg BID, thereby providing a "worst-case" scenario for selective, moderate CYP1A2 inhibition.

Duration of Treatment:

Pirfenidone on Days 1 and 6; ciprofloxacin on Days 2 through 7

Statistical Methods

Pharmacokinetics:

The PK population was defined as subjects who received both doses of pirfenidone (Days 1 and 6), had at least 4 plasma PK samples, were at least 80% compliant with ciprofloxacin dosing on Days 2, 3, and 4 (i.e., administered at least 3000 mg of the protocol-mandated doses), and who had administered the entire amount of all doses of ciprofloxacin on Days 5, 6, and 7 (3750 mg total).

Both noncompartmental methods and a previously derived population PK (i.e., compartmental) model were used to analyze the plasma concentration-time data and characterize individual subject PK parameters. Effects of ciprofloxacin coadministration on pirfenidone and its primary metabolite, 5-carboxy pirfenidone, $AUC_{0-\infty}$ and C_{max} were tested using accepted criteria for bioequivalence for paired data.

Safety:

The Safety population was defined as subjects who received any amount of pirfenidone or ciprofloxacin.

Results

Baseline Subject Characteristics:

The study group consisted of 17 males and 10 females, ranging in age from 18 to 49 years (median 24 years). The study group was predominantly white (21 subjects, 77.8%) with 2 subjects (7.4%) each of American Indian/Alaska Native, Asian, and black/African-American race. BMI ranged from 18.6 to 32.6 kg/m^2 (median 24.4 kg/m^2). Medical histories were generally unremarkable, and no subjects were receiving any concomitant medications at Baseline.

Pharmacokinetic Results:

For pirfenidone with coadministration of ciprofloxacin, the differences in C_{max} and T_{max} (time to peak plasma concentration) were modest between Day 1/2 and Day 6/7; the geometric mean C max was approximately 20% higher on Day 6/7 while median T_{max} was the same on both occasions (2 h). The apparent terminal elimination half-life for pirfenidone was slightly prolonged on Day 6/7, but remained relatively short (geometric mean of 4.1 h vs. 2.4 h on Day 1/2). The most pronounced effect of ciprofloxacin coadministration on pir-

fenidone was seen with $AUC_{0-\infty}$, which was approximately 78% higher with coadministration of ciprofloxacin on Day 6/7 compared with Day 1/2.

For 5-carboxy-pirfenidone, the differences in C_{max} and T_{max} were also modest when comparing Day 1/2 with Day 6/7; the trend for C_{max} was reversed (40% lower with ciprofloxacin coadministration on Day 6/7), and the median T_{max} estimates were again identical. The trends in apparent terminal elimination half-life were similar to those seen for pirfenidone; slightly prolonged on Day 6/7, but remaining relatively short (geometric mean of 4.0 h vs. 2.6 h on Day 1/2). The effect of ciprofloxacin coadministration on 5-carboxy-pirfenidone $AUC_{0-\infty}$ was less pronounced; the Day 6/7 geometric mean was only 7.7% lower than that on Day 1/2.

Based on bioequivalence criteria, the coadministration of ciprofloxacin with pirfenidone causes a statistically significant increase in $AUC_{0-\infty}$ (geometric mean ratio [GMR][90% confidence interval (CI)] of 1.81 [1.70-1.93]). The magnitude of the effect (<2-fold increase in exposure) indicates that ciprofloxacin would be classified as a mild inhibitor of pirfenidone clearance at the administered dose of 750 mg (EMEA 2010; US FDA 2006). The effect on pirfenidone C_{max} was more modest but still statistically significant (GMR [90% CI] of 1.23 [1.14-1.31]). There was not a statistically significant effect of ciprofloxacin coadministration on 5-carboxy-pirfenidone $AUC_{0-\infty}$ (GMR [90% CI] of 0.96 [0.92-1.00]). However, the delay in pirfenidone clearance resulted in a statistically significant decrease in the 5-carboxy-pirfenidone C_{max} (GMR [90% CI] of 0.62 [0.57-0.66]).

Safety Results:

Twenty-five treatment-emergent adverse events (TEAEs) were reported for 9 subjects (33.3%). For most of these 9 subjects, the greatest severity of AE was mild (7 subjects, 25.9%); while for 2 subjects (7.4%), the most severe AE reported was moderate. Both moderate AEs were considered not related to either study drug.

For 6 subjects, the strongest pirfenidone relationship for AEs, as assessed by the investigator, was probably related to pirfenidone. One subject experienced AEs considered related to pirfenidone on Day 1 (dosing with pirfenidone only); the remaining 5 subjects experienced AEs only on Day 6 (coadministration with ciprofloxacin

CONCLUSIONS

A statistically significant increase in both $AUC_{0-\infty}$ and C_{max} of pirfenidone was observed with administration of ciprofloxacin 750 mg BID (a high dose of a moderate and relatively selective CYP1A2 inhibitor) for 5 days. However, the magnitude of the effect was relatively modest: An 81% increase (i.e., <2-fold) for $AUC_{0-\infty}$ and a 23% increase in pirfenidone C_{max} were observed with coadministration of ciprofloxacin (see FIG. **1**).

TABLE 1

Summary statistics for plasma pharmacokinetic parameters, stratified by study day (N = 27).

Study Day	Statistic	C_{max} (μg/mL)	T_{max} (h)	$T_{1/2}$ (h)	$AUC_{0-\infty}$ (μg*hr/mL)
		Pirfenidone			
1/2 (Pre-Ciprofloxacin)	Mean (SD)	10.4 (2.14)	2.2 (0.64)	2.5 (0.6)	51.9 (14)
	% CV	20.5	28.8	23.8	27
	Median	10.4	2	2.4	53.2
	Min, Max	6.6, 14.4	1, 3	1.4, 3.6	30, 88.2
	Geometric Mean	10.7	2.2	2.4	50.8
	Geometric % CV	23.9	35.2	32.2	30.5
6/7 (During Ciprofloxacin)	Mean (SD)	12.7 (2.17)	2.6 (0.85)	4 (0.7)	93.2 (20)
	% CV	17.1	33.3	17.5	21.5
	Median	12.8	2	4	95.2
	Min, Max	7.3, 16.3	1, 4.1	2.8, 5.6	47.1, 126.6
	Geometric Mean	13	2.3	4.1	90.3
	Geometric % CV	18.5	39.8	19.1	24.5
		5-Carboxy-Pirfenidone			
1/2 (Pre-Ciprofloxacin)	Mean (SD)	6.1 (1.44)	2.3 (0.6)	2.7 (0.73)	30.9 (4.74)
	% CV	23.4	26.3	27.1	15.3
	Median	5.7	2	2.6	30.3
	Min, Max	4.4, 9.4	1, 3	1.4, 4.6	22.4, 42.9
	Geometric Mean	6.5	2.2	2.6	32.6
	Geometric % CV	27.4	35.2	39.2	16.8
6/7 (During Ciprofloxacin)	Mean (SD)	3.8 (0.8)	2 (0.76)	4.2 (0.93)	29.6 (4.52)
	% CV	21.1	38.6	22.3	15.3
	Median	3.8	2	4	29.1
	Min, Max	2.6, 5.4	1, 4	2.6, 6.1	19.7, 39.4
	Geometric Mean	3.8	2.1	4	30.1
	Geometric % CV	23.6	48.6	23.5	16.9

C_{max} = peak plasma concentration
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = apparent terminal elimination half-life
$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time zero to infinity

TABLE 2

Effect of ciprofloxacin coadministration on pirfenidone (N = 27).

Analyte/Parameter	Geometric Mean Ratio[a] (90% Confidence Interval)[b]
Pirfenidone	
$AUC_{0-\infty}$	1.81 (1.70, 1.93)
C_{max}	1.23 (1.14, 1.31)

TABLE 2-continued

Effect of ciprofloxacin coadministration on pirfenidone (N = 27).

Analyte/Parameter	Geometric Mean Ratio[a] (90% Confidence Interval)[b]
5-Carboxy-Pirfenidone	
$AUC_{0-\infty}$	0.96 (0.92, 1.00)
C_{max}	0.62 (0.57, 0.66)

[a]Ratio of Day 6/7 (during ciprofloxacin dosing) to Day 1/2 (pre-ciprofloxacin dosing)
[b]To be labeled equivalent, the 90% confidence interval for the geometric mean ratio must fall entirely between 0.8 and 1.25.

Example 2

In Vitro-In Vivo Extrapolation (IVIVE) Studies

In vitro data have been shown to be useful for the simulation of in vivo drug-drug interactions [Ito et al., *Drug Metabolism and Disposition* 33(6): 837-844 (2005); Karjalainen et al., Basic and Clinical Pharmacology & Toxicology 103: 157-165 (2008); McGinnity et al., *Drug Metabolism and Disposition* 36(6): 1126-1134 (2008); Zhang et al., *Acta Pharmacol Sin* 29(12): 1507-1514 (2008)]. In brief, the process involves combining in vitro knowledge regarding the properties of a potential inhibitor [IC_{50} values for various cytochrome P450 (CYP) enzymes] with the in vitro knowledge regarding the pathways of metabolism of a given substrate (fraction metabolized by various CYP enzymes). So called in vitro-in vivo extrapolations (IVIVE) allow for the modeling of predicted changes in substrate drug AUC (ΔAUC) values secondary to drug-drug interactions [McGinnity et al., *Drug Metabolism and Disposition* 36(6): 1126-1134 (2008)]. The results of IVIVE simulations conducted for pirfenidone are provided below and were compared to actual data from Example 1.

Ciprofloxacin-Pirfenidone IVIVE Simulations

Using the results of in vitro data for ciprofloxacin and hypothetical combinations of the fraction of pirfenidone metabolized by various CYP enzymes, the predicted ratio of the pirfenidone AUC before and during administration of ciprofloxacin were simulated. This was performed using Equation 1 below [taken from McGinnity et al., *Drug Metabolism and Disposition* 36(6): 1126-1134 (2008)]:

$$\Delta AUC = \frac{1}{\sum_{x=1}^{n}\left(\frac{fmx}{1+[I]\text{in},\,u/Kix}\right)+\left(1-\sum_{x=1}^{n} fmx\right)} \quad \text{Equation 1}$$

Where, $[I]_{in,u}$ is the free-drug concentration of the inhibitor (e.g., ciprofloxacin) entering the liver, K_{ix} is the K_i for ciprofloxacin for a given CYP and fm_x is the fraction of the substrate drug (pirfenidone) metabolized by that CYP enzyme. The estimates for $[I]_{in,u}$ and K_{ix} were taken from McGinnity et al. [*Drug Metabolism and Disposition* 36(6): 1126-1134 (2008)], while the estimates of fm_x were varied based on possible scenarios for pirfenidone based on existing in vitro data.

In these simulations, using hypothetical combinations of the fraction of pirfenidone metabolized by various CYP enzymes, the predicted ΔAUC for pirfenidone with concomitant ciprofloxacin administration were simulated. The estimates for $[I]_{in,u}$ and K_{ix} were taken from Zhang et al. [*Acta Pharmacol Sin* 29(12): 1507-1514 (2008)]. The results of the simulations for a ciprofloxacin dose of 750 mg BID, utilizing the "base case" and higher fractions metabolized are provided below in Table 3.

TABLE 3

Predicted impact of the 750 mg dose of ciprofloxacin co-administration on pirfenidone PK under several assumption scenarios for pirfenidone fraction metabolized by CYP1A2

CYP	$[I]_{in,u}$	K_i	fm	
Base Case				
1A2	78	67.5	0.48	
2C9	78	90	0.0925	
2C19	78	500	0.0925	
2D6	78	500	0.0925	
2E1			0.0925	
Predicted ΔAUC (fm_{1A2} = 0.48)				1.48
Postulated Predominance of CYP1A2 - 0.70				
1A2	78	67.5	0.70	
2C9	78	90	0.0375	
2C19	78	500	0.0375	
2D6	78	500	0.0375	
2E1			0.0375	
Predicted ΔAUC (fm_{1A2} = 0.70)				1.67
Postulated Predominance of CYP1A2 - 0.75				
1A2	78	67.5	0.75	
2C9	78	90	0.025	
2C19	78	500	0.025	
2D6	78	500	0.025	
2E1			0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.73
Postulated Predominance of CYP1A2 - 0.80				
1A2	78	67.5	0.80	
2C9	78	90	0.0125	
2C19	78	500	0.0125	
2D6	78	500	0.0125	
2E1			0.0125	
Predicted ΔAUC (fm_{1A2} = 0.80)				1.78

The results of the simulations for ciprofloxacin doses of 250 or 500 mg BID utilizing fm_{1A2} assumptions of 48% and 75% are provided below in Table 4; the only difference in the assumptions for these simulations is the lower $[I]_{in,u}$ due to the lower dose. This lower dose of ciprofloxacin would be expected to result in less of an effect on pirfenidone clearance. The predicted mean fold-change in pirfenidone AUC is 1.20-1.28 and 1.35-1.52 for dose of 250 mg BID and 500 mg BID, respectively, depending on assumptions for the fraction of pirfenidone metabolized by CYP1A2 in vivo.

TABLE 4

Predicted impact of the 250 or 500 mg dose of ciprofloxacin co-administration on pirfenidone PK under several assumption scenarios for pirfenidone fraction metabolized by CYP1A2

CYP	$[I]_{in,u}$	K_i	fm	
Base Case (Ciprofloxacin 250 mg BID)				
1A2	52	67.5	0.48	
2C9	52	90	0.0925	
2C19	52	500	0.0925	
2D6	52	500	0.0925	
2E1			0.0925	
Predicted ΔAUC (fm_{1A2} = 0.48)				1.20

TABLE 4-continued

Predicted impact of the 250 or 500 mg dose of ciprofloxacin co-administration on pirfenidone PK under several assumption scenarios for pirfenidone fraction metabolized by CYP1A2

CYP	$[I]_{in,u}$	K_i	fm	
Postulated Predominance of CYP1A2 - 0.75 (Ciprofloxacin 250 mg BID)				
1A2	52	67.5	0.70	
2C9	52	90	0.0375	
2C19	52	500	0.0375	
2D6	52	500	0.0375	
2E1			0.0375	
Predicted ΔAUC (fm_{1A2} = 0.70)				1.28
Base Case (Ciprofloxacin 500 mg BID)				
1A2	52	67.5	0.75	
2C9	52	90	0.025	
2C19	52	500	0.025	
2D6	52	500	0.025	
2E1			0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.35
Postulated Predominance of CYP1A2 - 0.75 (Ciprofloxacin 500 mg BID)				
1A2	52	67.5	0.80	
2C9	52	90	0.0125	
2C19	52	500	0.0125	
2D6	52	500	0.0125	
2E1			0.0125	
Predicted ΔAUC (fm_{1A2} = 0.80)				1.52

Hypothetical Inhibition of CYPs other than CYP1A2

Simulations were also run to predict the potential for drug-drug interactions with concomitant inhibitors of CYPs other than CYP1A2 such as CYP2C9, 2C19, 2D6, and 2E1. Given the fact that these other CYPs contribute to a smaller fraction of the in vivo metabolism of pirfenidone, hypothetical scenarios were simulated in which a drug had the theoretical ability to completely shut down one or more of CYP2C9, 2C19, 2D6, and 2E1. As shown in Table 5, complete inhibition of all four of these CYPs would only be predicted to result in an 8% increase in pirfenidone AUC. Inhibition of only one of these complementary pathways would not be expected to result in any increase in pirfenidone AUC. Note that these simulations assume that CYP1A2 is fully functional.

TABLE 5

Predicted impact of a hypothetical inhibitor of CYP2C9, 2C19, 2D6, and/or 2E1 on the PK exposure to pirfenidone with concomitant administration

CYP	$[I]_{in,u}$	K_i	fm	
Inhibition of All 4 Complementary CYPs				
1A2	2.2	5000	0.75	
2C9	2.2	0.0001	0.025	
2C19	2.2	0.0001	0.025	
2D6	2.2	0.0001	0.025	
2E1	2.2	0.0001	0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.08
Inhibition of 3 of the 4 Complementary CYPs				
1A2	2.2	5000	0.75	
2C9	2.2	0.0001	0.025	
2C19	2.2	0.0001	0.025	
2D6	2.2	0.0001	0.025	
2E1	2.2	5000	0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.05

TABLE 5-continued

Predicted impact of a hypothetical inhibitor of CYP2C9, 2C19, 2D6, and/or 2E1 on the PK exposure to pirfenidone with concomitant administration

CYP	$[I]_{in,u}$	K_i	fm	
Inhibition of 2 of the 4 Complementary CYPs				
1A2	2.2	5000	0.75	
2C9	2.2	0.0001	0.025	
2C19	2.2	0.0001	0.025	
2D6	2.2	5000	0.025	
2E1	2.2	5000	0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.03
Inhibition of 1 of the 4 Complementary CYPs				
1A2	2.2	5000	0.75	
2C9	2.2	0.0001	0.025	
2C19	2.2	5000	0.025	
2D6	2.2	5000	0.025	
2E1	2.2	5000	0.025	
Predicted ΔAUC (fm_{1A2} = 0.75)				1.00

Implications of IVIVE Simulation Results

Ciprofloxacin blocks only one, albeit major, pathway of pirfenidone metabolism (CYP1A2). A comprehensive review of all the relevant in vitro and in vivo data for pirfenidone coupled with IVIVE simulations suggests that CYP1A2 is responsible for 70-80% of the in vivo metabolism of pirfenidone (As shown in Table 6). IVIVE simulations in which a significantly lower or higher fraction metabolized by CYP1A2 were assumed resulted in ΔAUC predictions that were inconsistent with the observed AUC ratios in a Phase 1 clinical trial (see Example 1).

TABLE 6

Comparison of IVIVE simulation results with observations from a Phase 1 drug-drug interaction study (described in Example 1)

Interacting Drug	Source	fm_{1A2}	ΔAUC
Ciprofloxacin	IVIVE	0.48	1.48
		0.70	1.67
		0.75	1.73
		0.80	1.78
	Clinical study (Example 1)	—	1.81

While the present disclosure has been described in terms of various embodiments and examples, it is understood that variations and improvements will occur to those skilled in the art.

What is claimed is:

1. An improved method of administering pirfenidone therapy to treat a patient suffering from a fibrotic disorder, inflammatory disorder, or autoimmune disorder comprising reducing the dosage of pirfenidone administered to the patient by about one-half to about one-third during concomitant administration of ciprofloxacin at a dose of 750 mg twice daily (1500 mg/day).

2. A method of administering pirfenidone therapy to treat a patient suffering from a fibrotic disorder, inflammatory disorder, or autoimmune disorder, comprising administering to the patient a therapeutically effective amount of pirfenidone, and avoiding concomitant administration of ciprofloxacin at a dose of 750 mg.

3. The method of claim **1** wherein the pirfenidone dosage is reduced from about 2403 mg/day to a dosage ranging from

about 1400 mg/day to about 1650 mg/day, optionally 1602 mg/day, during ciprofloxacin administration.

4. The method of claim **1** wherein the pirfenidone dosage is reduced from about 1800 mg/day to a dosage ranging from about 1000 mg/day to about 1250 mg/day, optionally 1200 mg/day, during ciprofloxacin administration.

5. The method of claim **1** wherein the method is for avoiding the potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

6. The pirfenidone of claim **1** wherein the total daily dose of pirfenidone is administered to the patient in divided doses three times per day, with food.

7. The method of claim **1** wherein the pirfenidone is administered in unit dosage forms that are capsules or tablets.

8. The method of claim **7** wherein the amount of pirfenidone in the unit dosage form is 200 mg or 267 mg.

9. The method of claim **1** wherein during concomitant ciprofloxacin administration 534 mg of pirfenidone is administered to the patient three times per day, with food.

10. The method of claim **1** wherein during the concomitant administration of ciprofloxacin the pirfenidone is administered at a total daily dosage of 1602 mg.

11. The method of claim **1** wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of about 1600 mg.

12. The method of claim **1** wherein the patient has idiopathic pulmonary fibrosis (IPF).

13. An improved method of administering pirfenidone therapy to treat a patient comprising reducing the dosage of pirfenidone administered to the patient by about one-half to about one-third during concomitant administration of ciprofloxacin at a dose of 750 mg twice daily (1500 mg/day), wherein the patient suffers from a disease selected from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, Hermansky-Pudlak syndrome, neurofibromatosis, diabetic retinopathy, skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofacial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis, hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Huntington's disease; Parkinson's disease; acute or chronic pain; allergic rhinitis, allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synoviitis; muscle degeneration, bursitis; tendonitis; tenosynoviitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, osteoporosis, multiple myeloma-related bone disorders; metastatic breast carcinoma, colorectal carcinoma, graft-versus-host reaction; multiple sclerosis, lupus, fibromyalgia; AIDS, viral diseases, Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) cytomegalovirus; diabetes mellitus, acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, colorectal carcinoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; solid tumor angiogenesis, ocular neovascularization, infantile hemangioma; organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

14. The method of claim **10** wherein the patient has idiopathic pulmonary fibrosis (IPF).

15. The method of claim **10** wherein the patient suffers from a disease selected from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, myocardiac fibrosis, musculoskeletal fibrosis, post-surgical adhesions, renal fibrotic disease, fibrotic vascular disease, Hermansky-Pudlak syndrome, neurofibromatosis, lymph node fibrosis associated with HIV, inflammatory pulmonary fibrosis, pancreatic fibrosis; hepatic fibrosis; or renal fibrosis.

16. The method of claim **14** wherein the total daily dose of pirfenidone is administered to the patient in divided doses three times per day.

17. The method of claim **16** wherein the pirfenidone is administered with food.

18. The method of claim **13** wherein during concomitant ciprofloxacin administration the pirfenidone is administered at a total daily dosage of 1602 mg.

* * * * *

EXHIBIT 16

US009561217B2

(12) **United States Patent**
Kiyonaka et al.

(10) **Patent No.: US 9,561,217 B2**
(45) **Date of Patent: *Feb. 7, 2017**

(54) **PHARMACEUTICAL COMPOSITION CONTAINING AS AN ACTIVE INGREDIENT 5-METHYL-1-PHENYL-2-(1H)-PYRIDONE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

A tablet characterized by comprising 5-methyl-1-phenyl-2-(1H)-pyridone as the main ingredient and, based on the main ingredient, 10 to 50 wt. % excipient, 5 to 40 wt. % disintegrator, 1 to 10 wt. % binder, 0.5 to 5 wt. % lubricant, 2 to 6 wt. % coating basis, and 0.05 to 3 wt. % light-shielding agent, wherein the odor or bitterness of the 5-methyl-1-phenyl-2-(1H)-pyridone is masked and the light stability is improved.

20 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION CONTAINING AS AN ACTIVE INGREDIENT 5-METHYL-1-PHENYL-2-(1H)-PYRIDONE

TECHNICAL FIELD

The present invention relates to a tablet containing as the main ingredient 5-methyl-1-phenyl-2-(1H)-pyridone.

BACKGROUND ART

5-Methyl-1-phenyl-2-(1H)-pyridone (nonproprietary name: pirfenidone) is a medicine for pulmonary fibrosis as indication. Various effects of pirfenidone have been reported, for example, 1) treating effect for fibrosis in lung, arteriosclerotic lesion, or the like is described in JP Laid-Open (Tokukai) No. H02-215719, 2) a similar effect to 1) of pirfenidone analogs is described in JP Laid-Open (Tokuhyo) No. H08-510251, 3) usefulness for treating inflammation in respiratory organs or cutis is described in U.S. Pat. No. 3,974,281, U.S. Pat. No. 4,042,699, and U.S. Pat. No. 4,052,509, and 4) inhibiting effect to the synthesis and release of TNF-α is described in JP Laid-Open (Tokuhyo) No. H11-512699.

In the above-mentioned 1) and 2), exemplified as a dosage form of pirfenidone are capsule, tablet, powder, granule, syrup, injection, cream, ointment, insufflation, eye lotion, suppository, and pill, preferable is capsule, injection, cream, and ointment, and working examples are only capsule and ointment. A tablet of pirfenidone and its preparation are not described concretely.

With regard to the dosage of pirfenidone, 600 mg to 2400 mg is administrated three times a day in above-mentioned 1). In test example 1 of 2), capsule containing 800 mg, 1200 mg, and 1600 mg of pirfenidone are described. In order to obtain a sufficient therapeutic effect, pirfenidone must be administrated much higher dose in comparison with a usual medicine.

In general, there are eight types of capsule: No. 000, 00, 0, 1, 2, 3, 4, and 5. The bigger the number is, the smaller the size is. The general amount of a medicine contained in each capsule depending on the bulk density or compressibility of the medicine, as follows: about 60 mg to 100 mg in No. 5 capsule, about 100 mg to 170 mg in No. 4 capsule, about 140 mg to 220 mg in No. 3 capsule, about 180 mg to 300 mg in No. 2 capsule, about 240 mg to 390 mg in No. 1 capsule, and about 340 mg to 540 mg in No. 0 capsule. While No. 2 to No. 4 capsules have often been used for administration to human, a smaller types such as No. 3 to No. 5 capsules are becoming more popular in light of easy administration. A capsule usually contains not only an active ingredient, but also a pharmaceutical additive such as excipient, binder, and disintegrator, for improving the stability and efficacy of the active ingredient.

For example, if the amount of pirfenidone per one dose is 600 mg as mentioned above, amount of granules or mixed powder of pirfenidone to be filled in a capsule is about 800 mg to 850 mg. In encapsulating such an amount a No. 000 capsule or two No. 0 capsules are needed, and a patient has a strong pain during the administration. In case of much higher dose, it is impossible to prepare a practical capsule

DISCLOSURE OF INVENTION

In General, a tablet is readily orally administrated than a capsule. The present inventors investigated a formulating of pirfenidone into a tablet which is considered to be effective

to improve the compliance in oral administration of a high dose of pirfenidone. In the process, problems were found such as 1) a characteristic odor or bitterness of pirfenidone, 2) low compressibility of pirfenidone itself, and 3) light-stability.

In the above situation, the inventors of the present invention have prepared a pirfenidone tablet improved for the compliance, which masks its odor or bitterness, and has the light-stability and rapid dissolution rate, being compact and of sufficient hardness in spite of high content of the main ingredient, whereby accomplished the present invention.

That is, the present invention relates to the following.

1) A tablet containing as the main ingredient 5-methyl-1-phenyl-2-(1H)-pyridone.

2) A tablet as described in 1), the weight of which is 100 to 1000 mg.

3) A tablet as described in 1) or 2), which contains 10 to 85 wt. % the main ingredient to the weight of the tablet.

4) A tablet as described in any one of 1) to 3), wherein the content of the main ingredient is 200 mg to 400 mg.

5) A tablet as described in any one of 1) to 4), which contains a light-shielding agent.

6) A tablet as described in 5), which contains a 0.05 to 3 wt. % of the shielding agent based on the main ingredient.

7) A tablet as described in any one of 1) to 4), which contains 10 to 50 wt. % excipient, 5 to 40 wt. % disintegrator, 1 to 10 wt. % binder, 0.5 to 5 wt. % lubricant, 2 to 6 wt. % coating basis, and 0.05 to 3 wt. % light-shielding agent based on the main ingredient.

8) A tablet as described in 7), which contains 0.01 to 1 wt. % plasticizer based on the main ingredient.

9) A tablet as described in any one of 1) to 4), which consists of a plain tablet containing 10 to 50 wt. % excipient, 5 to 40 wt. % disintegrator, 1 to 10 wt. % binder, and 0.5 to 5 wt. % lubricant on the main ingredient, and coating layer containing 2 to 6 wt. % coating basis and 0.05 to 3 wt. % light-shielding agent based on the main ingredient.

10) A tablet as described in 9), which contains 0.01 to 1 wt. % plasticizer based on the main ingredient in a coating layer.

11) A tablet as described in any one of 1) to 4), which consists of a plain tablet containing 10 to 50 wt. % excipient selected from the group of lactose, corn starch, and crystalline cellulose, 5 to 40 wt. % disintegrator selected from the group of carmellose calcium, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone, 1 to 10 wt. % binder selected from the group of hydroxypropylcellulose and polyvinylpyrrolidone, and 0.5 to 5 wt. % lubricant selected from the group of magnesium stearate and talc on the main ingredient, and a coating layer containing 2 to 6 wt. % coating basis selected from the group of hydroxypropylmethylcellulose and hydroxypropylcellulose, 0.01 to 1 wt. % plasticizer selected from the group of triethyl citrate and triacetin, and 0.05 to 3 wt. % light-shielding agent selected from the group of titanium oxide and ferric oxide based on the main ingredient.

12) A tablet as described in 11), which consists of a plain tablet containing 10 to 50 wt. % lactose, 5 to 40 wt. % carmellose calcium, 1 to 10 wt. % hydroxypropylcellulose, and 0.5 to 5 wt. magnesium stearate on the main ingredient, and a coating layer containing 2 to 6 wt. % hydroxypropylmethylcellulose, 0.01 to 1 wt. % triethyl citrate and 0.05 to 3 wt % titanium oxide based on the main ingredient.

13) A tablet as described in any one of 1) to 4), which consists of a plain tablet containing 20 to 30 wt. % excipient selected from the group of lactose, corn starch, and crystalline cellulose, 7.5 to 15 wt. % disintegrator selected from the

group of carmellose calcium, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone, 2 to 5 wt. % binder selected from the group of hydroxypropylcellulose and polyvinylpyrrolidone, and 0.5 to 3 wt. % lubricant selected from the group of magnesium stearate and talc on the main ingredient, and a coating layer containing 2 to 4 wt. % coating basis selected from the group of hydroxypropylmethylcellulose and hydroxypropylcellulose, 0.01 to 1 wt. % plasticizer selected from the group of triethyl citrate and triacetin, and 0.8 to 3 wt. % titanium oxide as a light-shielding agent based on the main ingredient.

14) A tablet as described in 13), which consists of a plain tablet containing 20 to 30 wt. % lactose, 7.5 to 15 wt. % carmellose calcium, 2 to 5 wt. % hydroxypropylcellulose, and 0.5 to 3 wt. magnesium stearate on the main ingredient, and a coating layer containing 2 to 4 wt. % hydroxypropylmethylcellulose, 0.01 to 1 wt. % triethyl citrate and 0.8 to 3 wt. % titanium oxide based on the main ingredient.

In the present specification, the term "excipient" means an excipient used in usual pharmaceutical preparations. Examples of the excipient include silicic acids such as light anhydrous silicic acid, synthetic aluminum silicate, and magnesium aluminometasilicate, inorganic salts such as calcium phosphate, calcium carbonate, and calcium sulfate, sugars such as lactose, sucrose, dextrose, mannitol, and sorbitol, starches such as corn starch, a starch, carboxymethyl starch, celluloses such as crystalline cellulose, and low substituted hydroxypropylcellulose, gum Arabic, dextran and pullulan. Lactose, corn starch, and crystalline cellulose are more preferable.

In the present specification, the term "disintegrator" means an additive agent which is used in order to disintegrate and disperse a tablet to minute particles t in the digestive organ. Examples of the disintegrator include corn starch, carboxymethylcellulose, carboxymethylcellulose calcium, low substituted hydroxypropylcellulose, carmellose sodium, crosscarmellose sodium, carboxymethylstarch sodium, and cross-linked polyvinylpyrrolidone. Carmellose calcium, low substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, and the like are more preferable.

In the present specification, the term "binder" means a binder used in usual pharmaceutical preparations. Examples of the binder include hydroxypropylcellulose, hydroxypropylmethylcellulose, and methylcellulose, polyvinylpyrrolidone. Hydroxypropylcellulose, polyvinylpyrrolidone, and the like are more preferable.

In the present specification, as "lubricant" are exemplified talc, calcium stearate, sodium stearate, and magnesium stearate. Magnesium stearate, talc, and the like are more preferable.

In the present specification, as "coating basis" are exemplified sucrose, talc, precipitated calcium carbonate, gelatin, gum Arabic, pullulan, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer, cellulose acetate phthalate, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, hydroxypropylmethylcellulose phthalate, hydroxymethylpropylmethylcellulose acetate succinate, and carboxymethylethylcellulose. Hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like are more preferable.

In the present specification, the term "light-shielding agent" means a light-shielding agent used in usual pharmaceutical preparations. Examples of the light-shielding agent include titanium oxide and ferric oxide. Titanium oxide, and the like are more preferable.

In the present specification, the term "plasticizer" means a plasticizer used in usual pharmaceutical preparations. Examples of the plasticizer include triethyl citrate, triacetin, glycerin fatty acid ester, and phthalic acid ester. Triethyl citrate, triacetin, and the like are more preferable.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention tablet is prepared in the following A) to D) processes.

A) A mixed powder containing pirfenidone, an excipient, and a disintegrator is granulated by spraying a binder with a fluid bed granulator to give granules.

B) The obtained granules are mixed with a disintegrator, a lubricant, and the like and is compressed at a force of 8 to 18 kN, preferably 11 to 15 kN to give pirfenidone plain tablets.

C) A coating solution containing a coating basis, a plasticizer (if necessary), and a light-shielding agent etc. is prepared.

D) The target pirfenidone tablet is obtained by coating the pirfenidone plain tablet obtained in B) with the above-mentioned coating solution.

In the above-mentioned processes, additives used in a usual solid preparation may be added appropriately.

The present invention relates to a tablet containing 5-methyl-1-phenyl-2-(1H)-pyridone as the main ingredient and preferable is a 100 to 1000 mg weight of tablet. 150 to 700 mg is more preferable and 240 to 480 mg is the most preferable. The amount of the active ingredient is preferably 10 to 85 wt. % the main ingredient to the tablet. 25 to 85 wt. % is more preferable and 50 to 85 wt. % is the most preferable. It is preferable that the content of the main ingredient is 200 mg to 400 mg.

The designed tablet is more compact, easier to take and contains a more amount of the main ingredient than capsule, thus effectively exhibiting the efficacy.

That is, the present invention tablet includes a more compact tablet than a capsule containing 5-methyl-1-phenyl-2-(1H)-pyridone as the main ingredient.

Further the present inventors have discovered the problem of light-stability of pirfenidone tablet in the preparation, and found a pirfenidone tablet improving the light-stability with a light-shielding agent. Furthermore they found preferable are a tablet including 0.05 to 3 wt. % light-shielding agent and a tablet including a light-shielding agent in the coating layer.

That is, the present invention tablet includes a tablet improving the light-stability and containing 5-methyl-1-phenyl-2-(1H)-pyridone as the main ingredient.

Preferable amounts of respective components except the main ingredient in a plain tablet are shown by wt. % to pirfenidone as the main ingredient. In consideration of the compliance, it is preferable that the amount of the other components is as small as possible because the amount of pirfenidone as the main ingredient is much. But the hardness of a tablet may decrease if the amounts of the other components are too little. An excipient is preferably a) 10 to 50 wt. %. b) 15 to 40 wt. % is more preferable. c) 20 to 30 wt. % is the most preferable. A disintegrator is preferably d) 5 to 40 wt. %. e) 5 to 25 wt. % is more preferable. f) 7.5 to 15 wt. % is the most preferable. A binder is preferably g) 1 to 10 wt. %. h) 1 to 7.5 wt. % is more preferable. i) 2 to 5 wt. % is the most preferable. A lubricant is preferably j) 0.5 to 5 wt. %. k) 0.5 to 4 wt. % is more preferable. l) 0.5 to 3 wt. % is the most preferable.

Preferable amounts of respective components in a coating solution are shown by wt. % to pirfenidone as the main ingredient. The components include a coating basis in order to mask a characteristic odor or bitter of pirfenidone, and a light-shielding agent to improve the light-stability, preferably that the amounts of while are as small as possible like the plain tablet. A coating basis is preferably in) 2 to 6 wt. %. n) 2 to 5 wt. % is more preferable. o) 2 to 4 wt. % is the most preferable. A light-shielding agent is preferably p) 0.05 to 3 wt. %. q) 0.05 to 2 wt. % is more preferable. r) 0.8 to 1.5 wt. % is the most preferable. A plasticizer is preferably s) not included or t) 0.05 to 1 wt. % if included.

Preferable amounts of the above-mentioned components to pirfenidone in the present invention tablet are shown as follows. That is, (excipient, disintegrator, binder, lubricant, coating basis, light-shielding agent, plasticizer)=(a, d, g, j, m, p, s), (a, d, g, j, m, p, t), (a, d, g, j, m, q, s), (a, d, g, j, m, q, t), (a, d, g, j, m, r, s), (a, d, g, j, m, r, t), (a, d, g, j, n, p, s), (a, d, g, j, n, p, t), (a, d, g, j, n, q, s), (a, d, g, j, n, q, t), (a, d, g, j, n, r, s), (a, d, g, j, n, r, t), (a, d, g, j, o, p, s), (a, d, g, j, o, p, t), (a, d, g, j, o, q, s), (a, d, g, j, o, q, t), (a, d, g, j, o, r, s), (a, d, g, j, o, r, t), (a, d, g, k, m, p, s), (a, d, g, k, m, p, t), (a, d, g, k, m, q, s), (a, d, g, k, m, q, t), (a, d, g, k, m, r, s), (a, d, g, k, m, r, t), (a, d, g, k, n, p, s), (a, d, g, k, n, p, t), (a, d, g, k, n, q, s), (a, d, g, k, n, q, t), (a, d, g, k, n, r, s), (a, d, g, k, n, r, t), (a, d, g, k, o, p, s), (a, d, g, k, o, p, t), (a, d, g, k, o, q, s), (a, d, g, k, o, q, t), (a, d, g, k, o, r, s), (a, d, g, k, o, r, t), (a, d, g, l, m, p, s), (a, d, g, l, m, p, t), (a, d, g, l, m, q, 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i, j, n, q, s), (c, f, i, j, n, q, t), (c, f, i, j, n, r, s), (c, f, i, j, n, r, t), (c, f, i, j, o, p, s), (c, f, i, j, o, p, t), (c, f, i, j, o, q, s), (c, f, i, j, o, q, t), (c, f, i, j, o, r, s), (c, f, i, j, o, r, t), (c, f, i, k, m, p, s), (c, f, i, k, m, p, t), (c, f, i, k, m, q, s), (c, f, i, k, m, q, t), (c, f, i, k, m, r, s), (c, f, i, k, m, r, t), (c, f, i, k, n, p, s), (c, f, i, k, n, p, t), (c, f, i, k, n, q, s), (c, f, i, k, n, q, t), (c, f, i, k, n, r, s), (c, f, i, k, n, r, t), (c, f, i, k, o, p, s), (c, f, i, k, o, p, t), (c, f, i, k, o, q, s), (c, f, i, k, o, q, t), (c, f, i, k, o, r, s), (c, f, i, k, o, r, t), (c, f, i, l, m, p, s), (c, f, i, l, m, p, t), (c, f, i, l, m, q, s), (c, f, i, l, m, q, t), (c, f, i, l, m, r, s), (c, f, i, l, m, r, t), (c, f, i, l, n, p, s), (c, f, i, l, n, p, t), (c, f, i, l, n, q, s), (c, f, i, l, n, q, t), (c, f, i, l, n, r, s), (c, f, i, l, n, r, t), (c, f, i, l, o, p, s), (c, f, i, l, o, p, t), (c, f, i, l, o, q, s), (c, f, i, l, o, q, t), (c, f, i, l, o, r, s), (c, f, i, l, o, r, t).

The present invention tablet has excellent light-stability as shown in the examples mentioned later. In spite of high content of the main ingredient, the tablet is compact, sufficiently hard and readily administrable.

The dosage varies with the conditions of the patients, administration route, their age, and body weight. In the case of oral administration, the dosage is thought to be preferable between about 1200 mg to about 1800 mg per a day. The amount per one administration is between 400 mg to 600 mg because of three division a day, and it is preferable to take two tablets each containing the main ingredient of between 200 mg to 300 mg.

The following examples and test examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

EXAMPLE

Example 1

Preparation of Pirfenidone Tablets

Pirfenidone (2,000 g) was mixed with 560 g of lactose and 50 g of carmellose calcium. The mixture was granulated by spraying a 5 (W/W) % aqueous solution of hydroxypropylcellulose (60 g) with a fluid bed granulator. Carmellose calcium and magnesium stearate were added to the granules at the ratios of 5.6 and 1.1 wt. % to the weight of the granules, respectively. The obtained mixture was compressed at a force of 13 kN and to give plain pirfenidone tablets each containing 200 mg of pirfenidone (size: 12.0× 6.0 mm, weight: 285 mg/tablet).

The plain tablets were coated by spraying a 10 wt. % aqueous solution containing hydroxypropylmethylcellulose (66.7 g), triethyl citrate (6.7 g), and titanium oxide 26.6 g in an amount of 10 mg per tablet with a High-coator, to give the objective pirfenidone tablets.

The components of a pirfenidone tablet is shown below.

TABLE 1

Component	Amount	Note
Pirfenidone	200.0 mg	
Lactose	56.0 mg	
Carmellose calcium	20.0 mg	Intra-granular: 5.0 mg Extera-granular 15.0 mg
Hydroxypropylcellulose	6.0 mg	
Magnesium stearate	3.0 mg	
Total of weight of a plain tablet	285.0 mg	
Hydroxypropylmethylcellulose 2910	6.67 mg	
Titanium oxide	2.66 mg	
Triethyl citrate	0.67 mg	
Magnesium stearate	trace	0.02 mg
Talc	trace	0.02 mg
Total weight of coating	10.00 mg	
Total weight of a coated tablet	295.0 mg	

Example 2

Light Exposure Testing

Light exposure test of pirfenidone was carried out under the following condition, using "drug substance" obtained by

packing 500 mg of milled pirfenidone drug substance in a heat-sealed transparent SP (Striped Package), "compressed drug substance" obtained by statically compressing 300 mg of milled pirfenidone drug substance, "the plain tablets" obtained in the above Example 1, and "the coated tablets" obtained in the above Example 1. The results are shown in table 2.

(Test Condition)

light irradiation apparatus: light stability test apparatus (LTL400-D5) (Nagano Science Equipment Mfg. Co., Ltd.)

fluorescent light: D65 fluorescent lamp for color comparing and test

temperature and humidity: 25° C., room humidity

illumination intensity: 3570 Lx

exposure dose: 1,200,000 Lx·hr

coloring difference measure apparatus: Color analyzer TC-1800MK-II

measurement method: reflected ray measurement

color specification system: CIELAB

measurement condition: second degree visual field

standard light: C

TABLE 2

Sample	Color difference (ΔE)	Discoloration
Drug substance	0.73	slight
Compressed drug substance	3.62	remarkable
Plain tablets	5.08	remarkable
Coated tablets	0.75	slight

Table 2 showed that remarkable color difference was not observed in the case of the pirfenidone drug substance, but a pirfenidone compressed drug substance and a pirfenidone plain tablet have a problem in light-stability. However, a pirfenidone coated tablet solves the problem in light-stability. A pirfenidone coated tablet is confirmed to have no problem in odor or bitterness.

INDUSTRIAL APPLICABILITY

The present invention provides a compact and sufficiently hard tablet containing a high content of pirfenidone which is necessary to be administered in high dose. And at the same time, the present invention solves the problem of its odor or bitterness and provides a readily administrable tablet. Furthermore, it solves the problem of light-stability caused by tableting pirfenidone and provides the stability requested as a medicine.

The invention claimed is:

1. A coated dosage form comprising a compressed tablet comprising 5-methyl-1-phenyl-2-(1H)-pyridone as an active ingredient; and a coating comprising a light shielding agent disposed on the compressed tablet.

2. The dosage form of claim **1**, wherein the light shielding agent is selected from the group consisting of titanium oxide, ferric oxide, and any mixture thereof.

3. The dosage form of claim **1**, wherein the light-shielding agent is present in an amount ranging from 0.05 to 3 wt % based on the weight of the active ingredient.

4. The dosage form of claim **1**, wherein the coating further comprises a coating basis.

5. The dosage form of claim **4**, wherein the coating basis is selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, and any mixture thereof.

6. The dosage form of claim **4**, wherein the coating basis is 2 to 6 wt % based on the weight of the active ingredient.

7. The dosage form of claim **1**, wherein the coating further comprises 0.01 to 1 wt % plasticizer based on the weight of the active ingredient.

8. The dosage form of claim **7**, wherein the plasticizer is selected from the group consisting of triethyl citrate, triacetin, and any mixture thereof.

9. The dosage form of claim **1**, wherein the amount of 5-methyl-1-phenyl-2-(1H)-pyridone is about 200 mg to 400 mg.

10. The dosage form of claim **1**, wherein the active ingredient comprises 50 to 85 wt % based on the weight of the dosage form.

11. The dosage form of claim **1**, comprising intragranular and extragranular components, wherein the intragranular component comprises the 5-methyl-1-phenyl-2-(1H)-pyridone and the extragranular component comprises a disintegrator.

12. The dosage form of claim **11**, wherein the disintegrator is selected from the group consisting of carmellose calcium, carmellose sodium, croscarmellose sodium, low substituted hydroxypropylcellulose, cross-linked polyvinylpyrrolidone, and any mixture thereof.

13. The dosage form of claim **11**, wherein the disintegrator is provided in an amount of 5 to 40 wt % based on the weight of the active ingredient.

14. The dosage form of claim **11**, wherein the intragranular component further comprises an excipient and a binder.

15. The dosage form of claim **14**, wherein the excipient is selected from the group consisting of lactose, corn starch, crystalline cellulose, and any mixture thereof.

16. The dosage form of claim **14**, wherein the binder is selected from the group consisting of hydroxypropylcellulose, polyvinylpyrrolidone, and any mixture thereof.

17. The dosage form of claim **11**, wherein the extragranular component further comprises a lubricant.

18. The dosage form of claim **17**, wherein the lubricant is selected from the group consisting of magnesium stearate, talc, and any mixture thereof.

19. The dosage form of claim **18**, wherein the lubricant is included in an amount of 0.5 to 5 wt % based on the weight of the active ingredient.

20. The dosage form of claim **1**, further comprising an excipient, a disintegrator, a binder, and a lubricant.

* * * * *

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

GENENTECH, INC. and INTERMUNE, INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*
Jack B. Blumenfeld 302-658-9200
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street; P.O. Box 1347; Wilmington, DE 19899

DEFENDANTS

SANDOZ, INC., SANDOZ INTERNATIONAL GMBH and SANDOZ AG

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ❒ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question *(U.S. Government Not a Party)*
- ❒ 2 U.S. Government Defendant
- ❒ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	❒ 1	❒ 1	Incorporated *or* Principal Place of Business In This State	❒ 4	❒ 4
Citizen of Another State	❒ 2	❒ 2	Incorporated *and* Principal Place of Business In Another State	❒ 5	❒ 5
Citizen or Subject of a Foreign Country	❒ 3	❒ 3	Foreign Nation	❒ 6	❒ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ❒ 110 Insurance
- ❒ 120 Marine
- ❒ 130 Miller Act
- ❒ 140 Negotiable Instrument
- ❒ 150 Recovery of Overpayment & Enforcement of Judgment
- ❒ 151 Medicare Act
- ❒ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ❒ 153 Recovery of Overpayment of Veteran's Benefits
- ❒ 160 Stockholders' Suits
- ❒ 190 Other Contract
- ❒ 195 Contract Product Liability
- ❒ 196 Franchise

REAL PROPERTY
- ❒ 210 Land Condemnation
- ❒ 220 Foreclosure
- ❒ 230 Rent Lease & Ejectment
- ❒ 240 Torts to Land
- ❒ 245 Tort Product Liability
- ❒ 290 All Other Real Property

TORTS

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- ❒ 310 Airplane
- ❒ 315 Airplane Product Liability
- ❒ 320 Assault, Libel & Slander
- ❒ 330 Federal Employers' Liability
- ❒ 340 Marine
- ❒ 345 Marine Product Liability
- ❒ 350 Motor Vehicle
- ❒ 355 Motor Vehicle Product Liability
- ❒ 360 Other Personal Injury
- ❒ 362 Personal Injury - Medical Malpractice

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- ❒ 365 Personal Injury - Product Liability
- ❒ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ❒ 368 Asbestos Personal Injury Product Liability

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- ❒ 446 Amer. w/Disabilities - Other
- ❒ 448 Education

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- ❒ 535 Death Penalty

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- ❒ 555 Prison Condition
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- ☒ 835 Patent - Abbreviated New Drug Application
- ❒ 840 Trademark

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- ❒ 862 Black Lung (923)
- ❒ 863 DIWC/DIWW (405(g))
- ❒ 864 SSID Title XVI
- ❒ 865 RSI (405(g))

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- ❒ 870 Taxes (U.S. Plaintiff or Defendant)
- ❒ 871 IRS—Third Party 26 USC 7609

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- ❒ 376 Qui Tam (31 USC 3729(a))
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- ❒ 410 Antitrust
- ❒ 430 Banks and Banking
- ❒ 450 Commerce
- ❒ 460 Deportation
- ❒ 470 Racketeer Influenced and Corrupt Organizations
- ❒ 480 Consumer Credit
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- ❒ 850 Securities/Commodities/ Exchange
- ❒ 890 Other Statutory Actions
- ❒ 891 Agricultural Acts
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- ❒ 895 Freedom of Information Act
- ❒ 896 Arbitration
- ❒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ❒ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

☒ 1 Original Proceeding ❒ 2 Removed from State Court ❒ 3 Remanded from Appellate Court ❒ 4 Reinstated or Reopened ❒ 5 Transferred from Another District *(specify)* ❒ 6 Multidistrict Litigation - Transfer ❒ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
35 U.S.C. § 271

Brief description of cause:
Patent Infringement

VII. REQUESTED IN COMPLAINT:

❒ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ❒ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions):

JUDGE Andrews DOCKET NUMBER See Attached List

DATE 01/31/2019

SIGNATURE OF ATTORNEY OF RECORD /s/ Jack B. Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

LIST OF RELATED CASES

Genentech, Inc., et al. v. Laurus Labs Ltd., et al.; C.A. No. 19-078 (RGA)

Genentech, Inc., et al. v. Aurobindo Pharma Limited, et al.; C.A. No. 19-103 (RGA)

Genentech, Inc., et al. v. Laurus Labs Ltd., et al.; C.A. No. 19-104 (RGA)

Genentech, Inc., et al. v. Aurobindo Pharma Limited, et al.; C.A. No. 19-105 (RGA)

Genentech, Inc., et al. v. Lupin Ltd., et al.; C.A. No. 19-109 (RGA)

Genentech, Inc., et al. v. Lupin Ltd., et al.; C.A. No. 19-110 (RGA)

Genentech, Inc., et al. v. Micro Labs Ltd., et al.; C.A. No. 19-111 (RGA)

Genentech, Inc., et al. v. Apotex Inc., et al.; C.A. No. 19-120 (RGA)

Genentech, Inc., et al. v. Apotex Inc., et al.; C.A. No. 19-123 (RGA)

Genentech, Inc., et al. v. Shilpa Medicare Limited, et al.; C.A. No. 19-130 (RGA)

Genentech, Inc., et al. v. ScieGen Pharmaceuticals Inc., et al.; C.A. No. 19-131 (RGA)

Genentech, Inc., et al. v. ScieGen Pharmaceuticals Inc., et al.; C.A. No. 19-132 (RGA)

Genentech, Inc., et al. v. Teva Pharmaceuticals USA, Inc., et al.; C.A. No. 19-136 (RGA)

Genentech, Inc., et al. v. Accord Healthcare, Inc., et al.; C.A. No. 19-141 (RGA)

Genentech, Inc., et al. v. Accord Healthcare, Inc., et al.; C.A. No. 19-142 (RGA)

Genentech, Inc., et al. v. Macleods Pharmaceuticals Ltd., et al.; C.A. No. 19-154 (RGA)

Genentech, Inc., et al. v. Granules Pharmaceuticals, Inc., et al.; C.A. No. 19-164 (RGA)

Genentech, Inc., et al. v. Alembic Pharmaceuticals, Ltd., et al.; C.A. No. 19-177 (UNA)

Genentech, Inc., et al. v. Hetero Labs Limited, et al.; C.A. No. 19-178 (UNA)

Genentech, Inc., et al. v. Amneal Pharmaceuticals LLC, et al.; C.A. No. 19-190 (UNA)

Genentech, Inc., et al. v. Amneal Pharmaceuticals LLC, et al.; C.A. No. 19-195 (UNA)