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

[0005] The present disclosure is based on the discovery of an adverse drug interaction between pirfenidone and fluvoxamine.

[0006] The present disclosure generally relates to improved uses and 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 the present disclosure, the patient may have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. In the present disclosure, the therapeutically effective amount of pirfenidone being administered may be a daily dosage of 2400 mg or 2403 mg per day. In the present 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 the present disclosure, 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.

[0006a] In one aspect of the present disclosure, there is provided a use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, characterized in that the treating comprises reducing the dose of pirfenidone in patients receiving a strong inhibitor of CYP1A2.

[0007] The present disclosure also 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 despite the patient being in need of fluvoxamine therapy.

[0008] The present disclosure further 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 in need of and thus 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 present disclosure provides an improvement that comprises avoiding or discontinuing administration of fluvoxamine and administering a therapeutically effective amount of pirfenidone.

[0009] As used herein, an adverse drug interaction can include reduced clearance of pirfenidone, the potential for reduced clearance of pirfenidone, increased exposure to pirfenidone, or the potential for increased exposure to pirfenidone.

[0010] The present disclosure also provides pirfenidone for use in treating a patient in need of pirfenidone therapy, characterized in that the treating comprises avoiding, contraindicating or discontinuing concomitant use (or co-administration) of fluvoxamine. In some embodiments, the concomitant use of fluvoxamine is avoided, contraindicated or discontinued, in order to avoid reduced clearance of pirfenidone, or the potential for reduced clearance of pirfenidone. In some embodiments, the concomitant use of fluvoxamine is avoided, contraindicated or discontinued, in order to avoid increased exposure to pirfenidone, or the potential for increased exposure to pirfenidone. Administration of pirfenidone in patients that concomitantly use or are being administered fluvoxamine results in about a 6-fold increase in pirfenidone exposure. It is understood that any of the embodiments or examples described herein with respect to methods of treatment apply to this embodiment of the present disclosure 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 2400 or 2403 mg per day.

[0011] Similarly, the present disclosure further 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, contraindicating or discontinuing concomitant use (or co-administration) of fluvoxamine. It is understood that any of the embodiments or examples described herein with respect to methods of treatment or "pirfenidone for use" in treating a patient apply to this embodiment of the present disclosure 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 2400 or 2403 mg per day.

[0012] 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.

[0013] In some embodiments, the patient is a patient in need of therapy with a CYP1A2 inhibitor. In some embodiments, the patient is a patient in need of therapy with a strong CYP1A2 inhibitor, or a moderate to strong CYP1A2 inhibitor. In some embodiments, the patient is a patient in need of fluvoxamine therapy. In some embodiments, the patient is a patient who is avoiding concomitant use of fluvoxamine, e.g. because concomitant use of pirfenidone with fluvoxamine is contraindicated. In some embodiments, the patient is a patient who was or is being administered a strong CYP1A2 inhibitor, or a moderate to strong CYP1A2 inhibitor, e.g. fluvoxamine. In some embodiments, the patient is a patient who has discontinued use of a strong CYP1A2 inhibitor, or a moderate to strong CYP1A2 inhibitor prior to the initiation of pirfenidone therapy in order to avoid reduced clearance (or increased exposure to) pirfenidone, or the potential for reduced clearance of (or increased exposure to) pirfenidone. In some embodiments, the patient is a patient who has discontinued use of fluvoxamine prior to the initiation of pirfenidone therapy in order to avoid reduced clearance of pirfenidone, or the potential for reduced clearance of pirfenidone. In some embodiments, the patient is a patient who has discontinued use of fluvoxamine prior to the initiation of pirfenidone therapy in order to avoid increased exposure to pirfenidone, or the potential for increased exposure to pirfenidone. In some embodiments, the patient is a patient who has discontinued administration of the strong CYP1A2 inhibitor, or moderate to strong CYP1A2 inhibitor, e.g., fluvoxamine, within 1 month, or within 2 weeks, prior to starting pirfenidone therapy, or concurrent with starting pirfenidone therapy. It is understood that any of the embodiments or examples described herein with respect to methods of treatment apply to this embodiment of the present disclosure that provides for characterization of the patients to be treated with pirfenidone.

[0014] The present disclosure also provides 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. The alternative therapy that is not fluvoxamine is a drug that is not a strong or moderate to strong inhibitor of cytochrome P450 1A2 (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) .

[0015] The present disclosure further 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.

[0016] 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.

[0017] 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.

[0018] 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.

What Is Claimed Is:

1. Use of pirfenidone in the manufacture of a medicament for treating a patient in need of pirfenidone therapy, characterized in that the treating comprises reducing the dose of pirfenidone in patients receiving a strong inhibitor of CYP1A2.

2. The use of claim 1 wherein the CYP1A2 inhibitor is a moderate to strong inhibitor of CYP1A2 and another CYP enzyme selected from the group consisting of CYP2C9, CYP2C19, CYP2D6 and/or CYP2E1.

3. The use of claim 1 wherein the CYP1A2 inhibitor is a strong CYP1A2 inhibitor.

4. The use of any of claims 1-3 wherein the CYP1A2 inhibitor is discontinued prior to starting pirfenidone therapy to avoid an adverse drug interaction with pirfenidone, or to avoid a reduced clearance of pirfenidone.

5. The use of any one of claims 1-4 wherein the CYP1A2 inhibitor is discontinued within 1 month prior to starting pirfenidone therapy.

6. The use of any one of claims 1-5 wherein the CYP1A2 inhibitor is discontinued within 2 weeks prior to starting pirfenidone therapy.

7. The use of any of claims 1-3 wherein the CYP1A2 inhibitor is avoided during pirfenidone therapy.

8. The use of any of claims 1-7 wherein the patient is in need of therapy with a CYP1A2 inhibitor.

9. The use of any of claims 1-3 or 8 wherein the CYP1A2 inhibitor is used with caution.

10. The use of any one of claims 1-9 wherein the pirfenidone is to be administered at a total daily dosage of about 1800 mg.

11. The use of any one of claims 1-9 wherein the pirfenidone is to be administered at a total daily dosage of about 2400 mg or 2403 mg.

12. The use of any one of claims 1-9 wherein the CYP1A2 inhibitor is fluvoxamine.

13. The use of any one of claims 1-9 wherein the CYP1A2 inhibitor is enoxacin.

14. The use of any one of claims 1-9 wherein the CYP1A2 inhibitor is ciprofloxacin, amiodarone or propafenone.

15. The use of claim 1 wherein the dose of pirfenidone is reduced in a patient receiving a strong inhibitor of CYP1A2.

16. The use of claim 1 characterized in that the dose of pirfenidone is reduced to a total daily dose of 801 mg/day in the patient receiving a strong inhibitor of CYP1A2.

17. The use of any one of claims 15-16 wherein the strong inhibitor of CYP1A2 is fluvoxamine.

18. The use of any one of claims 15-16 wherein the strong inhibitor of CYP1A2 is enoxacin.

19. The use of any one of claims 1-18 wherein the patient has idiopathic pulmonary fibrosis (IPF).

20. The use of any of claims 1-18 wherein the patient suffers from a disease selected from idiopathic pulmonary fibrosis, 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 auto-immune 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.

21. The use of any one of claims 1-18 wherein the patient is in need of an anti-fibrotic agent.

22. The use of any one of claims 1-18 wherein the patient has pulmonary fibrosis, myocardiac fibrosis, musculoskeletal fibrosis, pancreatic fibrosis, hepatic fibrosis, renal fibrosis, fibrotic vascular disease or scleroderma.

23. The use of any one of claims 1-22 wherein pirfenidone is to be administered to the patient three times per day, with food.