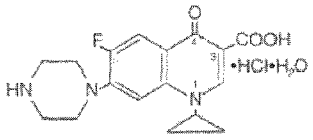
a molecular weight of 385.8, its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:



[0006] Ciprofloxacin was previously classified as a moderate inhibitor of CYP1A2 by the FDA [FDA Draft Guidance for Industry Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling, September 2006]; this description was recently revised in February 2012 [FDA Draft Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, February 2012].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~~

[0006a] In a first aspect of the present disclosure, there is provided a use of pirfenidone for the manufacture of a medicament for treating a patient in need of pirfenidone therapy, wherein the pirfenidone therapy comprises reducing the dosage of pirfenidone to be administered to a patient to about 1602 mg/day during concomitant administration of ciprofloxacin at a dose of 750 mg twice daily (1500 mg/day).

[0006b] In a second aspect of the present disclosure, there is provided a package or kit comprising (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling for the uses of pirfenidone according to the first aspect.

[0006c] In a third aspect of the present disclosure, there is provided a use of (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling for the manufacture of a package or kit for the uses of pirfenidone according to the first aspect.

[0007] 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.

[0008] 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.

[0009] ~~In one aspect, t~~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.

[0010] ~~In the first aspect, f~~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.

[0011] 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.

[0012] ~~In the first aspect, t~~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.

[0013] 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.

[0014] ~~In a second aspect, t~~The disclosure also 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.

[0015] 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~~present disclosure 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~~present disclosure 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~~present disclosure 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.

[0016] 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~~disclosure, the dosage unit may be a capsule, including a capsule containing 267 mg pirfenidone and pharmaceutically acceptable excipients.

[0021] 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.

[0022] ~~A further aspect of T~~the 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 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.

[0023] For simplicity of dosing and improved safety, the ~~invention~~present disclosure also contemplates that, for patients concurrently being administered ciprofloxacin (e.g. at any dose, 250mg, 500mg or 750mg 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).

[0024] For simplicity of dosing and improved safety, the ~~invention~~present disclosure also contemplates that, for patients concurrently being administered ciprofloxacin (e.g. at any dose, 250mg, 500mg or 750mg 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).

[0025] 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."

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.

[0029] ~~In another aspect, t~~The disclosure also 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

[0030] **Figure 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

[0031] 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. Patent Number 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%).

[0032] 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.

[0033] 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

CLAIMS

1. Use of ~~P~~pirfenidone ~~for use~~ for the manufacture of a medicament for ~~in~~ treating a patient in need of pirfenidone therapy, wherein the pirfenidone therapy comprises reducing the dosage of pirfenidone to be administered to a patient to about 1602 mg/day during concomitant administration of ciprofloxacin at a dose of 750 mg twice daily (1500 mg/day).

2. The ~~pirfenidone for~~ use according to claim 1 wherein the ~~method~~ use is for avoiding the potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

3. The ~~pirfenidone for~~ use according to any one of claim 1 or claim 2 wherein the total daily dose of pirfenidone is to be administered to the patient in divided doses three times per day, with food.

4. The ~~pirfenidone for~~ use according to any of claims 1-3 wherein the pirfenidone is to be administered in unit dosage forms that are capsules or tablets.

5. The ~~pirfenidone for~~ use according to claim 4 wherein the amount of pirfenidone in the unit dosage form is 267 mg.

6. The ~~pirfenidone for~~ use according to any one of claims 1-5 wherein the patient has idiopathic pulmonary fibrosis (IPF).

7. The ~~pirfenidone for~~ use according to any of claims 1-5 wherein the patient has a fibrotic disorder, inflammatory disorder, or autoimmune disorder.

8. The ~~pirfenidone for~~ use according to any of claims 1-5 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

9. A package or kit comprising (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling for the uses of pirfenidone according to any one of ~~the embodiments of~~ claims 1-8.

10. Use of (a) pirfenidone, optionally in a container, and (b) a package insert, package label, instructions or other labeling for the manufacture of a package or kit for the uses of pirfenidone according to any one of claims 1-8.