[0005] 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, September 16, 2008). Specifically, several CYP isoforms (CYP1A2, 2C9, 2C19, 2D6 and 2E1) were involved in the earliest stages of oxidative metabolism of pirfenidone.

[0006] Activity of CYPs in patients who smoke is significantly increased over their non-smoking counterparts.

SUMMARY

[0007] The present disclosure is based upon the discovery of an adverse reaction (reduced pirfenidone exposure) in patients taking pirfenidone who also smoke.

[0008] The present disclosure 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. The patient can have idiopathic pulmonary fibrosis (IPF) and the medicament is for treatment of IPF. 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. 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. 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.

[0008a] 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 avoiding or discontinuing concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone.

[0008b] In another 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 using caution with concomitant use or co-administration of a strong inducer of cytochrome P450 1A2 (CYP1A2) to avoid reduced exposure to pirfenidone.

[0009] The present 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 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, phenytoin, primidone, and St. John's wort.

[0010] The present disclosure also 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 present disclosure 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.

[0011] 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®).

[0012] Thus, the present disclosure 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 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 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.

[0013] Similarly, the present disclosure also 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 embodiments or examples described herein with respect to methods of treatment 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 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.

[0014] 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.

[0015] 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 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.

[0016] The present disclosure also provides 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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,