Pirfenox®

(Pirfenidone)

Highnoon

COMPOSITION
Pirfenox 200mg Tablet:
Each film-coated tablet contains: Pirfenidone 200mg

DESCRIPTION
Pirfenidone is antifibrotic drug used for mild to moderate idiopathic pulmonary fibrosis.

MECHANISM OF ACTION
The exact mechanism of action of pirfenidone is not yet understood but is believed to slow down the progression of idiopathic pulmonary fibrosis (IPF) by exerting both antifibrotic and anti-inflammatory properties.

PHARMACOKINETICS
Pirfenidone absorbed after oral doses; taking doses with food reduces peak plasma concentrations by about 50% but has only moderate effect on exposure, resulting in a lower incidence of adverse effects. It is metabolized primarily by the cytochrome P450 isoenzyme CYP1A2, with some contribution by CYP2C9, CYP2C19, CYP2D6, and CYP2E1. The major metabolite is 5-carboxy-pirfenidone. About 80% of a dose is excreted in urine with 24 hours, less than 1% as unchanged drug. The terminal elimination half-life after single dose is reported to be about 2.4 hours.

INDICATIONS
- It is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

DOSAGE AND ADMINISTRATION
The initial dose for adults is 200 mg, three times a day (600 mg/day), after a meal. Gradually increase the dose to 600 mg, three times a day (1,800 mg/day), under observation (as per Recommendations for Dosage Adjustment below). Furthermore, appropriately increase or decrease the dose from time to time depending upon the symptoms.

Recommendations for Dosage Adjustment
- Start with 200 mg tablets given three times a day (600 mg/day). After 2 weeks, gradually increase the dose by 200 mg at a time. It is desirable to maintain or achieve a final dose of 600 mg at a time (1,800 mg/day). Patients who miss 14 consecutive days or more of pirfenidone treatment should re-initiate therapy by undergoing the initial dose titration regimen (see Recommendations for Dose Adjustment above) up to the recommended daily dose. For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previously recommended daily dose without titration.

Dose adjustments and other considerations for safe use
Gastrointestinal events: In patients who experience intolerance to therapy due to gastrointestinal side effects, it is recommended to administer pirfenidone after food to prevent/reduce side effects. If symptoms persist pirfenidone may be reduced to 1-2 tablets given 2-3 times/day after food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve.
Photosensitivity reaction or rash: Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sunblock daily and to avoid sun exposure. The dose of pirfenidone may be reduced to 3 tablets/day (1 tablet three times a day). If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice. Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.
Hepatic function: In the event of significant elevation of alanine and /or aspartate aminotransferases (ALT/AST) with or without bilirubin elevation, the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed below.
Recommendations in case of ALT/AST elevations
If a patient exhibits >3 but ≤5 × the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting pirfenidone therapy:
- o Discontinue confounding medications, exclude other causes, and monitor the patient closely.
- o Repeat liver chemistry tests as clinically indicated.
- o The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re-titration to the full dosage as tolerated.

If a patient exhibits >3 but ≤5 × ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:
- o Permanently discontinue pirfenidone.
- o Do not rechallenge patient with pirfenidone.

If a patient exhibits >5 × ULN ALT and/or AST:
- o Permanently discontinue pirfenidone.
- o Do not rechallenge patient with pirfenidone.

Special populations Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in some individuals with mild to moderate hepatic impairment, caution should be used with pirfenidone treatment in this population. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor. Pirfenidone has not been studied in patients with severe hepatic impairment or end stage liver disease, and it should not be used in patients with these conditions. It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Pirfenidone therapy should not be used in patients with severe renal impairment (CrCl<30 ml/min) or end stage renal disease requiring dialysis.

Pediatric population
There is no relevant use of pirfenidone in the pediatric population in the treatment of IPF.

Elderly
No dose adjustment is necessary in patients 65 years and older.

ADVERSE REACTIONS
The most commonly reported adverse events are; liver enzyme elevations, drug-induced liver injury, photosensitivity reaction, rash, gastrointestinal disorders, nausea, diarrhea, abdominal pain (upper abdominal pain, abdominal distension, and stomach discomfort), upper respiratory tract infection, fatigue, headache, dyspepsia, dizziness, vomiting, taste altered, anorexia, gastroesophageal reflux, sinusitis, insomnia, weight decreased, arthralgia, myalgia, pruritus, decreased appetite, asthenia, dysgeusia, non-cardiac chest pain, agranulocytosis, neutropenia, leucopenia, blood dyscrasias, angioedema, urinary tract infection, somnolence, hot flush, dyspnea, cough, gastritis, constipation, flatulence, erythema, dry skin, rash erythematous, rash macular, rash pruritic and sunburn.

DRUG INTERACTIONS
CYP1A2 Inhibitors
Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.
In the case of moderate inducers of CYP1A2 (e.g. omeprazole), concomitant use may theoretically result in a lowering of pirfenidone plasma levels. Co-administration of medicinal products that act as potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. rifampicin) may result in significant lowering of pirfenidone plasma levels. These medicinal products should be avoided whenever possible.
Strong CYP1A2 Inhibitors: The concomitant administration of pirfenidone and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to pirfenidone. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of pirfenidone and avoided during pirfenidone treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of pirfenidone as needed.
Moderate CYP1A2 Inhibitors: Concomitant administration of pirfenidone and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to pirfenidone. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.
Concomitant CYP1A2 and other CYP Inhibitors: Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during pirfenidone treatment.

CYP1A2 Inducers
The concomitant use of pirfenidone and a CYP1A2 inducer may decrease the exposure of pirfenidone and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to pirfenidone treatment and avoid the concomitant use of pirfenidone and a strong CYP1A2 inducer.

Cigarette smoking and inducers of CYP1A2
Pirfenidone clearance is significantly higher in cigarette smokers than non-smokers, presumably due to the higher CYP1A2 enzyme activity in smokers. Smoking has the potential to induce hepatic enzyme production and thus increase medicinal product clearance and decrease exposure. Concomitant use of strong inducers of CYP1A2 including smoking should be avoided during pirfenidone therapy based on the observed relationship between cigarette smoking and its potential to induce CYP1A2. Patients should be encouraged to discontinue use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone.

CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant use of fluvoxamine.
- Severe hepatic impairment or end stage liver disease.
- Severe renal impairment (CrCl<30 ml/min) or end stage renal disease requiring dialysis.

WARNINGS AND PRECAUTIONS
- Cases of drug-induced liver injury (DILI) including severe liver injury with fatal outcomes have been observed with pirfenidone. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with pirfenidone, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.
- Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sunblock daily and to avoid sun exposure. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash.
- The dose of pirfenidone may be reduced to 3 tablets/day (1 tablet three times a day). If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice. Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.
- Gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastroesophageal reflux disease and abdominal pain are more frequently reported adverse reactions. The most common gastrointestinal events that led to dosage reduction or interruption are nausea, diarrhea, vomiting, and dyspepsia. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions. In patients who experience intolerance to therapy due to gastrointestinal side effects, it is recommended to administer pirfenidone after food to prevent/reduce side effects. If symptoms persist pirfenidone may be reduced to 1-2 tablets given 2-3 times/day after food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve.
- Drowsiness, dizziness and fatigue may occur due to pirfenidone, which may cause the patient to stagger. Patients on pirfenidone should, therefore, be advised not to operate or drive any machinery or motor vehicles. Patients on pirfenidone should, therefore, be advised not to operate or drive any machinery or motor vehicles.

PREGNANCY AND LACTATION
Pregnancy: There are no adequate data from the use of pirfenidone in pregnant women. It is advisable not to prescribe pirfenidone to pregnant women or to women who are likely to be pregnant.

Lactation: Lactating mothers receiving treatment with pirfenidone should be advised to avoid breastfeeding. It is unknown whether pirfenidone or its metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue from pirfenidone therapy, taking into account the benefit of breast-feeding for the child and the benefit of pirfenidone therapy for the mother.
Pediatric Use: Safety and effectiveness have not been established in pediatric patients.
Geriatric Use: No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.
Patient with Hepatic Impairment
It should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of pirfenidone as needed. The safety, efficacy, have not been studied in patients with severe hepatic impairment. It is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment.
Patient with Renal Impairment
It should be used with caution in patients with mild (CLcr 50–80 mL/min), moderate (CLcr 30–50 mL/min), or severe (CLcr less than 30 mL/min) renal impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of pirfenidone as needed. The safety, efficacy, have not been studied in patients with end-stage renal disease requiring dialysis. Use of pirfenidone in patients with end-stage renal diseases requiring dialysis is not recommended.

OVERDOSAGE
There is limited clinical experience with overdosage. In the event of a suspected overdosage, appropriate supportive medical care should be provided, including monitoring of vital signs and observation of the clinical status of the patient.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Pirfenox 200mg Tablets: Alu. Alu. Blister Pack of 3 x 10's.

پیرفینوکس®

(پیرفینیڈون)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
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