Pirfenidone Tablets 200 mg
PIRFENEX

The use of pirfenidone has been shown to cause an abnormal chromosomal structure on exposure to light in genotoxicity tests; therefore, it is important to explain to the patient about the potential of the drug to cause carcinogenesis of the skin on exposure to light. Pirfenidone should only be prescribed under the supervision of a physician familiar with the treatment of idiopathic pulmonary fibrosis.

COMPOSITION
Each film-coated tablet contains
Pirfenidone……200 mg
Colour: Titanium Dioxide

DOSAGE FORM
Oral tablet

PHARMACOLOGY

Pharmacodynamics
Pirfenidone is a pyridine molecule with anti-inflammatory and antifibrotic activities that have been reported both *in vitro* and *in vivo*. The mechanism of action of pirfenidone has not been fully established.

IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1–beta (IL-1β) and pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli. Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

Ex vivo, pirfenidone inhibited fibroblast proliferation, differentiation and related collagen synthesis and inhibits its degradation. Pirfenidone reduced the production of other mediators of fibrogenesis, such as fibronectin and connective tissue growth factor [CTGF]. Moreover, in a murine macrophage-like cell line [RAW264.7], pirfenidone inhibited TNF-alpha synthesis *in vitro*, whereas it increased the production of IL-10 (with anti-inflammatory activity) in the murine endotoxin shock model *in vivo.* Pirfenidone has also been shown to reduce the levels of platelet-derived growth factors, A and B in bronchoalveolar lavage in a hamster model of bleomycin- induced lung fibrosis.

Pharmacokinetics

Plasma Concentrations

Plasma concentrations and pharmacokinetic parameters of pirfenidone in 6 healthy adult men, given 200 mg, 400 mg and 600 mg as a fasting, single oral administration are shown in Figure 1 and Table 1.

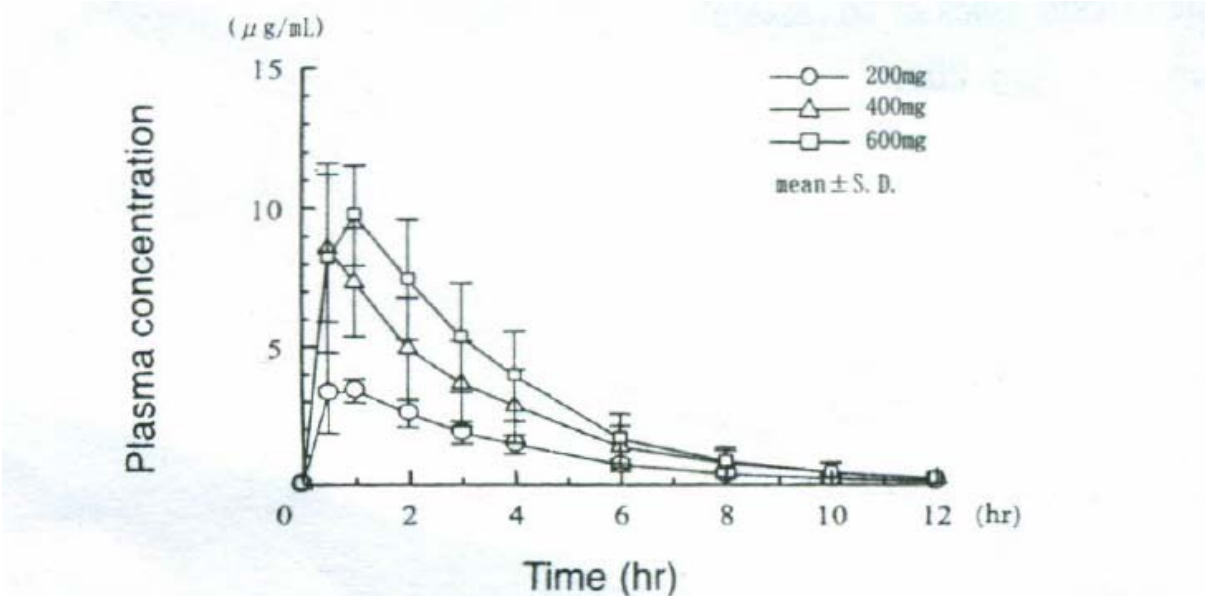

Figure 1: Plasma concentrations on fasting after a single dose

Table 1: Pharmacokinetic parameters (n = 6)

Dose quantity (mg)	C_{max} (μg/mL)	T_{max} (hr)	AUC_{0-48} (μg.hr/mL)	$T_{1/2}$ (hr)
200	3.88 ± 0.82	0.75 ± 0.27	13.97 ±2.71	2.10 ± 0.45
400	9.24 ± 1.74	0.58 ± 0.20	29.10 ± 11.77	1.96 ± 0.55
600	10.57 ± 1.78	0.83 ± 0.26	37.03 ± 11.97	1.76 ± 0.40

(Measurement method: HPLC) (Mean ± S.D.)

Similarly, the plasma concentrations achieved after repeated doses of 200 mg, 400 mg and 600 mg, respectively, and by gradually increasing the dosages to three times a day at morning, afternoon and evening after every meal for 6 days (dose administration on the first day and the sixth day being twice a day, that is, in the morning and in the afternoon) in 12 healthy adult males has been reported in table 2.

With regards to every dose on the first day and the sixth day, the plasma concentrations showed a similar trend of change. After administration on the first day, both the C_{max} and the AUC were increased in accordance with the proportional increase in the dosage quantity.

Table 2: Pharmacokinetic parameters (n = 12)

One time dose quantity	Days of dose administration (Total)	C_{max0-4} (μg/mL)	T_{max0-4} (hr)	$C_{max4-24}$ (μg/mL)	$T_{max4-24}$ (hr)	AUC_{0-24} (μg.hr/ mL)	$T_{1/2}$ (hr)

(mg)							
200	1	2.71 ± 0.91	1.08 ± 0.47	2.83 ± 1.12	6.04 ± 1.05	19.17 ± 6.46	2.17 ± 0.30
	6	3.06 + 1.28	1.08 ± 0.82	2.70 ± 0.51	6.29 ± 0.96	22.03 ± 5.47	2.25 ± 0.29
400	1 (7)	4.94 ± 1.29	1.79 ± 0.89	6.22 ± 1.59	5.79 ± 1.36	46.13 ± 10.01	2.42 ± 0.48
	6 (12)	6.19 + 1.89	1.17 ± 0.54	5.91 ± 2.09	6.38 ± 1.15	48.69 ± 11.21	2.36 ± 0.38
600	1 (13)	8.20 ± 1.29	1.25 ± 0.45	9.21 ± 1.97	6.33 ± 1.15	77.22 ± 15.44	2.53 ± 0.42
	6 (18)	8.19 ± 1.54	1.71 ± 0.54	10.00 ± 1.70	6.13 ± 1.00	82.31 ± 16.50	2.55 ± 0.45

(Method of measurement: HPLC) (Mean ± S.D.)

A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that pirfenidone be administered with food to reduce the incidence of nausea and dizziness.

***Distribution*:** Pirfenidone binds to human plasma proteins, primarily to serum albumin. Single oral dosing of [^{14}C]-pirfenidone 100 mg/kg to rats indicated a higher radioactive concentration in internal organs as compared to blood plasma.

Serum protein binding rate The serum protein binding rate was measured by the ultra-filtration method in a healthy adult administered a single oral dose of 600 mg when fasting. After 1 hour and 3 hours of administration, the serum protein binding was 54 – 62%.

Metabolism: *In vitro* metabolism studies with hepatic microsomes indicate that approximately 48% of pirfenidone is metabolised via CYP1A2 with other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1 each contributing less than 13%. *In vitro* and *in vivo* studies to date have not detected any activity of the major metabolite (5-carboxy-pirfenidone), even at concentrations or doses greatly above those associated with activity of pirfenidone itself. This suggests that it will not be affected by drugs that inhibit the CYP 450 enzymes.

***Excretion*:** The oral clearance of pirfenidone appears modestly saturable. In a multiple-dose, dose-ranging study in healthy older adults administered doses ranging from 267 mg to 1335 mg three times a day, the mean clearance decreased by approximately 25% above a dose of 801 mg three times a day. Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours. Approximately 80% of an orally administered dose of pirfenidone is cleared in the urine within 24 hours of dosing.

The majority of pirfenidone is excreted as the 5-carboxy-pirfenidone metabolite (>95% of that recovered), with less than 1% of pirfenidone excreted unchanged in urine.

Effect of Diet

The plasma concentrations and pharmacokinetic parameters in 6 healthy adult males after a single oral administration of 400 mg after meals and when fasting are shown in Figure 2 and Table 3. Because of the meals, there is a large reduction in C_{max} and a smaller effect on AUC, compared to the fasted state and the T_{max} is significantly delayed.

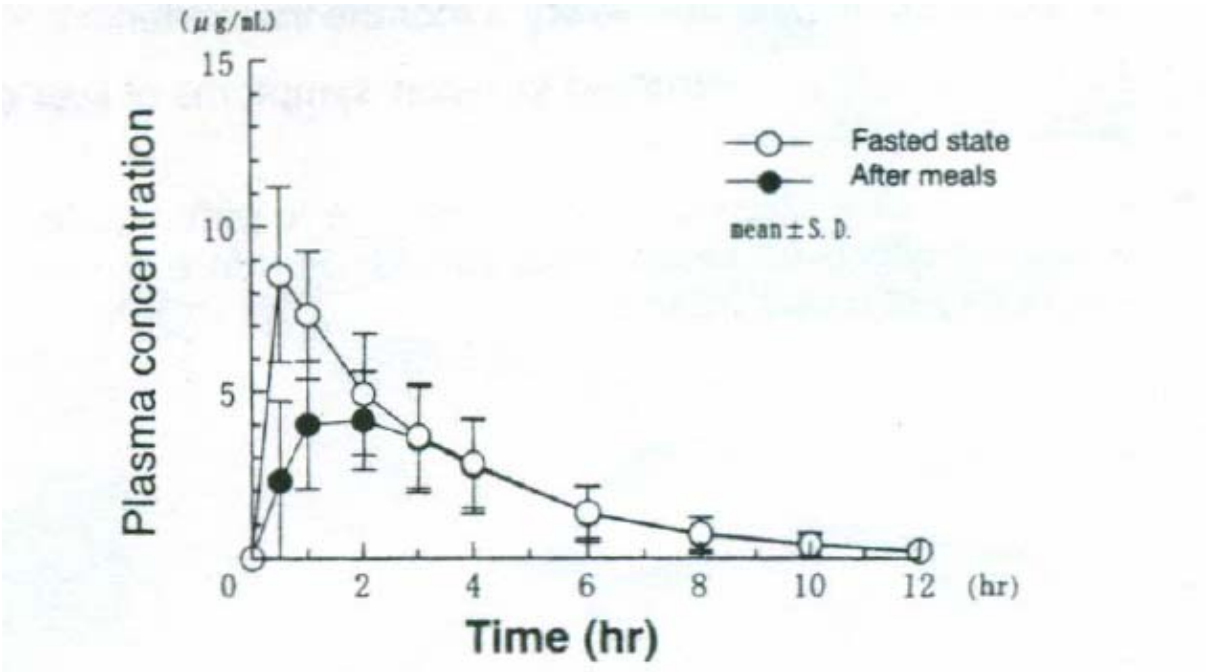

Figure 2: Plasma concentrations after meals and when fasting

Table 3: Pharmacokinetic parameters (n = 6)

Dose quantity (mg)		**C_{max} (μg/mL)**	**T_{max} (hr)**	**AUC_{0-40} [μg.hr/mL)**	**$T_{1/2}$ (hr)**
400	After meal (postprandial)	4.88 ± 1.72	1.83 ± 0.75	22.13 ± 10.63	1.77 ± 0.55
	Fasting	9.24 ± 1.74	0.58 ± 0.2	29.10 ± 11.77	1.96 ± 0.55

(Method of measurement: HPLC) (Mean ± S.D.)

Special populations

Hepatic impairment

The pharmacokinetics of pirfenidone and the 5-carboxy-pirfenidone metabolite were compared in subjects with moderate hepatic impairment (Child-Pugh Class B) and in subjects with normal hepatic function. Results showed that there was a mean increase of 60% in pirfenidone exposure after a single dose of 801 mg pirfenidone in patients with moderate hepatic impairment. Pirfenidone should be used with caution in patients with mild to moderate hepatic impairment and patients should be

monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (*see* **Recommendations for Dose Adjustment** and **WARNINGS AND PRECAUTIONS**). Pirfenidone is contraindicated in severe hepatic impairment and end stage liver disease (*see* **Recommendations for Dose Adjustment** and **CONTRAINDICATIONS**).

Renal impairment
No clinically relevant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild to severe renal impairment compared with subjects with normal renal function. The parent drug is predominantly metabolised to 5-carboxy-pirfenidone, and the pharmacokinetics of this metabolite is altered in subjects with moderate to severe renal impairment. However, the predicted amount of metabolite accumulation at steady state is not pharmacodynamically important because the terminal elimination half-life is only 1–2 hours in these subjects. No dose adjustment is required in patients with mild to moderate renal impairment who are receiving pirfenidone. The use of pirfenidone is contraindicated in patients with severe renal impairment (CrCl <30ml/min) or end stage renal disease requiring dialysis (see **Recommendations for Dose Adjustment** and **CONTRAINDICATIONS**).

Population pharmacokinetic analyses from 4 studies in healthy subjects or subjects with renal impairment and one study in patients with IPF showed no clinically relevant effect of age, gender or body size on the pharmacokinetics of pirfenidone.

INDICATIONS
Pirfenidone 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.

Pirfenidone tablet is to be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness (*see* **UNDESIRABLE EFFECTS).** It is recommended to administer pirfenidone after food/ meals to prevent/reduce side effects.

Recommendations for Dose Adjustment
Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine tablets per day over a 14-day period as follows:

- Days 1 to 7: one tablet, three times a day (600 mg/day)
- Days 8 to 14: two tablets, three times a day (1200 mg/day)
- Day 15 onward: three tablets, three times a day (1800 mg/day)

Patients who miss 14 consecutive days or more of pirfenidone treatment should re-initiate therapy by undergoing the initial 2-week titration regimen up to the recommended daily dose.
For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previous 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, patients should be reminded to take the medicinal product with food. If symptoms persist pirfenidone may be reduced to 1-2 tablets given 2-3 times/day with 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 (*see* **WARNINGS AND PRECAUTIONS**). 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. (*see* **WARNINGS AND PRECAUTIONS**).

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 under *(see* **WARNINGS AND PRECAUTIONS***).*

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 (*see* **WARNINGS AND PRECAUTIONS**). 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 (see **WARNINGS AND PRECAUTIONS**). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see **WARNINGS AND PRECAUTIONS** and **Recommendations for Dose Adjustment**).

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.

Paediatric population
There is no relevant use of pirfenidone in the paediatric population in the treatment of IPF.

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

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients,
- Concomitant use of fluvoxamine (*see* **Drug Interactions** under **WARNINGS AND PRECAUTIONS**)
- Severe hepatic impairment or end stage liver disease (*see* **WARNINGS AND PRECAUTIONS** and **Recommendations for Dose Adjustment**)
- Severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis (*see* **WARNINGS AND PRECAUTIONS** and **Recommendations for Dose Adjustment**).

WARNINGS AND PRECAUTIONS

Photosensitivity reaction and rash
Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with Pirfenidone. It is recommended to wear long-sleeved clothing when outdoors, wear a hat or use an umbrella, and apply effective sunscreens It is recommended to wear long-sleeved clothing when outdoors, wear a hat or use an umbrella, and apply effective sunscreens(SPF50+, PA+++) in order to avoid the UV rays and to avoid other medicinal products known to cause photosensitivity.
Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash (*see* **Recommendations for Dose Adjustment**).
The use of pirfenidone has been shown to cause an abnormal chromosomal structure on exposure to light in genotoxicity tests; therefore, it is important to explain to the patient about the potential of the drug to cause carcinogenesis of the skin on exposure to light.

Hepatic function
Pirfenidone may cause liver dysfunction accompanied by a rise in the aspartate transaminase (AST) and alanine transaminase (ALT) levels, suggestive of jaundice. It is therefore, recommended that the liver enzymes be periodically monitored. Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with pirfenidone, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (*see* **Recommendations for Dose**

Adjustment). Patients should be instructed to report symptoms of liver disease (e.g. dark urine and/or jaundice) to their physician. In the event of significant elevation of liver aminotransferases the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed below. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, the following dose adjustments may be necessary.

Recommendations in case of ALT/AST elevations

- If a patient exhibits an aminotransferase elevation to >3 to ≤5 x ULN after starting pirfenidone therapy, confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. If clinically appropriate the dose of pirfenidone should be reduced or interrupted. Once liver function tests are within normal limits pirfenidone may be re-escalated to the recommended daily dose if tolerated.
- If a patient exhibits an aminotransferase elevation to ≤5 x ULN accompanied by symptoms or hyperbilirubinaemia, pirfenidone should be discontinued and the patient should not be rechallenged.
- If a patient exhibits an aminotransferase elevation to >5 x ULN, pirfenidone should be discontinued and the patient should not be rechallenged.

Hepatic impairment

In subjects with moderate hepatic impairment (i.e. Child-Pugh Class B), pirfenidone exposure was increased by 60%. Pirfenidone should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B) given the potential for increased pirfenidone exposure.
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 individuals with severe hepatic impairment and pirfenidone should not be used in patients with severe hepatic impairment.

Dizziness

Dizziness has been reported in patients taking pirfenidone. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination. In clinical studies, most patients who experienced dizziness had a single event, and most events resolved, with a median duration of 22 days. If dizziness does not improve or if it worsens in severity, dose adjustment or even discontinuation of pirfenidone may be warranted.

Fatigue

Fatigue has been reported in patients taking pirfenidone. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination.

Weight loss

Weight loss has been reported in patients treated with pirfenidone (*see* **UNDESIRABLE EFFECTS**). Physicians should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.

Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed. Pirfenidone may cause dizziness and fatigue, which could influence the ability to drive or use machines. Patients on pirfenidone should, therefore, be advised not to operate or drive any machinery or motor vehicles.

Drug Interactions
Pirfenidone is primarily metabolised by CYP1A2. *In vitro* metabolism studies with hepatic microsomes indicate that approximately 48% of pirfenidone is metabolised via CYP1A2 with other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1 each contributing less than 13%.Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with pirfenidone.

Fluvoxamine and inhibitors of CYP1A2
Pirfenidone is contraindicated in patients with concomitant use of fluvoxamine (see section 4.3). Fluvoxamine should be discontinued prior to the initiation of Pirfenidone therapy and avoided during pirfenidone therapy due to the reduced clearance of pirfenidone. Other therapies that are inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. CYP2C9, 2C19, and 2D6) should be avoided during pirfenidone treatment.
Special care should also be exercised if CYP1A2 inhibitors are being used concomitantly with potent inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone such as CYP2C9 (e.g. amiodarone, fluconazole), 2C19 (e.g. chloramphenicol) and 2D6 (e.g. fluoxetine, paroxetine).
Pirfenidone should be used with caution in patients treated with other moderate or strong inhibitors of CYP1A2 (e.g. ciprofloxacin, amiodarone, propafenone).

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.

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.

Renal Impairment
There is limited experience with pirfenidone in patients with renal impairment.

Hepatic Impairment

Pirfenidone may cause liver dysfunction accompanied by a rise in the AST and ALT levels, suggestive of jaundice. It is, therefore, recommended that the liver enzymes be periodically monitored.
In case of liver enzyme abnormalities, pirfenidone should be discontinued and appropriate treatment to correct the liver dysfunction should be initiated.

Pregnancy
It is advisable not to prescribe pirfenidone to pregnant women or to women who are likely to be pregnant. There are no data from the use of pirfenidone in pregnant women. No adverse effects on fertility were observed in preclinical studies.

Lactation
Nursing 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.

Paediatric Use
Safety of pirfenidone in infants with low birth weight, newborn babies, nursing infants, babies or children has not been established.

Geriatric Use
Elderly patients generally have declined physiological function; hence, pirfenidone should be administered with caution.

UNDESIRABLE EFFECTS
The most common adverse effects of pirfenidone are photosensitivity, loss of appetite (anorexia), stomach discomfort and nausea, and elevated gamma glutamyl transpeptidase levels and AST (SGOT) and ALT (SGPT) levels.

The most commonly reported (≥10%) adverse reactions during clinical study experience with pirfenidone at a dose of 2403 mg/day compared to placebo, respectively, were nausea (32.8% versus 13.3%), rash (28.7% versus 8.6%), fatigue (22.3% versus 13.3%), diarrhoea (21.7% versus 13.5%), dyspepsia (16.8% versus 5.5%), and photosensitivity reaction (12.2% versus 1.7%).

Serious adverse reactions were recorded at similar frequencies among patients treated with 2403 mg/day of pirfenidone and placebo in clinical studies.

Table 4 shows the adverse reactions reported at a frequency of ≥2% in 345 patients receiving pirfenidone at the recommended dose of 2403 mg/day in two pivotal Phase 3 studies. Adverse reactions are listed by System Organ Class and within each frequency grouping [Very common (≥1/10), Common (≥1/100 to <1/10)] the adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse reactions by SOC and MedDRA frequency

Infections and infestations	
Common	Upper respiratory tract infection; urinary tract infection
Metabolism and nutrition disorders	
Common	Weight decreased; anorexia; decreased appetite
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Common	Dizziness; headache; somnolence; dysgeusia
Vascular disorders	
Common	Hot flush
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea; cough; productive cough
Gastrointestinal disorders	
Very Common Common	Dyspepsia; nausea; diarrhoea Gastroesophageal reflux disease; vomiting; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort;gastritis; constipation; flatulence
Hepatobiliary disorders	
Common	ALT increased; AST increased; gamma glutamyl transferase increased
Skin and subcutaneous tissue disorders	
Very Common Common	Photosensitivity reaction; rash Pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic
Musculoskeletal and connective tissue disorders	
Common	Myalgia; arthralgia

General disorders and administration site conditions	
Very Common Common	Fatigue Asthenia; non-cardiac chest pain
Injury poisoning and procedural complications	
Common	Sunburn

OVERDOSAGE
Inadequate information available. In the event of a suspected overdose, supportive medical care should be provided including monitoring of vital signs and close observation of the clinical status of the patient.

STORAGE AND HANDLING INSTRUCTIONS
Store in a cool dry place

PACKAGING INFORMATION
PIRFENEX…… Blister pack of 10 tablets

Last updated: March 2011.