

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**

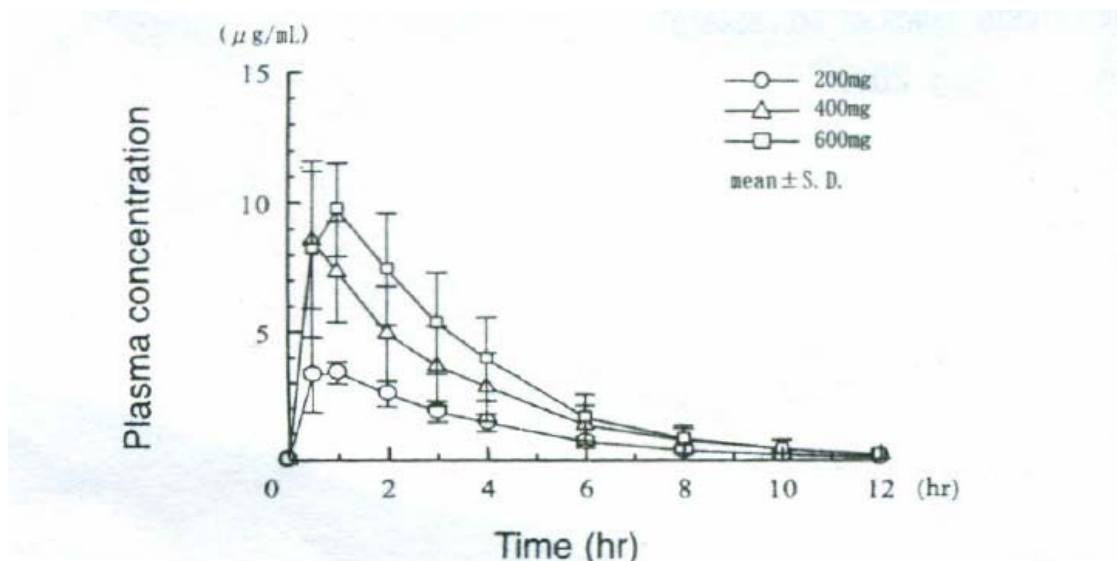
**Pharmacodynamics**

Pirfenidone is a pyridine molecule with anti-inflammatory and antifibrotic activities that have been reported both *in vitro* and *in vivo*. *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 <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	AUC <sub>0-48</sub> (µg.hr/mL)	T <sub>1/2</sub> (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<sub>max</sub> 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 (mg)	Days of dose administration (Total)	C <sub>max0-4</sub> (µg/mL)	T <sub>max0-4</sub> (hr)	C <sub>max4-24</sub> (µg/mL)	T <sub>max4-24</sub> (hr)	AUC <sub>0-24</sub> (µg.hr/mL)	T <sub>1/2</sub> (hr)
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.)

**Distribution:** Single oral dosing of [<sup>14</sup>C]-pirfenidone 100 mg/kg to rats indicated a higher radioactive concentration in internal organs as compared to blood plasma.

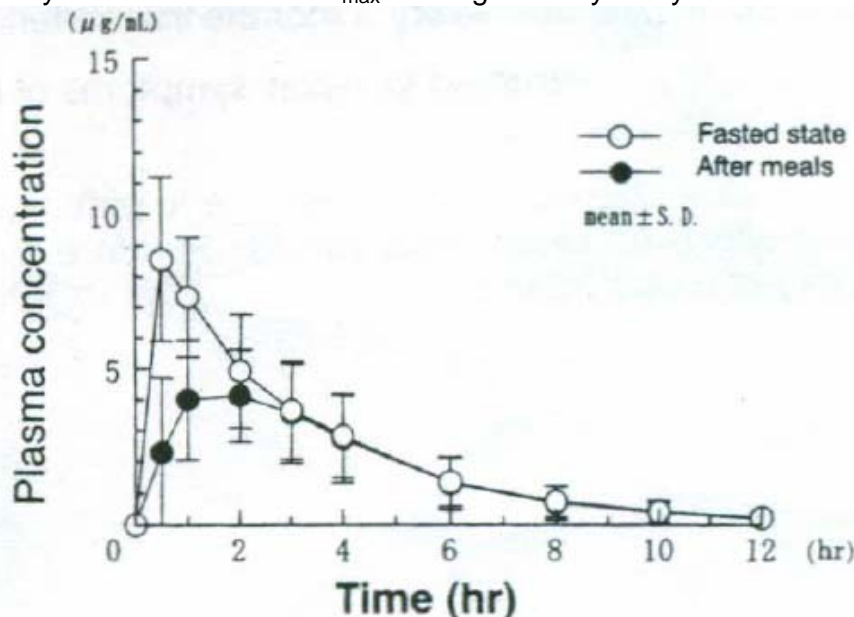
**Serum protein binding rate** The serum protein binding rate was measured by the ultra-filtration method in a healthy adult administered a single oral dose of 600 mg when fasting. After 1 hour and 3 hours of administration, the serum protein binding was 54 – 62%.

**Metabolism:** Pirfenidone is metabolized by a number of cytochrome (CYP) enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1) in human liver microsomes. This suggests that it will not be affected by drugs that inhibit the CYP 450 enzymes.

**Excretion:** At 48 hours, the urinary excretion rate of unchanged drug was less than 1%. Pirfenidone-5-carboxylic acid is the major metabolite.

#### 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, the C<sub>max</sub> and the AUC were significantly decreased and the T<sub>max</sub> was significantly delayed.



## Figure 2: Plasma concentrations after meals and when fasting

Table 3: Pharmacokinetic parameters (n = 6)

Dose quantity (mg)		C <sub>max</sub> (µg/mL)	T <sub>max</sub> (hr)	AUC <sub>0-40</sub> [ug.hr/mL]	T <sub>1/2</sub> (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.)

## INDICATIONS

Pirfenidone is indicated for the treatment of idiopathic pulmonary fibrosis.

## 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).
- In case of gastrointestinal symptoms or weight loss, decrease the dose or discontinue treatment with pirfenidone. However, if symptoms increase, try to achieve and maintain a dose of 400 mg at a time (1,200 mg/day).
- It is recommended to administer pirfenidone after food/ meals to prevent/reduce side effects.

### Recommendations for Dose Modification in cases of Liver Function Abnormality

[see **WARNINGS AND PRECAUTIONS** for recommendations on liver function monitoring)

- **> 3 to 5 x the upper limit of normal [ULN] aminotransferase elevation:** Confounding medications should be discontinued and the patient monitored closely. Daily dose may be maintained at full dose if clinically appropriate, or reduced or interrupted (e.g. until liver function tests are within normal limits) with subsequent re-escalation to full dose as tolerated.
- **> 5 x ULN aminotransferase elevation of ≤ 5 x ULN aminotransferase elevation accompanied by symptoms or hyperbilirubinaemia:** Treatment should be permanently discontinued.

## CONTRAINDICATIONS

Pirfenidone is contraindicated in patients with a history of hypersensitivity to the drug component.

## **WARNINGS AND PRECAUTIONS**

- 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. Due to this, patients should be advised to take appropriate measures to protect themselves against exposure to light.
  - 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.
  - If rash or itching occurs, the patient must be advised to contact the doctor immediately
- 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.

### ***Recommendations for liver function monitoring***

Liver enzymes should be measured prior to initiation of therapy in all patients, then monthly for the first 6 months and every 3 months thereafter.

Patients should be instructed to report symptoms of liver disease (e.g. dark urine and/or jaundice) to their physician.

- Drowsiness and dizziness 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.

### **Drug Interactions**

- Pirfenidone clearance is reduced the co-administration of fluvoxamine, which inhibits CYP1A2 and several other CYP isoforms. Strong CYP1A2 inhibitors should, therefore, be used with caution in patients receiving pirfenidone due to the potential for reduced clearance
- Pirfenidone clearance is significantly higher in cigarette smokers than non-smokers, presumably due to the higher CYP1A2 enzyme activity in smokers.

### **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.

**Lactation**

Nursing mothers receiving treatment with pirfenidone should be advised to avoid breastfeeding.

**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.

**OVERDOSAGE**

Inadequate information available.

**STORAGE AND HANDLING INSTRUCTIONS**

Store in a cool dry place.

**PACKAGING INFORMATION**

**PIRFENEX** Tablets..... Blister pack of 10 tablets

*Last updated: October 2010*