

## PIRFENIDONE MONOGRAPH

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The first and only approved drug for IPF

**pirfenex** tablets  
pirfenidone 200mg

Restrains Pulmonary Fibrosis

# Preface

*Idiopathic Pulmonary Fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. As is well known, the disease presents a rough path for the patient as well as the treating physician. IPF has an unrelenting progressive course, and the response to existing treatment is limited. In fact the prognosis in IPF is worse than for many cancers.*

*Still, with increased awareness and better diagnostic facilities, there has been a definite improvement in the diagnosis of IPF. It has moved from being a diagnosis of exclusion to a distinct clinical entity. Till now there is no approved treatment for IPF, but exciting times are ahead. Newer drugs and treatment strategies are being developed.*

*Pirfenidone is the first pharmacologic agent approved for the treatment of IPF. It is an antifibrotic agent with preclinical and clinical data to support its use in IPF. The introduction of pirfenidone 200 mg tablets in India therefore brings renewed hope for both patients and physicians involved in treating this disease.*

## CHAPTER 1

# Recent Advances in IPF

Idiopathic Pulmonary Fibrosis (IPF) is a devastating, progressive fibrotic lung disease with a median survival of 3-5 years. It is defined as *a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with a histopathologic appearance of usual interstitial pneumonia (UIP) on surgical (thoroscopic or open) lung biopsy*. Though the precise incidence and prevalence of IPF are not known, of the over 150 recognized types of interstitial lung diseases; IPF is the commonest and one of the most deleterious.

**Table 1: Mortality in IPF and other diseases**

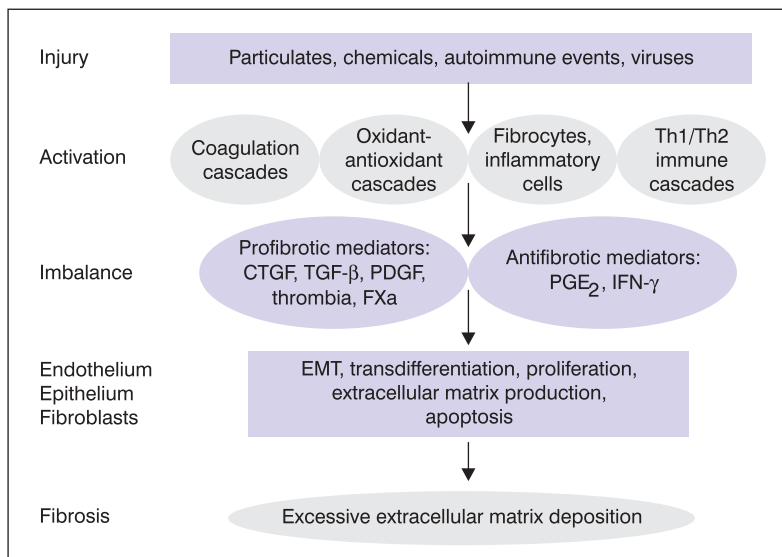
Disease	Mortality
IPF	50% at 5 yr (13)
COPD FEV <sub>1</sub> <30% predicted	50% at 3 yr (60)
COPD and long-term oxygen therapy	50% at 5 yr (61)
Acute myocardial infarction (seen in emergency room)	25% at 5 yr (62)
Coronary bypass surgery (3 vessels)	30% at 4 yr (63)
Lung cancer	85% at 5 yr (64)
Breast cancer	20% at 5 yr (64)
Prostate cancer	15% at 5 yr (64)
Cirrhosis with variceal bleeding	50% at 4 yr (65)

COPD: Chronic Obstructive Pulmonary Disease

Symptoms of IPF are often subtle, such that patients wait 6 months or longer until they decide to seek medical attention. Average duration of symptoms before presentation is 24 months. Martinez and colleagues studied patients with mild-to-moderate IPF and found that some patients had minimal deterioration of lung function or oxygenation, others had frequent hospitalizations for respiratory illness & others experienced acute deterioration of their lung disease. Whether the patient with IPF has a slow or rapid progression of the disease, overall prognosis is generally poor.

The last decade has seen important progress in the pathogenesis of IPF. It was believed that, in fibrosis, an exaggerated and uncontrolled healing response occurs, in which the key initiating features are inflammatory cell influx and release of pro-fibrotic products. It was this view that led to the belief that fibrosis could be prevented through inhibition of the inflammatory response and this was the rationale for the use of corticosteroids and azathioprine. Therefore the conventional management of IPF has been primarily based on the concept that suppressing inflammation would prevent progression to fibrosis. These drugs are thus non specific and associated with significant adverse events, poor quality of life and response rates less than 20%.

However there is little evidence that inflammation is prominent in early disease. A growing body of research now argues that fibrosis, proceeds independently of the inflammatory events. It has been recently proposed that a multiple-pathway mechanism is at play in the pathogenesis of IPF. The clotting cascade, anti-oxidant pathways, apoptosis, inflammatory cytokines, angiogenesis and vascular remodelling, growth factors, surfactant and matrix regulatory factors have all been implicated in fibrosis in animal models. Furthermore, these cascades initiate changes in the behaviour and morphology of multiple cell types, including epithelial cells, fibroblasts, endothelial cells, resident and migratory inflammatory cells, and circulating fibroblast progenitor cells (fibrocytes).



**Fig. 1: A new model for the pathogenesis of idiopathic pulmonary fibrosis: injury activates multiple inflammatory, cell signaling and repair pathways. Activation of these cascades causes an imbalance in pro- and antifibrotic mediators. In turn, these mediators activate multiple cell types, causing changes in cellular functioning and cell-cell interactions that ultimately result in progressive fibrosis.**

Th: T-helper cell; CTGF: connective tissue growth factor; FXa: factor Xa; PG: prostaglandin; IFN- $\gamma$ : interferon- $\gamma$ ; EMT: epithelial-mesenchymal transition.

The new insights into IPF pathogenic mechanisms disclosing the role of fibrogenesis has led to the discovery of various anti-fibrotic agents as potential targets for IPF. Pirfenidone is one such molecule that has been under investigation for the last several years.

Pirfenidone is a novel compound with demonstrated anti-inflammatory, anti-fibrotic and antioxidant activities that makes it a suitable candidate molecule for managing IPF. Currently it is the first and only drug which has been approved for the treatment of IPF and is available in Japan. The introduction of pirfenidone in our country opens a new ray of hope to the numerous patients suffering from IPF.

*Am J Respir Crit Care Med* 1999; 160: 1771-1777  
*Ann Intern Med* 2005; 142: 963-967  
*Eur Respir J* 2007; 30: 835-839  
*Ann Intern Med* 2001; 134: 136-151

## CHAPTER 2

# Pharmacological Properties of Pirfenidone

Pirfenidone is a small non-peptide molecule of low molecular weight (185.2 daltons). The chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone and its empirical formula is C<sub>12</sub>H<sub>11</sub>NO. The structure of pirfenidone is shown in the figure below.

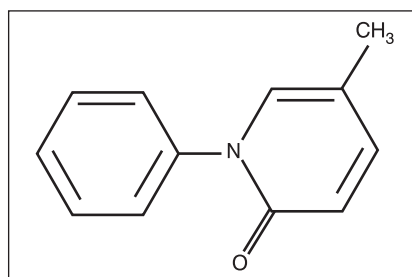


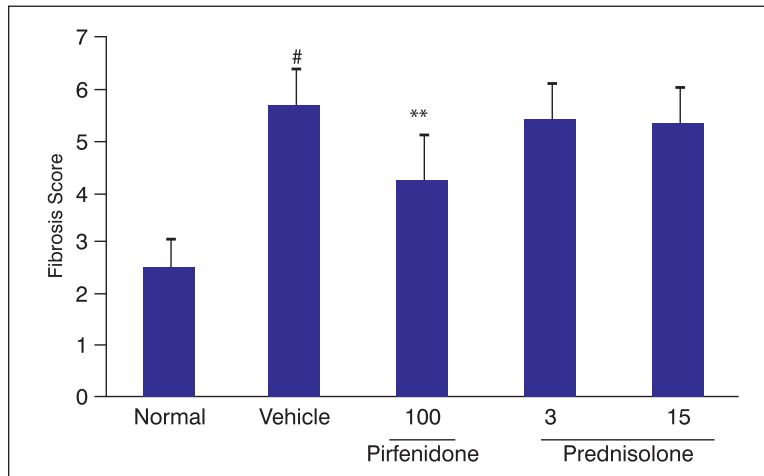
Fig. 2: Chemical structure of pirfenidone

## PRE-CLINICAL STUDIES

### *Pirfenidone has both anti-fibrotic and anti-inflammatory properties.*

Pirfenidone has been shown to ameliorate the bleomycin- and cyclophosphamide-induced lung fibrosis in hamsters and mice models. The dietary intake of pirfenidone, starting after the second dose in a 3-dose regimen, also minimized the accumulation of collagen in the lungs and retarded the progression of ongoing lung fibrosis in hamsters. Subsequently, the study showed that pirfenidone attenuated the bleomycin-induced overexpression of heat shock protein (HSP)–47, a collagen specific molecular chaperone in the lungs, in mice.

*In vitro* studies have demonstrated the ability of pirfenidone to inhibit transforming growth factor beta (TGF-β)–stimulated collagen synthesis, decrease the extracellular matrix, and block the mitogenic effects of platelet-derived growth factor in adult human lung fibroblasts derived from patients with IPF. When compared with prednisolone, in mice models pirfenidone significantly attenuated bleomycin- induced pulmonary fibrosis and prevented bleomycin-induced decrease in lung interferon (IFN-γ), suppressed elevation of lung basic fibroblast growth factor (bFGF) and TGF-β1 levels. Unlike pirfenidone, prednisolone was unable to reduce the fibrosis score.



**Fig. 3: Quantitative examination of anti-fibrotic effects of pirfenidone and prednisolone on bleomycin-induced pulmonary fibrosis in mice.**

#P<0.01 (normal group versus vehicle group by Student's t test).

\*\*P<0.01 (pirfenidone- and prednisolone-treated groups versus vehicle group by Dunnett's multiple comparison test).

#### PIRFENIDONE EXHIBITS ANTI-INFLAMMATORY AND ANTI-FIBROTIC PATHWAYS

- Inhibits fibroblast proliferation & differentiation related to collagen synthesis
- Inhibits production & activity of TGF- $\beta$
- Reduces production of fibronectin & connective tissue growth factor (CTGF)
- Inhibits TNF- $\alpha$  synthesis & I-CAM
- Increases production of IL-10
- Reduces levels of PDGF A&B in BAL of bleomycin-induced lung fibrosis

*J Lab Clin Med* 1995; 125: 779-785.  
*Toxicol Lett.* 1997; 90: 125-132  
*Exp Lung Res* 1998; 24: 119-132  
*Eur Respir J* 2004; 24: 57-65  
*J Clin Pharmac* 2007; 47: 1268-1276  
*Eur J Pharmacol* 2008; 590: 400-408  
*IDrugs* 2004; 7: 166-172  
*Expert Opin Investg Drugs* 2006; 15: 823-828

## PHARMACOKINETICS

The pharmacokinetic characteristics and dose proportionality of pirfenidone were investigated in healthy Chinese volunteers following single oral doses of 200, 400 or 600 mg and multiple oral doses of pirfenidone 400 mg 3 times daily for 5 consecutive days in a phase I clinical trial. Pirfenidone displayed linear pharmacokinetics in the dose range of 200 to 600 mg after single oral doses.

- Pirfenidone was rapidly absorbed following single oral doses, with maximum plasma concentrations reached 0.33 to 1 hour after administration.
- Mean  $t_{1/2}$  ranged from 2 to 2.5 hours and clearance after single-dose administration was approximately 9.6 L/h.

In comparing the single-dose with the multiple-dose profile, the pharmacokinetic analysis of pirfenidone showed very similar properties.

- The pharmacokinetic parameters estimated from the multiple doses were similar to those from single 400 mg doses under fed conditions, indicating no significant accumulation of pirfenidone with repeated dosing.
- There is no evidence of decreasing plasma concentrations upon multiple dosing, which would be indicative of a cytochrome P450 enzyme inductive effect of pirfenidone.

The assessed pharmacokinetic parameters showed relatively low inter individual variation.

Concomitant food intake significantly ( $P < .01$ ) altered the bioavailability of pirfenidone, as indicated by decreasing AUC,  $C_{max}$ , and increasing  $t_{max}$ .

There were no significant differences in pharmacokinetic parameters between the female and male subjects. Hence, no adjustment of dosage on the basis of sex appears needed.

*J Clin Pharmac* 2007; 47: 1268-1276

# Clinical Studies with Pirfenidone in IPF

## PHASE II STUDIES

### 1. RESULTS OF A PROSPECTIVE, OPEN-LABEL, PHASE II STUDY

#### *Study Overview*

Ganesh Raghu & colleagues from the University of Washington conducted an initial phase II test to evaluate the clinical usefulness with tolerability of pirfenidone in advanced IPF patients who had deteriorated despite conventional therapy or who were unable to tolerate or unwilling to try conventional therapy. Treatment was administered on a compassionate basis (open-label). Diagnosis of IPF was based on typical clinical and histological features of UIP confirmed by surgical lung biopsy (SLB).

Primary endpoints included overall survival and measurable change in lung function after 12 months of therapy. **Improvement** in pulmonary function measures was defined as a 10% or greater increase in predicted value of FVC or TLC, 20% or greater increase in  $DL_{CO}$ , or 3% increase in oxygen saturation with the same fraction of inspired oxygen (FIO<sub>2</sub>), resting or exertional. A decrease of similar magnitude for each measure was considered **deterioration**. Patients who did not demonstrate improvement or deterioration were considered **stable**.

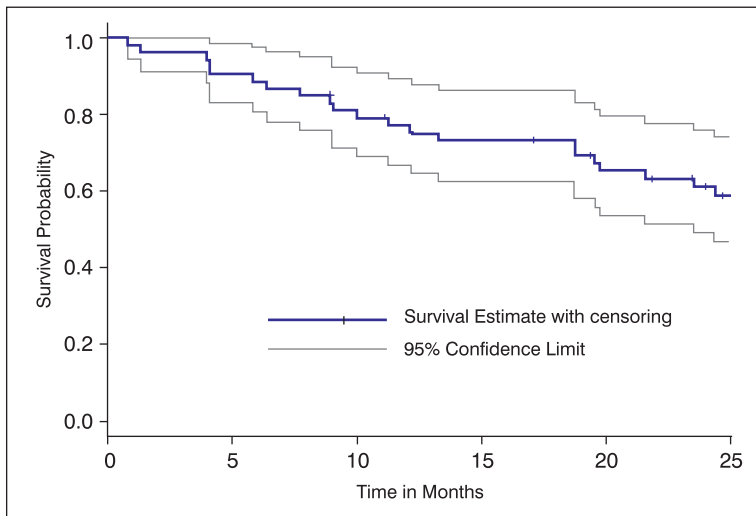
Over a period of 15 days, oral pirfenidone was slowly increased to 40 mg/kg/day up to a maximum of 3,600 mg/day in divided doses. Pirfenidone was continued as long as the patient was enrolled in the study (over 2 years for many patients). Adjunct immunosuppressive therapy was stopped on day 1 and prednisolone was tapered over 6–8 weeks. Patients were not allowed to take other concurrent medications that are currently used in IPF (including colchicine).

#### *Results*

Of the 54 patients enrolled, 42 had confirmed IPF based on SLB, and with typical features of IPF and 4 by typical features alone whose features included typical HRCT findings of UIP. Mean age was 62; mean duration of symptoms was 4.6 years.

Twenty-one patients died during 25 months of follow-up. The 1-yr survival was 78% (95% CI: 66%, 89%) and the 2-yr survival was 63% (95% CI: 50%, 76%).





**Fig. 4: Overall Kaplan-Meier Survival curve with 95% CI**

**Table 2: Change in Lung Function**

	6-mo Follow-up			1-yr Follow-up		
	FVC	TLC	DL <sub>co</sub>	FVC	TLC	DL <sub>co</sub>
Stable	19/41 (46%)	10/24 (42%)	18/31 (58%)	15/31 (48%)	10/23 (43%)	11/27 (41%)
Improved	10/41 (24%)	7/24 (29%)	7/31 (23%)	7/31 (23%)	5/23 (22%)	9/27 (33%)
Deteriorated	12/41 (29%)	7/24 (29%)	6/31 (19%)	9/31 (29%)	8/23 (35%)	7/27 (26%)
Total (with measures)	41/54 (75%)	24/54 (44%)	31/54 (57%)	31/54 (57%)	23/54 (43%)	27/54 (50%)
Died before follow-up	6/54 (11%)	6/54 (11%)	6/54 (11%)	12/54 (22%)	12/54 (22%)	12/54 (22%)
Transplant before follow-up	0	0	0	1/54 (2%)	1/54 (2%)	1/54 (2%)
Data not available*	7/54 (13%)	24/54 (44%)	17/54 (31%)	10/54 (19%)	18/54 (33%)	14/54 (26%)

\*Patient alive but unable to perform PFT or keep appointment.

Oxygen saturation during exertion as well as requirement for supplemental oxygen remained stable during the first 12 months of follow-up. A patient’s smoking history was also not found to be a significant predictor of survival. Adverse effects were relatively minor.

83% patients were able to discontinue prednisone within 2 months after study entry and the dose of pirfenidone could be tapered to 10-15 mg/day in 8 patients. All patients who were taking immunosuppressives tolerated discontinuation of the immunosuppressive therapy at study entry.

*Am J Respir Crit Care Med* 1999; 159: 1061-1069.

## 2. RESULTS OF A MULTICENTRE, PHASE II PLACEBO CONTROLLED TRIAL FROM JAPAN

### *Study Overview*

Azuma et al, from Japan conducted a randomized, placebo-controlled, prospective study assessing the safety and efficacy of pirfenidone in IPF patients. Previous studies have shown that decreased oxygen saturation by pulse oximetry (SpO<sub>2</sub>) during 6 minutes of walking predicted survival in IPF. Based on this the primary endpoint was represented by the changes (from baseline to 6–9 months) in the lowest value for arterial blood oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) during the 6-min exercise treadmill testing. The diagnosis of IPF was in accordance with the international consensus statement. Eligible patients were 20–75 years of age with adequate oxygenation at rest (PaO<sub>2</sub> ≥ 70 mmHg) and demonstrated SpO<sub>2</sub> of 90% or less during exertion while breathing air in 1 month before enrolment. Concomitant prednisolone of 10 mg/day or less was allowed while immunosuppressants or other anti-inflammatory/antifibrotic drugs were not allowed to be used concomitantly.

Secondary endpoints were changes in resting PFT, disease progression by HRCT patterns, episodes of acute exacerbation of IPF, change in serum markers of pneumocyte damage, & changes in quality of life measurements.

A dose–titration schedule was followed for all patients: patients received oral tablets (pirfenidone or placebo) at a dose of 200 mg three times a day for the first 2 days, 400 mg three times a day for the 2 following days, and 600 mg three times a day (maximum dose) for the last 3 days. The maximum dose was maintained in patients tolerating it throughout the study.

### *Results*

There were 107 patients enrolled (n = 72 in the pirfenidone and n = 35 in the placebo group). At 6 and 9 months from the lowest baseline, SpO<sub>2</sub> improved in the pirfenidone group but worsened in the placebo group; however, the between-group differences were not statistically significant. The same analysis performed in the ‘fit’ subgroup found similar trends and, moreover, the between-group differences at both 6 and 9 months were statistically significant. [ $\Delta$ SpO<sub>2</sub>, the difference area between the SpO<sub>2</sub> areas at baseline and 6 months was analysed in two subgroups: the ‘fit’ subgroup, which did not desaturate (maintained SpO<sub>2</sub> ≥ 80%) during exercise; and the ‘unfit’ subgroup, which desaturated during exercise].

Among the secondary end points, exacerbation number was significantly reduced and lung function (VC) was improved or stabilised. Episodes of acute exacerbation of IPF occurred exclusively in the placebo group during the 9 months (p < 0.0031). [The definition of acute exacerbation of IPF was prespecified as manifestation of all of the following: worsening, otherwise unexplained clinical features within 1 month: progression of dyspnea over a few days to less than 5 weeks, new radiographic/HRCT parenchymal abnormalities without pneumothorax or pleural effusion (e.g., new, superimposed ground-

glass opacities), a decrease in the PaO<sub>2</sub> by 10 mm Hg or more, and exclusion of apparent infection based on absence of *Aspergillus* and pneumococcus antibodies in blood, urine for *Legionella pneumophila*, and sputum culture].

The reduction of ground-glass and reticular opacities was recognized as improved patterns of the HRCT images. The proportion of patients who improved at 6 months was 15% (10/65) for the pirfenidone group and 7% (2/29) for the placebo group ( $p < 0.0921$ ). There were no differences observed in the extent or severity of the honeycomb pattern. No significant changes were found in the quality of life or serum markers of pneumocyte activity.

Based on the interim 6-month analysis of the secondary end points, the study's Data and Safety Monitoring Board recommended an early termination of study (planned initially to last 1 year) on ethical grounds and also advised the initiation of pirfenidone in the placebo group.

*Am J Respir Crit Care Med* 2005; 171: 1040–1047

## PHASE III TRIALS

### 1. THE CAPACITY TRIAL

#### Study Overview

The CAPACITY trial consisted of two multi-national, randomized, double-blind, placebo-controlled Phase III trials (CAPACITY 1 and CAPACITY 2) designed to evaluate the safety and efficacy of pirfenidone in IPF patients with mild to moderate impairment in lung function.

A total of 779 patients were enrolled in the CAPACITY trials at 110 sites in 11 countries. The mean age of participants was 66. To be eligible for the study, patients had to have a definitive diagnosis made by high-resolution CT scan or by biopsy, and a FVC  $\geq 50$  % of predicted values and a DL<sub>CO</sub>  $\geq 35$  % of predicted value.

CAPACITY 1 enrolled a total of 344 patients. Patients were randomized 1:1 to receive a total daily dose of 2403 mg pirfenidone, or placebo. CAPACITY 2 enrolled a total of 435 patients, and patients were randomized 2:2:1 to receive a total daily dose of 2403 mg pirfenidone, or placebo, or a total daily dose of 1197 mg pirfenidone, respectively, administered in three divided doses.

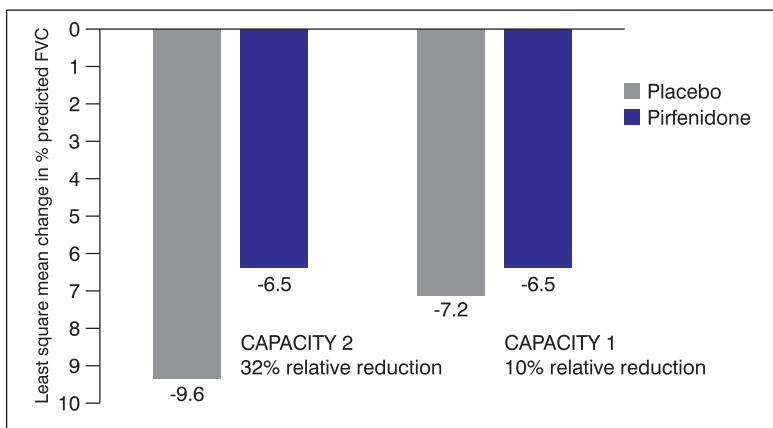
The primary endpoint of both CAPACITY studies was change in % predicted Forced Vital Capacity (FVC) after 72 weeks of treatment.

## Results

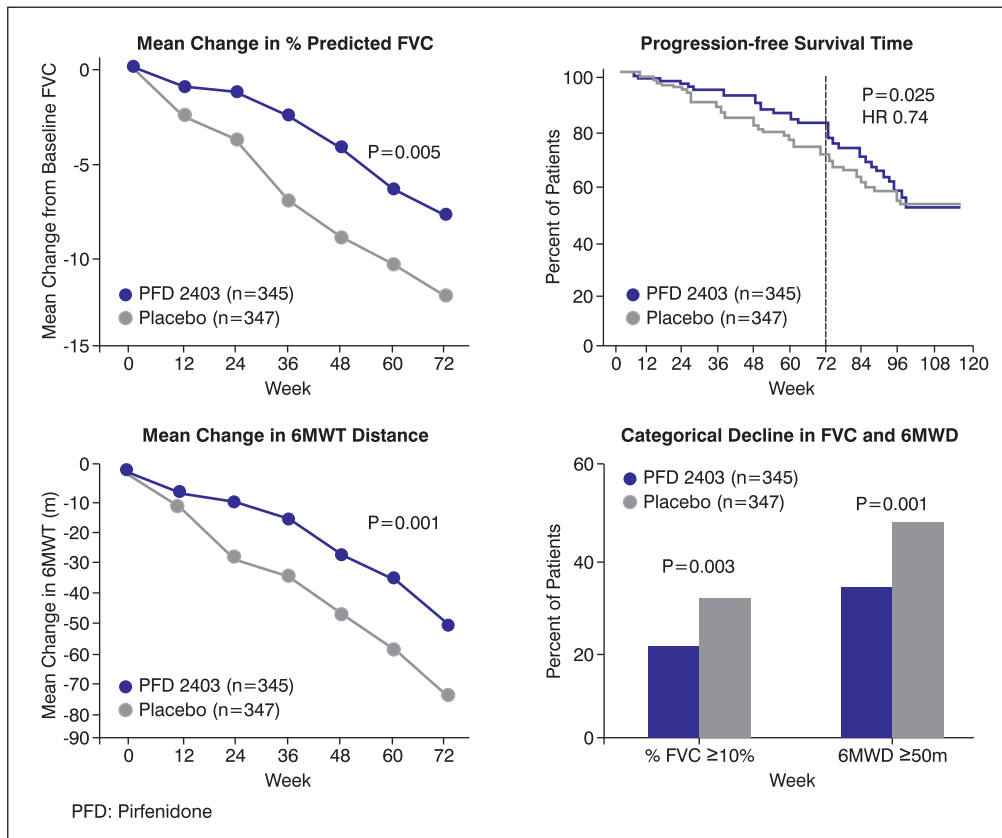
The primary endpoint of change in % predicted FVC at week 72 was met with statistical significance in CAPACITY 2 ( $p=0.001$ ), along with the secondary endpoints of categorical change in FVC and progression-free survival (PFS), defined as time to either death, a 10% decrease in FVC or a 15% decrease in  $DL_{CO}$  (diffusing capacity of the lung for carbon monoxide). The primary endpoint was not met in CAPACITY 1 ( $p=0.501$ ), but evidence of a pirfenidone treatment effect on the primary endpoint was observed at several periods in that trial. Importantly, greater than 80% of patients in the trials completed treatment and greater than 90 % completed the study.

An exploratory analysis of pooled data from both trials revealed that treatment with pirfenidone resulted in a 30% relative reduction in the percentage of patients who experienced an absolute decline in percent predicted FVC of at least 10%. This magnitude of decline is considered clinically meaningful, as a 10% decline in percent predicted FVC has been shown in multiple studies to be an independent predictor of mortality in patients with IPF.

Exploratory analyses of pooled data from the two CAPACITY studies also demonstrated a statistically significant treatment effect on the primary endpoint of change in percent predicted FVC at week 72, progression-free survival time and change in six-minute walk test distance.



**Fig. 5: Mean change in FVC over 72 weeks(L) from baseline**



**Fig. 6: CAPACITY: Pooled Efficacy Results**

The overall efficacy and safety of pirfenidone in the treatment of IPF has been provided by the two CAPACITY studies. In CAPACITY 2, pirfenidone demonstrated a robust treatment effect on the primary endpoint and key secondary endpoints.

Although the effect of pirfenidone did not achieve statistical significance on the primary endpoint in CAPACITY 1, the overall treatment effect of pirfenidone was in many respects similar in both studies. The totality of the data from these two studies suggests that pirfenidone has a positive treatment effect on patients with IPF.

*www.Medicalnewstoday.com accessed on 4<sup>th</sup> February 2009*

## 2. RESULTS OF A RANDOMISED, PHASE III CLINICAL TRIAL FROM JAPAN

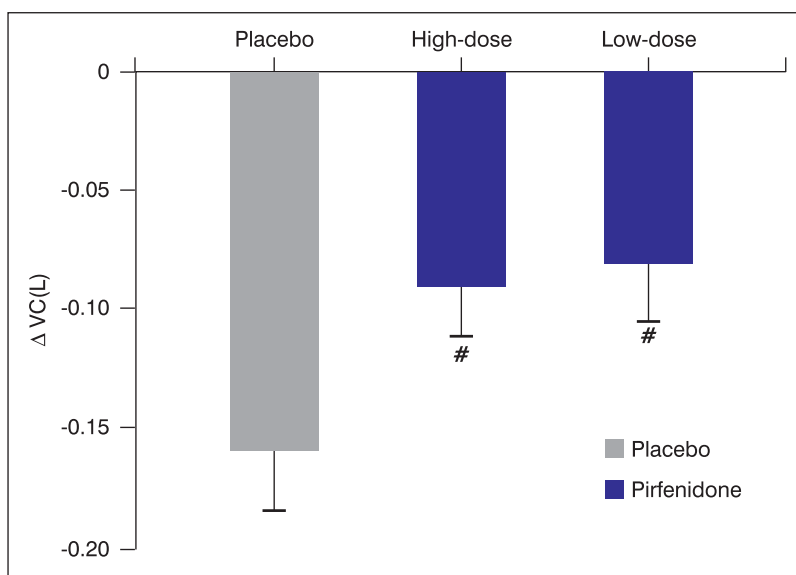
### Study Overview

A multicentre, double-blind, placebo-controlled, randomised phase III clinical trial was conducted in Japanese patients with well-defined IPF to determine the efficacy and safety of pirfenidone, over 52 weeks. Of 275 patients randomised (high-dose, 1,800 mg/day; low-dose, 1,200 mg/day; or placebo groups in the ratio 2:1:2), 267 patients were evaluated for the efficacy of pirfenidone. The primary end-point was the change in vital capacity (VC) assessed at week 52. Secondary end-points included the progression-free survival (PFS) time.

Although concomitant use of corticosteroid of 10 mg/day (as the prednisone equivalent) was permitted during the study period, concomitant use of immunosuppressants and other experimental agents under investigation for IPF was not allowed.

### Results

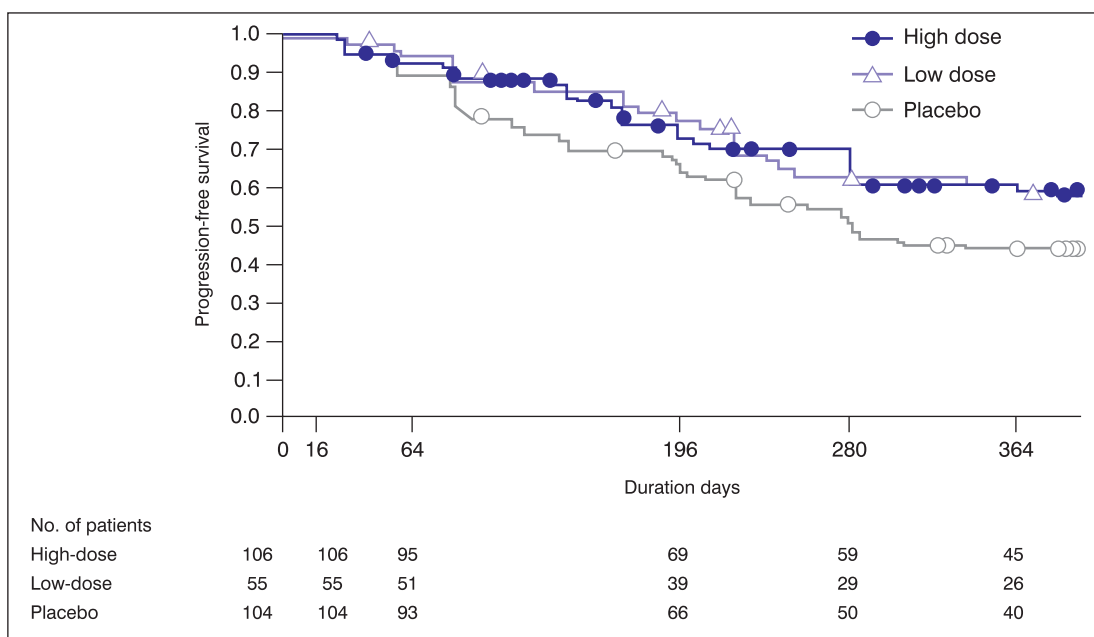
Significant differences were observed in VC decline (primary end-point) between the placebo group (-0.16 L) and the high-dose group (-0.09 L) ( $p < 0.0416$ ).



**Fig. 7:** Effects of pirfenidone on vital capacity (VC) at week 52. Data are presented as mean  $\pm$  SE. #:  $p < 0.1$ , comparison of adjusted means based on ANCOVA (negative and positive of the changes represent deterioration and improvement from baseline, respectively). The last observation carried forward method was used for drop-outs in each group. Placebo group. N=103; high-dose group: n=104; low-dose group: n=54.

The incidence of acute exacerbation during the study or within 28 days after the termination of the study was 5.6%, 5.5% and 4.8% in the high-dose, low-dose and placebo groups, respectively. No significant differences were seen among the three groups. Although between the low-dose and the placebo groups the differences of mean changes in TLC and changes in DL<sub>CO</sub> were statistically significant ( $p < 0.0408$  and  $p < 0.0768$ , respectively) at week 52, there were no significant differences in the changes of other PFTs or serum markers among the three groups.

The distribution of PFS time was compared between the high-dose and placebo groups with the log-rank test, and a significant difference was found ( $p < 0.0280$ ; fig). In addition, a marginally significant difference was found in the distribution between the low-dose and placebo groups ( $p < 0.0655$ ).



**Fig. 8:** Kaplan-Meier plot of progress-free survival time among idiopathic pulmonary fibrosis patient groups. Symbols on the curve represent the censored points where patients discontinued the study treatment due to causes other than progression of the disease. Kaplan-Meier curves were compared with the log-rank test:  $p = 0.0280$  between the high-dose group and placebo group;  $p = 0.0655$  between the low-dose group and placebo group;  $p = 0.9106$  between the high-dose group and low-dose group.

Further stratified sampling showed significant difference in improving PaO<sub>2</sub> in the high-dose group of patients, and decreasing biomarkers in the low-dose groups of patients, both of those groups with VC more than median VC (2400 mL) and/or median %VC (76.5%) treated with pirfenidone for 52 weeks.

Pirfenidone was relatively well tolerated in patients with IPF. In conclusion, the result of the phase III clinical trial demonstrate that pirfenidone, a novel antifibrotic agent, preserves VC and improves PFS better than placebo in Japanese patients with IPF with mild functional impairment without serious adverse events. Also

due to enhanced effects of pirfenidone in the early phase of IPF the authors recommended pirfenidone as an initial therapeutic agent against IPF.

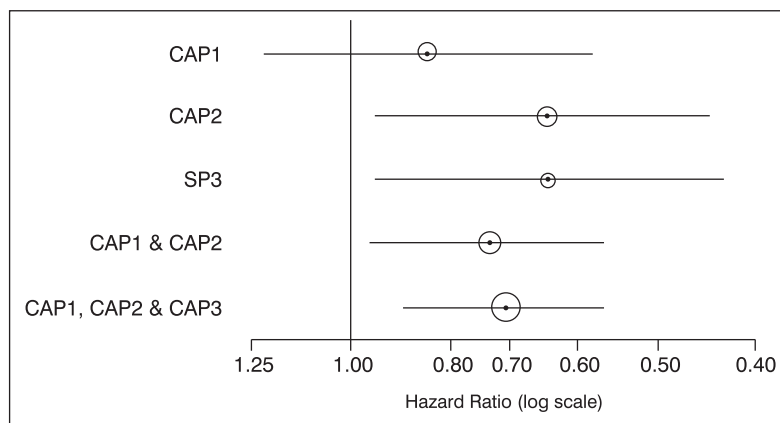
*Eur Respir J 2010; 35: 821–829  
Abst 666; ERS 2010*

## Effect Of Pirfenidone On Lung Function And Progression-Free Survival In Patients With IPF: A Meta-Analysis Of Three Phase 3 Studies

Noble et al reported standardized estimates of treatment effect with pirfenidone by comparing the results across studies (CAPACITY trials & the phase III trial from Japan) at the 2010 American Thoracic Society Annual Conference.

As per the results of this meta-analysis pirfenidone reduced the risk of death or disease progression by 29% (PFS-HR 0.71) which is highly relevant to patients suffering from IPF.

*Am J Respir Crit Care Med 2010; 181:A1257*



**Fig. 9: Meta analysis of Phase III studies on pirfenidone in IPF**

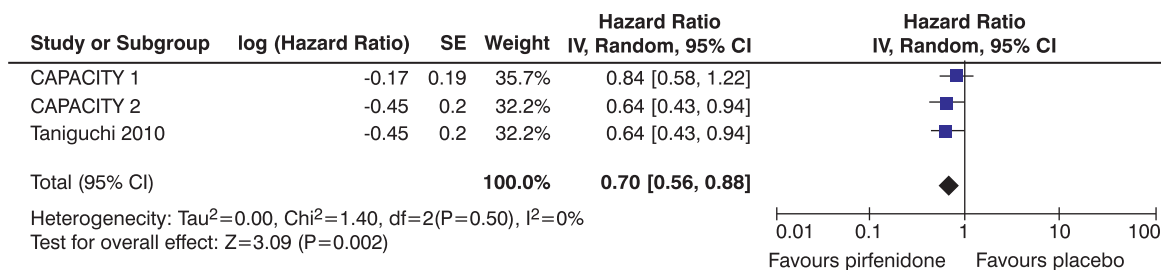
## COCHRANE REVIEW ON NON-STEROID AGENTS FOR IPF

A recently published Cochrane Review has assessed the efficacy of all non-steroid agents in adults with IPF. 15 randomised studies comparing 10 non-steroid drugs with placebo or steroids conducted on 3033 adults with IPF were included in the analysis. The primary outcome was overall survival (OS) and PFS and the secondary outcome was absolute or percent predicted change from baseline in lung function measured as VC or FVC.

The drugs included were interferon gamma-1beta, pirfenidone, cyclophosphamide, azathioprine, colchicine, N-acetylcysteine, anticoagulant therapy, etanercept, imatinib and bosentan.



Based on available data, pirfenidone appeared to improve progression-free survival by 30% and pulmonary function in patients with IPF. More data are needed on overall survival and quality of life on treatment. Amongst the others, interferon gamma-1beta did not affect survival. Other agents evaluated in single studies either failed to provide evidence for a benefit or need to be assessed in larger randomised controlled trials.



Forest plot of comparison: 2 Pirfenidone versus placebo, outcome: 2.1 Progression-free survival

**Fig. 10: Forest plot of comparison for pirfenidone trials in IPF**

## CHAPTER 4

# Safety & Tolerability of Pirfenidone

The safety of pirfenidone has been evaluated in all the studies which have been conducted on the molecule till date. The commonest adverse event noted is photosensitivity which is typically reversible and non-lethal. Similarly, the other adverse events like nausea and diarrhea were easily controlled. Overall very few patients dropped out of the studies because of the side-effects.

The safety and tolerability of pirfenidone from the CAPACITY and other two open-label (OLS) studies was presented at the Annual Conference of the European Respiratory Society, 2009 in Vienna. In the CAPACITY trials, 779 patients were randomized to pirfenidone or placebo for  $\geq 72$  wks. A total of 686 patients received pirfenidone in the OLS.

79% and 82 % of pirfenidone and placebo patients, respectively, completed therapy, and 13% and 8%, respectively, discontinued due to adverse events (AE). The incidence of serious AEs and Grade 3/4 laboratory abnormalities was similar across groups. AEs with an incidence  $\geq 10\%$  and  $2 \times$  higher in pirfenidone vs. placebo are listed in the table below.

**Table 3: Major AEs seen with Pirfenidone**

	Pirfenidone (n %)	Placebo (n %)
Nausea	36	17
Rash	32	12
Dyspepsia	19	8
Vomiting	14	4
Photosensitivity	12	2
Anorexia	11	4

Transaminase (liver enzyme) elevations were slightly more common in the pirfenidone group, generally low-grade and without clinical sequelae (or secondary effect). Fewer deaths were observed in the pirfenidone group relative to the placebo group and this difference was driven by a reduction in IPF-related deaths.

*Abst 2823, ERS 2010*

In the Phase III study from Japan, photosensitivity, anorexia, dizziness and elevated  $\gamma$ -glutamyl-transpeptidase ( $\gamma$ -GTP) were significantly more common in the high-dose group than in the placebo group, and photosensitivity, asteatotic eczema, abdominal discomfort and decrease in white blood cells were significantly more common in the low-dose group than in the placebo group. In contrast, respiratory tract infection, such as nasopharyngitis and upper respiratory tract inflammation, was significantly less common in the high-dose group than the placebo group.

Photosensitivity was the major adverse event observed in 51% of the patients in the high-dose group and 53% in low-dose group. Of the patients who developed photosensitivity, 70% and ~80% in the high-dose and the low-dose groups, respectively, were mild cases and the remainders were moderate cases. However, only three patients (~3%) discontinued the study due to photosensitivity.

This comprehensive safety review shows that pirfenidone is safe and generally well tolerated.

# Indications, Dosage & Administration

## INDICATIONS

Pirfenidone is indicated for the treatment of Idiopathic pulmonary fibrosis.

## DOSAGE & 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 (1800 mg/day) under observation (as per recommendations for dosage adjustment). 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 (1800 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 (1200 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 & precautions for recommendations of liver function monitoring)*

- **> 3 to 5× ULN aminotransferase elevation** – Confounding medications should be discontinued and patient monitored closely. Daily dose may be maintained at full dose if clinically appropriate, or reduced or interrupted (eg., until liver function tests are within normal limits) with subsequent re-escalation to full dose as tolerated
- **> 5× ULN aminotransferase elevation or ≤ 5× ULN aminotransferase elevation accompanied by symptoms or hyperbilirubinemia** – Treatment should be permanently discontinued.

## CHAPTER 6

# Important Warnings & Precautions for the Use of Pirfenidone

- The use of pirfenidone has 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 umbrella and apply effective sunscreens (SPF50+, PA+++ ) in order to avoid UV rays.
  - If rash or itching occurs the patient must be advised to contact the doctor immediately.
- Pirfenidone may cause liver dysfunction accompanied by rise in the aspartate transaminase (AST) and alanine transaminase (ALT) levels suggestive of jaundice. It is therefore recommended to periodically monitor the liver enzymes.

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

Liver enzymes should be measured prior to initiation of therapy in all patients, then monthly for first 6 months and every 3 months thereafter. Patients should be instructed to report symptoms of liver disease (eg., dark urine and/or jaundice) to their physician

- Drowsiness and dizziness may occur due to pirfenidone which may cause staggering in the patient. Patients on pirfenidone should therefore be advised not to engage in the operation of machinery and motor vehicles.

## CHAPTER 7

# Pirfenex: Place in Therapy

IPF is a fatal disease characterized by a progressive, debilitating, and inevitable loss of lung function. Patients with IPF have no therapeutic option, for which any benefit has been demonstrated, and yet frequently receive therapies with significant risks.

The benefit-risk profile of pirfenidone supports its use in the treatment of IPF, a devastating and inevitably fatal disease. Clinical studies provide evidence that pirfenidone provides a clinically relevant benefit to patients by reducing decline in lung function. While reversal of the disease may not be feasible due to the presence of fixed and irreversible fibrosis, the slowing of progression in loss of lung volume constitutes a clear benefit to patients. The collective data further support the benefit of pirfenidone in other domains of the disease, including exercise tolerance and progression-free survival.

The safety profile of pirfenidone indicates that adverse events are primarily related to tolerability rather than morbidity, are readily monitored, are typically reversible, and nonlethal.

The totality of the data from the studies of pirfenidone, in the setting of this irreversible fatal disease and urgent unmet medical need, establishes for the first time a therapeutic option with a favorable benefit-risk profile and supports the use of pirfenidone for the treatment of patients with IPF.

## CHAPTER 8

# Pirfenex: Prescribing Information

*For the Use of a Pulmonologist Only***Pirfenidone 200 mg tablets**

The use of pirfenidone has 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 IPF.

**COMPOSITION**

Pirfenidone 200 mg

**DOSAGE FORMS**

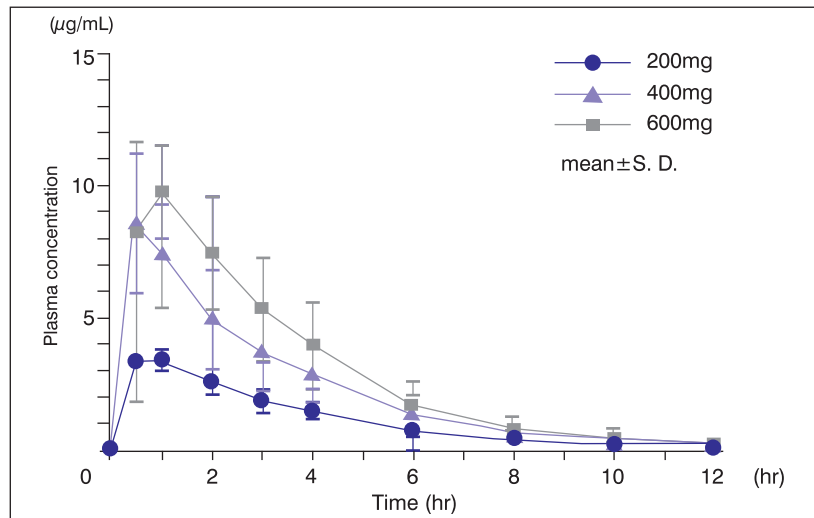
Oral Tablets

**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. Pirfenidone inhibited the production and activity of TGF- $\beta$ , a cytokine that stimulates 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 concentration***

Plasma concentration and pharmacokinetic parameters of pirfenidone in 6 healthy adult men given 200 mg, 400 mg and 600 mg as fasting single oral administration are shown in Figure 11 & Table 4.



**Fig. 11: Plasma concentration on fasting after a single dose**

**Table 4: 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 by gradual increase as three times a day at morning, afternoon and evening after every meal for six days (dose administration first day and the sixth day twice a day at morning and afternoon) (total 18 days) in 12 healthy adult males has been reported in table 5.

With regards to every dose on the first day and sixth day, the plasma concentration showed similar trend of change. After the administration on the first day both C<sub>max</sub>, AUC were increased in accordance with the proportional increase in the dosage quantity.

**Table 5: Pharmacokinetic parameters (n=12)**

1 time dose quantity (mg)	Days of dose administration (Total)	C <sub>max 0-4</sub> (µg/mL)	T <sub>max 0-4</sub> (hr)	C <sub>max 4-24</sub> (µg/mL)	T <sub>max 4-24</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 higher radioactive concentration in internal organs as compared to blood plasma.

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

## Metabolism

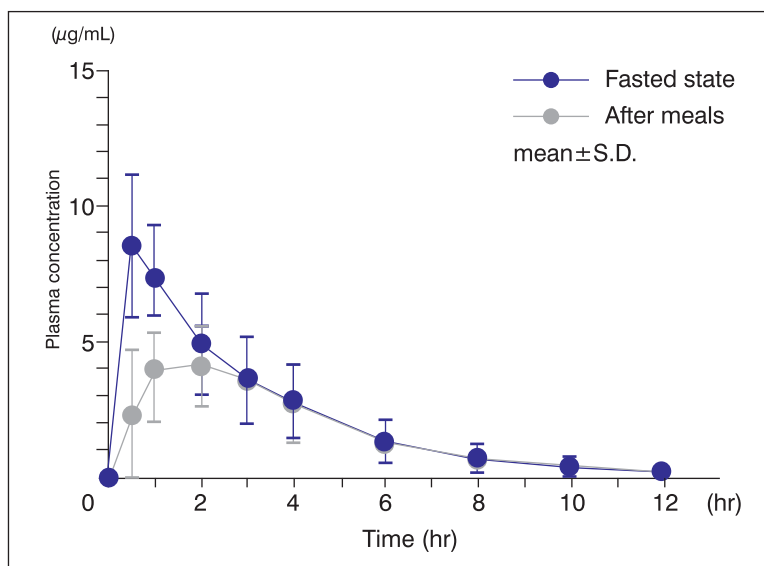
Pirfenidone is metabolized by a number of cytochrome (CYP) enzymes (CYP1A2, 2C9, 2C19, 2D6, 2E1) in human liver microsome. This suggests that it will not be affected by drugs which inhibits CYP 450 enzymes.

## Excretion

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

## Effect of Diet

The plasma concentration and pharmacokinetic parameters of 6 healthy adult males after single oral administration of 400 mg after meals and on fasting are shown in Figure 12 & Table 6.  $C_{max}$ , AUC were significantly decreased and  $T_{max}$  was significantly delayed.



**Fig. 12: Concentration in plasma after meals and fasting**

**Table 6: 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)
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±0.20	29.10±11.77	1.96±0.55

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

## INDICATIONS

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## DOSAGE & ADMINISTRATION

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### 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 (1800 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 (1200 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 & precautions for recommendations of liver function monitoring)

- **> 3 to 5× ULN aminotransferase elevation** – Confounding medications should be discontinued and patient monitored closely. Daily dose may be maintained at full dose if clinically appropriate, or reduced or interrupted (eg., until liver function tests are within normal limits) with subsequent re-escalation to full dose as tolerated
- **> 5× ULN aminotransferase elevation or ≤ 5× ULN aminotransferase elevation accompanied by symptoms or hyperbilirubinemia** – Treatment should be permanently discontinued.

## CONTRAINDICATION

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

## WARNING & PRECAUTIONS

- The use of pirfenidone has 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 umbrella and apply effective sunscreens (SPF50+, PA+++ ) in order to avoid UV rays.
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- Pirfenidone may cause liver dysfunction accompanied by rise in the aspartate transaminase (AST) and alanine transaminase (ALT) levels suggestive of jaundice. It is therefore recommended to periodically monitor the liver enzymes.

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

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

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

- Drowsiness and dizziness may occur due to pirfenidone which may cause staggering in the patient. Patients on pirfenidone should therefore be advised not to engage in the operation of machinery and motor vehicles.

## DRUG INTERACTIONS

- Pirfenidone clearance is reduced with 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 potential for reduced clearance.
- Pirfenidone clearance is significantly higher in cigarette smokers than non-smokers, presumably due to higher CYP1A2 enzyme activity in smokers.

## RENAL IMPAIRMENT

There is limited experience in patients with renal dysfunction.

## HEPATIC IMPAIRMENT

Pirfenidone may cause liver dysfunction accompanied by rise in the AST and ALT levels suggestive of jaundice. It is therefore recommended to periodically monitor the liver enzymes.

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 woman or to women who are likely to be pregnant.

## **LACTATION**

Women receiving treatment with pirfenidone should be advised to avoid breast-feeding.

## **PAEDIATRIC USE**

Safety 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, AST (SGOT) and ALT (SGPT) levels.

## **OVERDOSAGE**

Inadequate information.

## **STORAGE & HANDLING INSTRUCTIONS**

Store in a cool, dry place.

## **PACKAGING INFORMATION**

**Pirfenex** Blister pack of 10 tablets