PIRFENEX

21076161

210761

PIRFENEX

1. NAME OF THE MEDICINAL PRODUCT:

PIRFENEX

(Pirfenidone Tablets 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each film coated tablet contains:
Pirfenidone ……. 200 mg
Colour: Titanium Dioxide
Excipients with known effect: Lactose

3. PHARMACEUTICAL FORM:
Tablet

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:
Pirfenidone is indicated for the treatment of Idiopathic Pulmonary fibrosis (IPF).

4.2 Posology and method of 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 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, 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 (see section 4.4). 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 section 4.4).

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 (see section 4.4)

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.

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 section 4.4). 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 section 4.4). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see section 4.4) 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.

Method of administration

Pirfenidone tablets are for oral use. The tablets are to be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness (see sections 4.8 and 5.2).

4.3 Contraindications:
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,

- history of angioedema with pirfenidone (see section 4.4),
- concomitant use of fluvoxamine (see section 4.5),
- severe hepatic impairment or end stage liver disease (see sections 4.2 and 4.4),
- severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use:

Hepatic function

Elevations in ALT and AST >3 × upper limit of normal (ULN) have been reported in patients receiving therapy with pirfenidone. Rarely these have been associated with concomitant elevations in total serum bilirubin. 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 section 4.8). 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.

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 (see sections 4.5 and 5.2). Pirfenidone has not been studied in individuals with severe hepatic impairment and pirfenidone should not be used in patients with severe hepatic impairment.

Photosensitivity reaction and rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with pirfenidone. Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, 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 section 4.2).

Angioedema

Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of pirfenidone in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of pirfenidone should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. Pirfenidone should not be used in patients with a history of angioedema due to pirfenidone (see section 4.3).

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 (see section 4.7). 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 (see section 4.7).

Weight loss

Weight loss has been reported in patients treated with pirfenidone (see section 4.8). Physicians should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Approximately 70–80% of pirfenidone is Metabolized via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.

Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with pirfenidone.

Fluvoxamine and inhibitors of CYP1A2

In a Phase 1 study, the co-administration of pirfenidone and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes [CYP2C9, 2C19, and 2D6]) resulted in a 4-fold increase in exposure to pirfenidone in non-smokers.

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.

In vitro and *in vivo* extrapolations indicate that strong and selective inhibitors of CYP1A2 (e.g. enoxacin) have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold. If concomitant use of pirfenidone with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of pirfenidone should be reduced to 801 mg daily (one tablet, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with pirfenidone therapy. Discontinue pirfenidone if necessary (see sections 4.2 and 4.4).

Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily cannot be avoided, the dose of pirfenidone should be reduced to 1602 mg daily (two tablets, three times a day). Pirfenidone should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily.

Pirfenidone should be used with caution in patients treated with other moderate inhibitors of CYP1A2 (e.g. amiodarone, propafenone).

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).

Cigarette smoking and inducers of CYP1A2

A Phase 1 interaction study evaluated the effect of cigarette smoking (CYP1A2 inducer) on the pharmacokinetics of pirfenidone. The exposure to pirfenidone in smokers was 50% of that observed in non-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.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no data from the use of pirfenidone in pregnant women.

In animals placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid.

At high doses (≥1000 mg/kg/day) rats exhibited prolongation of gestation and reduction in foetal viability.

As a precautionary measure, it is preferable to avoid the use of pirfenidone during pregnancy.

Lactation

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (see section 5.3). A risk to the suckling child cannot be excluded.

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.

Fertility

No adverse effects on fertility were observed in preclinical studies (see section 5.3)

4.7 Effects on ability to drive and use machines
Pirfenidone may cause dizziness and fatigue, which could influence the ability to drive or use machines.

4.8 Undesirable effects:
The safety of pirfenidone has been evaluated in clinical studies including 1650 volunteers and patients. More than 170 patients have been investigated in open studies for more than five years and some for up to 10 years.

The most commonly reported adverse reactions during clinical study experience with pirfenidone at a dose of 2403 mg/day compared to placebo, respectively, were nausea (32.4% versus 12.2%), rash (26.2% versus 7.7%), diarrhoea (18.8% versus 14.4%), fatigue (18.5% versus 10.4%), dyspepsia (16.1% versus 5.0%), anorexia (11.4% versus 3.5%), headache (10.1% versus 7.7%), and photosensitivity reaction (9.3% versus 1.1%). Serious adverse reactions were recorded at similar frequencies among patients treated with 2403 mg/day of pirfenidone and placebo in clinical studies.

Table 1 shows the adverse reactions reported at a frequency of ≥2% in 623 patients receiving pirfenidone at the recommended dose of 2403 mg/day in three pivotal Phase 3 studies. Adverse reactions from post-marketing experience are also listed in Table 1. Adverse reactions are listed by System Organ Class (SOC) and within each frequency grouping [Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000)] the adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions by SOC and MedDRA frequency

Infections and infestations	
Common:	Upper respiratory tract infection; urinary tract infection
Blood and lymphatic system disorders	
Rare:	Agranulocytosis[1]
Immune system disorders	
Uncommon:	Angioedema[1]
Metabolism and nutrition disorders	
Very Common:	Anorexia
Common:	Weight decreased; decreased appetite
Psychiatric disorders	
Common:	Insomnia
Nervous system disorders	
Very Common:	Headache
Common:	Dizziness; somnolence; dysgeusia; lethargy
Vascular disorders	
Common:	Hot flush
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea; cough; productive cough
Gastrointestinal disorders	
Very Common:	Dyspepsia; nausea; diarrhoea
Common:	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
Rare:	Total serum bilirubin increased in combination with increases of ALT and AST[1]
Skin and subcutaneous tissue disorders	
Very Common:	Photosensitivity reaction; rash
Common:	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:	Fatigue
Common:	Asthenia; non-cardiac chest pain
Injury poisoning and procedural complications	
Common:	Sunburn

[1]Identified through post-marketing surveillance

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose:
There is limited clinical experience with overdose. Multiple doses of pirfenidone up to a dose of 4806 mg/day were administered as six 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation period. Adverse reactions were mild, transient, and consistent with the most frequently reported adverse reactions for pirfenidone.
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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:
Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants, ATC code: L04AX05
The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of *in*

Package leaflet: Information for the user

PIRFENEX

(Pirfenidone Tablets 200 mg)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Pirfenex is and what it is used for
Pirfenex contains the active substance pirfenidone and it is used for the treatment of Idiopathic Pulmonary fibrosis (IPF).

IPF is a condition in which the tissues in your lungs become swollen and scarred over time, and as a result makes it difficult to breathe deeply. This makes it hard for your lungs to work properly. Pirfenex helps to reduce scarring and swelling in the lungs, and helps you breathe better.

2. What you need to know before you take Pirfenex

Do not take Pirfenex

- if you are allergic to pirfenidone or any of the other ingredients of this medicine
- if you have previously experienced angioedema with pirfenidone, including symptoms such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing
- if you are taking a medicine called fluvoxamine (used to treat depression and obsessive compulsive disorder [OCD])
- if you have severe or end stage liver disease
- if you have severe or end stage kidney disease requiring dialysis.

If any of the above affects you, do not take Pirfenex. If you are unsure ask your doctor or pharmacist.

Warnings and precautions
Talk to your doctor or pharmacist before taking Pirfenex

- You may become more sensitive to sunlight (photosensitivity reaction) when taking Pirfenex. Avoid the sun (including sunlamps) whilst taking Pirfenex. Wear sunblock daily and cover your arms, legs and head to reduce exposure to sunlight (see section 7: Adverse effects).
- You should not take other medicines, such as tetracycline antibiotics (such as doxycycline), which may make you more sensitive to sunlight.
- You should tell your doctor if you suffer from kidney problems
- You should tell your doctor if you suffer from mild to moderate liver problems.
- You should stop smoking before and during treatment with Pirfenex. Cigarette smoking can reduce the effect of Pirfenex.
- Pirfenex may cause dizziness and tiredness. Be careful if you have to take part in activities where you have to be alert and co-ordinated.
- Pirfenex can cause weight loss. Your doctor will monitor your weight whilst you are taking this medicine.

You will need a blood test before you start taking Pirfenex and at monthly intervals for the first 6 months and then every 3 months thereafter whilst you are taking this medicine to check whether your liver is working properly. It is important that you have these regular blood tests for as long as you are taking Pirfenex.

Excipient
Pirfenex tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Children and adolescents
Do not give Pirfenex to children and adolescents under the age of 18.

Other medicines and Pirfenex
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.
This is especially important if you are taking the following medicines, as they may change the effect of Pirfenex.

Medicines that may increase side effects of Pirfenex:

- enoxacin (a type of antibiotic)
- ciprofloxacin (a type of antibiotic)
- amiodarone (used to treat some types of heart disease)
- propafenone (used to treat some types of heart disease)
- fluvoxamine (used to treat depression and obsessive compulsive disorder (OCD)).

Medicines that may reduce how well Pirfenex works:

- omeprazole (used in the treatment of conditions such as indigestion, gastroesophageal reflux disease)
- rifampicin (a type of antibiotic).

Pirfenex with food and drink
Do not drink grapefruit juice whilst taking this medicine. Grapefruit may prevent Pirfenex from working properly.

Pregnancy, breast-feeding and fertility
As a precautionary measure, it is preferable to avoid the use of Pirfenex if you are pregnant, planning to become pregnant, or think you might be pregnant as the potential risks to the unborn child are unknown.

If you are breast-feeding or plan to breast-feed speak to your doctor or pharmacist before taking Pirfenex. As it is unknown whether Pirfenex passes into breast milk, your doctor will discuss the risks and benefits of taking this medicine while breast-feeding if you decide to do so.

Driving and using machines
Do not drive or use machines if you feel dizzy or tired after taking Pirfenex.

3. How to take Pirfenex
Treatment with Pirfenex should be started and overseen by a specialist doctor experienced in the diagnosis and treatment of IPF.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your medicine will usually be given to you in increasing doses as follows:

- Start with 200 mg dose 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 800 mg at a time (2400 mg/day).

21076161

PACKAGING DEVELOPMENT

Product Name: Pirfenidone Tablets 200 mg	**Material No. 21076161**	**Version:** 01	**Item :** Leaflet	**Co-ordinator:** Shilpa	**Artist:** Shashikant	**Date:** 01-02-2019
Colours : **BLUE WOOL TEST VALUE 5-6 (LIGHT FASTENING DATA)** ■ Black				**INK:** Oil based Ink from DIC OR MICRO	
Design : Booklet	**Reference:** New			**Software :** Indesign CC	
Fonts : --------			**Links:-**		
Actual Size: 450 x 270 mm	**Size after Folding:** 50 x 34 mm	**2D Code: 21076161**		**Grain Direction :** Parallel to length	**Screen : #** __
Material: 40 GSM ITC Paper with perforated tape printed with "↑Tear Here↑"				**Varnish:** -	**Artwork Print Size:** ☐ **actual** ☐ **scaled**
Path: F:\Jobs\OTC\Shilpa\Iran\Pirfenex \ 21076161 Pirfenidone Tablets 200 mg Leaflet Iran.indd					

• **Instructions / Remark :** - • Any deviation must be brought to the notice of packaging development co-ordinator immediately. • For any clarification, please contact packaging development co-ordinator immediately. NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER • The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .	**Checked by**	**Artist**	**Cordinator**	**file loaded in Server**	**Section Head**
	Pharma Code ☐				
	2D Code ☐				
	QR Code ☐				
	Bar Code ☐				
	Artwork ☐				
	Spell check ☐				

- 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 previous recommended daily dose without titration.

The recommended maintenance daily dose of Pirfenex is 800 mg three times a day with food, i.e. total of 2400 mg/day.

Swallow the tablets whole with a drink of water, during or after a meal to reduce the risk of side effects such as nausea (feeling sick) and dizziness. If symptoms continue, see your doctor.

Dose reduction due to side effects
Your doctor may reduce your dose if you suffer from side effects such as, stomach problems, any skin reactions to sunlight or sun lamps, or significant changes to your liver enzymes.

If you take more Pirfenex than you should
If you take more Pirfenex than you should, contact your doctor, pharmacist or nearest hospital casualty department immediately if you have taken more tablets than you should, and take your medicine with you.

If you forget to take Pirfenex
If you forget a dose, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose. Each dose should be separated by at least 3 hours. Do not take more tablets each day than your prescribed daily dose.

If you stop taking Pirfenex
In some situations, your doctor may advise you to stop taking Pirfenex. If for any reason you have to stop taking Pirfenex for more than 14 consecutive days, your doctor will restart your treatment with a dose of 200 mg 3 times a day, gradually increasing this to a dose of 800 mg 3 times a day.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Pirfenex and tell your doctor immediately
- If you experience swelling of the face, lips and/or tongue, difficulty breathing or wheezing, which are signs of angioedema, a serious allergic reaction. This is an uncommon side effect.
- If you experience yellowing of the eyes or skin, or dark urine, potentially accompanied by itching of the skin, which are signs of abnormal liver function tests. These are rare side effects.

Other side effects may include
Talk to your doctor if you get any side effects.

Very common side effects (may affect more than 1 in 10 people):
- skin reactions after going out in the sun or using sunlamps
- feeling sick (nausea)
- tiredness
- diarrhoea
- indigestion or stomach upset
- loss of appetite
- headache.

Common side effects (may affect up to 1 in 10 people):
- infections of the throat or the airways going into the lungs and/or sinusitis
- bladder infections
- weight loss
- difficulty sleeping
- dizziness
- feeling sleepy
- changes in taste
- hot flushes
- shortness of breath
- cough
- stomach problems such as acid reflux, vomiting, feeling bloated, abdominal pain and discomfort, heart burn, feeling constipated and passing wind
- blood tests may show increased levels of liver enzymes
- skin problems such as itchy skin, skin redness or red skin, dry skin, skin rash
- muscle pain, aching joints/joint pains
- feeling weak or feeling low in energy
- chest pain
- sunburn.

Rare side effects (may affect up to 1 in 1,000 people):
- blood tests may show decrease in white blood cells.

Reporting of suspected adverse reactions
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the local reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pirfenex
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label, blister and carton after EXP. The expiry date refers to the last day of that month.

Store below 25°C.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Pirfenex contain
Active ingredient: Pirfenidone
Inactive ingredient: lactose (lactose monohydrate), croscarmellose sodium, hydroxy propyl cellulose, magnesium stearate and opadry white 04F58804.

What Pirfenex look like and contents of the pack
Carton containing 3 Blister strips of 10 tablets each

Marketing Authorisation Holder
Cipla Ltd. India

Leaflet Revised: January 2019

Cipla

vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis). 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).

Clinical efficacy
The clinical efficacy of pirfenidone has been studied in four Phase 3, multicentre, randomised, double-blind, placebo-controlled studies in patients with IPF. Three of the Phase 3 studies (PIPF-004, PIPF-006, and PIPF-016) were multinational, and one (SP3) was conducted in Japan.
PIPF-004 and PIPF-006 compared treatment with pirfenidone 2403 mg/day to placebo. The studies were nearly identical in design, with few exceptions including an intermediate dose group (1197 mg/day) in PIPF-004. In both studies, treatment was administered three times daily for a minimum of 72 weeks. The primary endpoint in both studies was the change from Baseline to Week 72 in percent predicted Forced Vital Capacity (FVC).
In study PIPF-004, the decline of percent predicted FVC from Baseline at Week 72 of treatment was significantly reduced in patients receiving pirfenidone (N=174) compared with patients receiving placebo (N=174; p=0.001, rank ANCOVA). Treatment with pirfenidone also significantly reduced the decline of percent predicted FVC from Baseline at Weeks 24 (p=0.014), 36 (p<0.001), 48 (p<0.001), and 60 (p<0.001). At Week 72, a decline from baseline in percent predicted FVC of ≥10% (a threshold indicative of the risk of mortality in IPF) was seen in 20% of patients receiving pirfenidone compared to 35% receiving placebo (Table 2).

Table 2 Categorical assessment of change from Baseline to Week 72 in percent predicted FVC in study PIPF-004

	Pirfenidone 2403 mg/day (N = 174)	Placebo (N = 174)
Decline of ≥10% or death or lung transplant	35 (20%)	60 (35%)
Decline of less than 10%	97 (56%)	90 (52%)
No decline (FVC change >0%)	42 (24%)	24 (14%)

Although there was no difference between patients receiving pirfenidone compared to placebo in change from Baseline to Week 72 of distance walked during a six minute walk test (6MWT) by the prespecified rank ANCOVA, in an *ad hoc* analysis, 37% of patients receiving pirfenidone showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo in PIPF-004.
In study PIPF-006, treatment with pirfenidone (N=171) did not reduce the decline of percent predicted FVC from Baseline at Week 72 compared with placebo (N=173; p=0.501). However, treatment with pirfenidone reduced the decline of percent predicted FVC from Baseline at Weeks 24 (p<0.001), 36 (p=0.011), and 48 (p=0.005). At Week 72, a decline in FVC of ≥10% was seen in 23% of patients receiving pirfenidone and 27% receiving placebo (Table 3).

Table 3 Categorical assessment of change from Baseline to Week 72 in percent predicted FVC in study PIPF-006

	Pirfenidone 2403 mg/day (N = 171)	Placebo (N = 173)
Decline of ≥10% or death or lung transplant	39 (23%)	46 (27%)
Decline of less than 10%	88 (52%)	89 (51%)
No decline (FVC change >0%)	44 (26%)	38 (22%)

The decline in 6MWT distance from Baseline to Week 72 was significantly reduced compared with placebo in study PIPF-006 (p<0.001, rank ANCOVA). Additionally, in an *ad hoc* analysis, 33% of patients receiving pirfenidone showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo in PIPF-006.

In a pooled analysis of survival in PIPF-004 and PIPF-006 the mortality rate with pirfenidone 2403 mg/day group was 7.8% compared with 9.8% with placebo (HR 0.77 [95% CI, 0.47–1.28]).

PIPF-016 compared treatment with pirfenidone 2403 mg/day to placebo. Treatment was administered three times daily for 52 weeks. The primary endpoint was the change from Baseline to Week 52 in percent predicted FVC. In a total of 555 patients, the median baseline percent predicted FVC and $\%DL_{CO}$ were 68% (range: 48–91%) and 42% (range: 27–170%), respectively. Two percent of patients had percent predicted FVC below 50% and 21% of patients had a percent predicted DL_{CO} below 35% at Baseline.

In study PIPF-016, the decline of percent predicted FVC from Baseline at Week 52 of treatment was significantly reduced in patients receiving pirfenidone (N=278) compared with patients receiving placebo (N=277; p<0.000001, rank ANCOVA). Treatment with pirfenidone also significantly reduced the decline of percent predicted FVC from Baseline at Weeks 13 (p<0.000001), 26 (p<0.000001), and 39 (p=0.000002). At Week 52, a decline from Baseline in percent predicted FVC of ≥10% or death was seen in 17% of patients receiving pirfenidone compared to 32% receiving placebo (Table 4).

Table 4 Categorical assessment of change from Baseline to Week 52 in percent predicted FVC in study PIPF-016

	Pirfenidone 2403 mg/day (N = 278)	Placebo (N = 277)
Decline of ≥10% or death	46 (17%)	88 (32%)
Decline of less than 10%	169 (61%)	162 (58%)
No decline (FVC change >0%)	63 (23%)	27 (10%)

The decline in distance walked during a 6MWT from Baseline to Week 52 was significantly reduced in patients receiving pirfenidone compared with patients receiving placebo in PIPF-016 (p=0.036, rank ANCOVA); 26% of patients receiving pirfenidone showed a decline of ≥50 m in 6MWT distance compared to 36% of patients receiving placebo.

In a pre-specified pooled analysis of studies PIPF-016, PIPF-004, and PIPF-006 at Month 12, all-cause mortality was significantly lower in pirfenidone 2403 mg/day group (3.5%, 22 of 623 patients) compared with placebo (6.7%, 42 of 624 patients), resulting in a 48% reduction in the risk of all-cause mortality within the first 12 months (HR 0.52 [95% CI, 0.31–0.87], p=0.0107, log-rank test).

The study (SP3) in Japanese patients compared pirfenidone 1800 mg/day (comparable to 2403 mg/day in the US and European populations of PIPF-004/006 on a weight-normalised basis) with placebo (N=110, N=109, respectively). Treatment with pirfenidone significantly reduced mean decline in vital capacity (VC) at Week 52 (the primary endpoint) compared with placebo (-0.09±0.02 l versus -0.16±0.02 l respectively, p=0.042).

5.2 Pharmacokinetic properties:
Absorption
Administration of pirfenidone with food results in a large reduction in C_{max} (by 50%) and a smaller effect on AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50-66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80-85% of the AUC observed in the fasted state. 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.

The bioavailability of pirfenidone has not been determined in humans.

Distribution
Pirfenidone binds to human plasma proteins, primarily to serum albumin. The overall mean binding ranged from 50% to 58% at concentrations observed in clinical studies (1 to 100 µg/ml). Mean apparent oral steady-state volume of distribution is approximately 70 l, indicating that pirfenidone distribution to tissues is modest.

Biotransformation
Approximately 70–80% of pirfenidone is metabolized via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1. *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.

Elimination
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.

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 (3 x 267 mg capsule) 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 sections 4.2 and 4.4). Pirfenidone is contraindicated in severe hepatic impairment and end stage liver disease (see sections 4.2 and 4.3).

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 substance is predominantly metabolized 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 sections 4.2 and 4.3).

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.

5.3 Preclinical safety data:
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In repeated dose toxicity studies increases in liver weight were observed in mice, rats and dogs; this was often accompanied by hepatic centrilobular hypertrophy. Reversibility was observed after cessation of treatment. An increased incidence of liver tumours was observed in carcinogenicity studies conducted in rats and mice. These hepatic findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving pirfenidone. These findings are not considered relevant to humans.

A statistically significant increase in uterine tumours was observed in female rats administered 1500 mg/kg/day, 37 times the human dose of 2403 mg/day. The results of mechanistic studies indicate that the occurrence of uterine tumours is probably related to a chronic dopamine-mediated sex hormone imbalance involving a species specific endocrine mechanism in the rat which is not present in humans.

Reproductive toxicology studies demonstrated no adverse effects on male and female fertility or postnatal development of offspring in rats and there was no evidence of teratogenicity in rats (1000 mg/kg/day) or rabbits (300 mg/kg/day). In animals placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid. At high doses (≥450 mg/kg/day) rats exhibited a prolongation of oestrous cycle and a high incidence of irregular cycles. At high doses (≥1000 mg/kg/day) rats exhibited a prolongation of gestation and reduction in fetal viability. Studies in lactating rats indicate that pirfenidone and/or its metabolites are excreted in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk.

Pirfenidone showed no indication of mutagenic or genotoxic activity in a standard battery of tests and when tested under UV exposure was not mutagenic. When tested under UV exposure pirfenidone was positive in a photoclastogenic assay in Chinese hamster lung cells.

Phototoxicity and irritation were noted in guinea pigs after oral administration of pirfenidone and with exposure to UVA/UVB light. The severity of phototoxic lesions was minimised by application of sunscreen.

Environmental Risk Assessment (ERA)
Pirfenidone is not considered to present a potential risk to surface water, microorganisms and ground water or to sediment-dwelling invertebrates.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients
Lactose (Lactose monohydrate) 200 mesh
Croscarmellose sodium
Hydroxy propyl cellulose
Magnesium stearate
Opadry white 04F58804

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
Carton containing 3 Blister strips of 10 tablets each

6.6 Instructions for use, handling and disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Cipla Ltd. India

8. MARKETING AUTHORISATION NUMBER (S)
9075513720298676

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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