AUSTRALIAN PRODUCT INFORMATION
PIRFENIDET (pirfenidone) Film coated tablets

1. NAME OF THE MEDICINE

Pirfenidone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PIRFENIDET 267 mg film coated tablets contain 267 mg pirfenidone.
PIRFENIDET 801 mg film coated tablets contain 801 mg pirfenidone.

List of excipients with known effect: Lactose monohydrate

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

PIRFENIDET 267 mg tablets are yellow, oval, biconvex, bevel-edged film coated tablets debossed with “D1” on one side and plain on other side.

PIRFENIDET 801 mg tablets are brown, oval, biconvex, bevel-edged film coated tablets debossed with “D2” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PIRFENIDET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF)

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Treatment with PIRFENIDET should be initiated by physicians experienced in the diagnosis and treatment of IPF.

Adults

The recommended daily dose of PIRFENIDET for patients with IPF is 801 mg three times a day with food, for a total of 2403 mg/day. It is recommended that dose titration occur with the 267 mg capsule or tablets.

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14 day period as follows:

- Days 1 to 7: a dose of 267 mg administered three times a day (801 mg/day)
- Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg/day)
- Day 15 onward: a dose of 801 mg administered three times a day (2403 mg/day)

Doses above 2403 mg/day are not recommended for any patient (see section 4.9 Overdose).

Missed doses

Patients who miss 14 consecutive days or more of PIRFENIDET treatment should re-initiate therapy by undergoing the initial 2 week titration regimen up to the recommended daily dose.

For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Dose Adjustments and Other Considerations

Gastrointestinal events

In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist the dose of PIRFENIDET may be reduced to 267 mg – 534 mg taken two to three times a day with food with re- escalation to the recommended daily dose as tolerated. Consider changing from the 801 mg dose form to a 267 mg dose form. If symptoms continue, patients may be instructed to interrupt treatment for one to two 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 exposure to the sun (see section 4.4 Special warnings and precautions for use). The dose of PIRFENIDET may be reduced to 801 mg each day (267 mg three times daily). If the rash persists after 7 days, PIRFENIDET 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 (see section 4.4 Special warnings and precautions for use). Once the rash has resolved, PIRFENIDET may be reintroduced and re- escalated up to the recommended daily dose at the discretion of the physician.

Hepatic function

If a patient exhibits an aminotransferase elevation >3 to ≤5 × ULN without bilirubin elevation after starting PIRFENIDET therapy, other causes should be excluded and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of PIRFENIDET should be reduced or interrupted. Once liver function tests are within normal limits, PIRFENIDET may be re-escalated to the recommended daily dose if tolerated.

If a patient exhibits an aminotransferase elevation >3 to ≤5 × ULN accompanied by hyperbilirubinemia or clinical signs or symptoms indicative of liver injury, PIRFENIDET should be discontinued and the patient should not be rechallenged.

If a patient exhibits an aminotransferase elevation to ≥5 × ULN, PIRFENIDET should be discontinued and the patient should not be rechallenged.

Special Populations

Elderly

No dose adjustment is necessary in patients 65 years and older (see section 4.4 Special Warnings and precautions for use).

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 PIRFENIDET treatment in this population. Patients should be monitored closely for signs of toxicity especially if concomitantly taking a known CYP1A2 inhibitor (see sections 4.4 Special warnings and precautions for use and 4.5 Interaction with medicines and other forms of interaction). PIRFENIDET has not been studied and is not recommended 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 Special warnings and precautions for use). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment. PIRFENIDET should be used with caution in patients with moderate (CrCl 30-50mL/min) due to lack of information relating to the metabolite (see section 5.2 Pharmacokinetic properties). PIRFENIDET has not been studied and is contraindicated in patients with severe renal impairment (CrCl <30mL/min) or end-stage renal disease requiring dialysis (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Concomitant use of fluvoxamine (see section 4.5 Interaction with medicines and other forms of interaction)
- History of angioedema with pirfenidone (see section 4.4 Special warnings and precautions for use).
- Severe hepatic impairment or end stage liver disease (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).
- Severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatic Function

Drug-Induced Liver Injury (DILI) in the form of transient and clinically silent elevations in transaminases, has been commonly reported in patients treated with PIRFENIDE. Uncommonly, these elevations were associated with concomitant bilirubin increases, and serious clinical consequences including isolated cases with fatal outcome have been reported post-marketing.

Patients treated with PIRFENIDET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the PIRFENIDET 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to PIRFENIDET have been reported in phase 3 trials.

The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Perform liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with PIRFENIDET in all patients, then monthly for the first 6 months and every 3 months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of liver injury, the dose of PIRFENIDET should be adjusted or treatment discontinued (see Section 4.2 Dosage and method of administration). For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments may be necessary (see Section 4.2 Dosage and method of administration).

Photosensitivity Reaction and Rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with PIRFENIDET. Patients should be instructed to use an effective 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. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash (see section 4.2 Dose and method of administration).

Cigarette Smoking and Inducers of CYP1A2

A Phase 1 interaction study evaluated the effect of cigarette smoking (CYP1A2 inducer) on the pharmacokinetics of PIRFENIDET. 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 clearance and decrease exposure to PIRFENIDE. Concomitant use of strong inducers of CYP1A2 including smoking should be avoided during PIRFENIDET 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.

Use in renal impairment

PIRFENIDET should be used with caution in patients with moderate (CrCl 30-50mL/min) renal impairment due to lack of information relating to the metabolite (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

The safety, efficacy, and pharmacokinetics of PIRFENIDET have not been studied in patients with severe renal impairment (CrCl < 30mL/min) or end-stage renal disease requiring dialysis. Use of PIRFENIDET is contraindicated in patients with severe renal impairment or end-stage renal diseases requiring dialysis.

Use in hepatic impairment

PIRFENIDET should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4 Special warnings and precautions for use).

The safety, efficacy, and pharmacokinetics of PIRFENIDET have not been studied in patients with severe hepatic impairment or end stage liver disease. PIRFENIDET is contraindicated in patients with severe hepatic impairment or end stage liver disease.

Angioedema/anaphylaxis

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 PIRFENIDET in the post-marketing setting. Reports of anaphylactic reactions have also been received. Therefore, patients who develop signs or symptoms of angioedema or severe allergic reactions following administration of PIRFENIDET should immediately discontinue treatment. Patients with angioedema or severe allergic reactions should be managed according to standard of care. PIRFENIDET should not be used in patients with a history of angioedema or hypersensitivity due to PIRFENIDET (see section 4.3 Contraindications).

Dizziness

Dizziness has been reported in patients taking PIRFENIDET. 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 Effects on ability to drive and use machines). 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 PIRFENIDET may be warranted.

Fatigue

Fatigue has been reported in patients taking PIRFENIDET. 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 Effects on ability to drive and use machines).

Weight Loss

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

Hyponatraemia

Hyponatraemia has been reported in patients treated with Esbriet (see section 4.8). As the symptopms of hyponatraemia may be subtle and masked by the presence of concomitant morbidities, regular monitoring of the relevant laboratory parameters is recommended, especially in the presence of evocative signs and symptoms such as nauseas, headache or dizziness.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with the use of PIRFENIDET in the postmarketing setting. If signs or symptoms of SCAR occur, interrupt PIRFENIDET treatment until the aetiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, permanently discontinue PIRFENIDET.

Paediatric use

The safety and efficacy of PIRFENIDET in paediatric patients has not been established.

Use in the elderly

No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

Effects on Laboratory Tests

No data available

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Pirfenidone is metabolized primarily via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Fluvoxamine and Inhibitors of CYP1A2

In a Phase 1 study, the co-administration of PIRFENIDET 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.

PIRFENIDET is contraindicated in patients with concomitant use of fluvoxamine (see section 4.3 Contraindications). Fluvoxamine should be discontinued prior to the initiation of PIRFENIDET therapy and avoided during PIRFENIDET therapy due to the reduced clearance of pirfenidone.

In vitro-in vivo extrapolations indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4 fold. If concomitant use of PIRFENIDET with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of PIRFENIDET should be reduced to 801 mg daily (267 mg three times a day). Patients should be closely monitored for emergence of adverse reactions associated with PIRFENIDET therapy. Discontinue PIRFENIDET if necessary (see section 4.2 Dose and method of administration)

Co-administration of PIRFENIDET and 750 mg of ciprofloxacin (a moderate and selective 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 PIRFENIDET should be reduced to 1602 mg daily (534 mg three times a day). PIRFENIDET should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily.

PIRFENIDET should be used with caution in patients treated with other moderate inhibitors of CYP1A2.

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e. CYP2C9, 2C19, 2D6, and 2E1) should be avoided during PIRFENIDET treatment.

Inducers of CYP1A2

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.

Effects of pirfenidone on transporters

Pirfenidone is not a substrate for P-glycoprotein. In vitro, pirfenidone inhibited P- glycoprotein-mediated transport by approximately 30% at 1 mM, the highest concentration tested. The predicted intestinal concentration of pirfenidone at the MRHD is 1.7 mM. Therefore, pirfenidone may inhibit intestinal P-glycoprotein during clinical use. The effects of pirfenidone on other transport proteins have not been investigated.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility indices were unaffected in male and female rats treated with pirfenidone at oral doses up to 1000 mg/kg/day. However, prolongation of the oestrous cycle and a high incidence of irregular cycles was observed in rats at doses ≥450 mg/kg/day (1.7-times the maximum recommended human dose based on body surface area).

Use in pregnancy – Category B3

There are no data from the use of PIRFENIDET 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. Pirfenidone was not teratogenic in rats or rabbits at oral doses up to 1000 mg/kg/day and 300 mg/kg/day in the respective species (approximately 4 and 2 times the maximum recommended human dose on a body surface area basis). In rats, treatment at ≥450 mg/kg/day was associated with delayed fetal ossification, and at 1000 mg/kg/day, prolongation of gestation and reduction in fetal viability were observed (the doses being approximately 2 to 4 times the MRHD). As a precautionary measure, it is preferable to avoid the use of PIRFENIDET during pregnancy.

Use in lactation

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Studies in lactating rats have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk. Postnatal body weight gain was reduced in the offspring of rats that received oral doses of pirfenidone at ≥300 mg/kg/day (approximately equal to the MRHD on a body surface area basis) during gestation and lactation. A risk to the breastfeeding child cannot be excluded.

A decision must be made whether to discontinue breast feeding or to discontinue from PIRFENIDET therapy, taking into account the benefit of breast feeding for the child and the benefit of PIRFENIDET therapy for the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of the ability to drive and use machines have been performed. PIRFENIDET may cause dizziness and fatigue, which could influence the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

The safety of PIRFENIDET 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 PIRFENIDET 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 PIRFENIDET and placebo in clinical studies.

The most common adverse reactions with an incidence of ≥10% and more frequent in the PIRFENIDET than placebo treatment group are listed in Table 1.

Table 1 Adverse reactions occurring in ≥10% of PIRFENIDET treated patients and more commonly than placebo in pivotal Studies

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	PIRFENIDET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain[1]	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhoea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-oesophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

[1] Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

In the bioequivalence and safety study, GP29830, where one 801 mg pirfenidone tablet was compared to three 267 mg pirfenidone capsules, a greater proportion of subjects experienced adverse effects in the tablet, fed treatment group (n =7 [15.9%]) compared with the capsule, fed treatment group (n =1 [2.3%]. All AEs were non-serious, mild in severity, and consistent with the known safety profile of PIRFENIDET. The slight increase in C_{max} of the tablet relative to capsules in the fed state is not expected to have a clinically meaningful effect.

Post marketing experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during post approval use of pirfenidone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Blood and Lymphatic System Disorders: Agranulocytosis

Immune System Disorders: Angioedema, Anaphylaxis

Hepatobiliary Disorders: Bilirubin increased in combination with increases of ALT and AST Clinically relevant Drug-Induced Liver Injury including isolated reports with fatal outcome.

Metabolism and nutrition disorders: Uncommon: Hyponatraemia

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS); toxic epidermal necrolysis (TEN); and drug reaction with eosinophilia and systemic symptoms (DRESS).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is limited clinical experience with overdose. Multiple dosages of PIRFENIDET up to a total 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 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, other immunosuppressants, ATC code: L04AX05.

Mechanism of Action

The mechanism of action of pirfenidone has not been fully established. Idiopathic pulmonary 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). Existing data indicate that pirfenidone exerts both anti-fibrotic and anti-inflammatory properties in animal models of inflammation and pulmonary fibrosis.

Pharmacodynamic effect

Pirfenidone attenuated the release of pro-inflammatory and pro-fibrotic cytokines in response to inflammatory stimuli in mice at clinically relevant doses. In addition, pirfenidone was able to prevent the development of lung fibrosis when given prophylactically, and arrest further fibrosis development, in the bleomycin-induced model of lung fibrosis. Pirfenidone did not reverse established lung fibrosis in rats at clinically relevant doses.

Clinical trials

The clinical efficacy of PIRFENIDET has been studied in three multinational, Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with idiopathic pulmonary fibrosis (IPF): PIPF 004, PIPF 006 (CAPACITY) and PIPF-016 (ASCEND).

PIPF 004 and PIPF 006 compared treatment with PIRFENIDET 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 in percent predicted FVC from baseline at Week 72 of treatment was significantly reduced in patients receiving PIRFENIDET (N = 174) compared with patients receiving placebo (N = 174; p = 0.001, rank ANCOVA). Treatment with PIRFENIDET also significantly reduced the decline in 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 PIRFENIDET 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 (34%)
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 PIRFENIDET compared to placebo in change from baseline to Week 72 of distance walked during a six minute walk test (6MWT) by the pre-specified rank ANCOVA, in an ad hoc analysis, 37% of patients receiving PIRFENIDET 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 PIRFENIDET (N = 171) did not reduce the decline in percent predicted FVC from baseline at Week 72 compared with placebo (N = 173; p = 0.501). However, treatment with PIRFENIDET reduced the decline in 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 PIRFENIDET 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 ($p < 0.001$, rank ANCOVA). Additionally, in an ad hoc analysis, 33% of patients receiving PIRFENIDET showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo.

In a pooled analysis of survival in PIPF 004 and PIPF 006 the mortality rate with PIRFENIDET 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 PIRFENIDET 2,403 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 %DLCO 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 DLCO below 35% at Baseline.

In study PIPF-016, the decline in percent predicted FVC from baseline at Week 52 of treatment was significantly reduced in patients receiving PIRFENIDET (N = 278) compared with patients receiving placebo (N = 277; $p<0.000001$, rank ANCOVA). Treatment with PIRFENIDET also significantly reduced the decline in 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 PIRFENIDET 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 PIRFENIDET compared with patients receiving placebo in PIPF-016 ($p=0.036$, rank ANCOVA); 26% of patients receiving PIRFENIDET 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 PIRFENIDET 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).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Administration of PIRFENIDET tablets with food results in a large reduction in C_{max} (by 40%) 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 (20-54 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 PIRFENIDET be administered with food to reduce the incidence of nausea and dizziness.

Bioequivalence between the tablets and capsules was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. In the fed state, the 801 mg tablet met bioequivalence criteria based on the AUC measurements compared to the capsules, while the 90% confidence intervals for C_{max} (108.26% - 125.60%) slightly exceeded the upper bound of standard bioequivalence limit.

The absolute 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 62% in studies conducted *in vitro* (1 to 100 µg/mL) and *ex vivo*. Mean apparent oral steady-state volume of distribution is approximately 70 L, indicating that pirfenidone distribution to tissues is modest.

Metabolism

In vitro metabolism studies with hepatic microsomes indicate that pirfenidone is metabolized primarily via CYP1A2 with lesser contribution from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1 (see section 4.5 Interaction with other medicines and other forms of interaction). The major metabolite, 5-carboxy-pirfenidone, displays no or only very weak pharmacological activity.

Excretion

The oral clearance of pirfenidone appears modestly saturable. In a multiple dose, dose ranging study in healthy older adults administered doses ranging from 267 mg to 1335 mg three times a day, the mean clearance decreased by approximately 25% above a dose of 801 mg three times a day. Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours. Approximately 80% of an orally administered dose of pirfenidone is cleared in the urine within 24 hours of dosing. The majority of pirfenidone is excreted as the 5-carboxy- pirfenidone metabolite (>95% of that recovered), with less than 1% of pirfenidone excreted unchanged in urine.

Pharmacokinetics in Special Populations

<u>Hepatic impairment</u>

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 Dose and method of administration and 4.4 Special warnings and precautions for use). PIRFENIDET is contraindicated in severe hepatic impairment and end stage liver disease (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

<u>Renal impairment</u>

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 metabolised to 5 carboxy-pirfenidone, for which pharmacodynamic and safety margins were not established. The $AUC_{0-\infty}$ of 5- carboxy-pirfenidone was significantly higher in the moderate (p=0.009) and severe (P<0.0001) renal impairment groups than in the group with normal renal function. 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 and there is no or minimal pharmacologic activity on the metabolite measured by TNF inhibitory effects.

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

Genotoxicity

Pirfenidone showed no indication of genotoxic activity in assays for bacterial mutagenicity, for chromosomal aberrations in vitro in mammalian cells, for clastogenicity in vivo in mice, and for DNA damage in rats. No significant mutagenic activity was observed with pirfenidone in bacteria when tested under UV exposure.

Carcinogenicity

An increased incidence of liver tumours (hepatocellular adenomas and carcinomas, and hepatoblastomas) was observed in 2-year carcinogenicity studies conducted by the oral route in rats and mice. This occurred at doses ≥750 mg/kg/day and ≥800 mg/kg/day in the respective species, associated with systemic exposure (plasma AUC) less than that of patients at the maximum recommended human dose. These hepatic findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving PIRFENIDET. These findings are considered unlikely to be relevant to humans but this cannot be excluded.

A statistically significant increase in uterine tumours (adenocarcinoma) was observed in female rats administered 1500 mg/kg/day, yielding systemic exposure (plasma AUC) similar to that in patients at the maximum recommended human dose of 2403 mg/day. The relevance of this finding to humans is unclear.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate
Croscarmellose sodium
Magnesium stearate
Copovidone

Film coating:
OPADRY II Complete Film Coating System 85F520195 YELLOW (267 mg tablets) or OPADRY II Complete Film Coating System 32K540099 PURPLE (801 mg tablets)

Film coating contains:
Polyvinyl alcohol
Macrogol 3350

Purified Talc
Titanium dioxide
Iron oxide black (801 mg)
Iron oxide red (801 mg)
Iron oxide yellow (267 mg

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

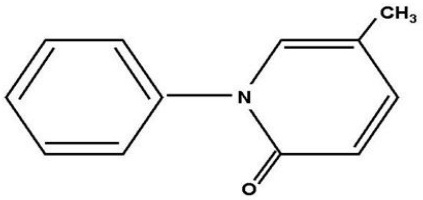
PIRFENIDET 267 mg and 801 mg film-coated tablets are approved in high-density polyethylene (HDPE) bottles of 90 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number: 53179-13-8

The chemical name of pirfenidone is 5-methyl-1-phenyl-2-1(H)-pyridone. It has a molecular formula of C12H11NO and a molecular weight of 185.23.
Pirfenidone is a white to pale yellow, non-hygroscopic powder. It is freely soluble in methanol, ethyl alcohol, acetone and chloroform. Sparingly soluble in 1.0 N HCl, water and 0.1N sodium hydroxide. The melting point is approximately 109°C.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Accord Healthcare
Level 24, 570 Bourke Street Melbourne
VIC 3000

Phone: 1800 134 988
Email: ds@commercialeyes.com.au

9. DATE OF FIRST APPROVAL

15 February 2023

10. DATE OF REVISION

17 October 2025

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of SCAR, SJS, TEN and DRESS
4.8	Addition of Skin and subcutaneous tissue disorders