SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pirfenidone Sandoz 801 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 801 mg pirfenidone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pirfenidone Sandoz 801 mg film-coated tablets are dark pink, oval, approximately 1.8 x 0.9 cm biconvex film-coated tablets, debossed with 'SD801' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pirfenidone is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).

4.2 Posology and method of administration

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

Posology

Adults

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)

The recommended maintenance daily dose of Pirfenidone is 801 mg three times a day with food for a total of 2403 mg/day.

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

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

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

Dose adjustments and other considerations for safe use

Gastrointestinal events: In patients who experience intolerance to therapy due to gastrointestinal undesirable effects, patients should be reminded to take the medicinal product with food. If symptoms persist, the dose of pirfenidone may be reduced to 267 mg – 534 mg, two to three times a day with food with re-escalation to the recommended daily dose as tolerated. 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 to use a sunblock daily and avoid exposure to the sun (see section 4.4). The dose of pirfenidone may be reduced to 801 mg each day (267 mg 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 (see section 4.4). 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.

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 in section 4.4.

Special populations

Elderly

No dose adjustment is necessary in patients 65 years and older (see section 5.2).

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. Pirfenidone therapy should not be used in patients with severe hepatic impairment or end stage liver disease (see section 4.3, 4.4 and 5.2).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment. Pirfenidone should be used with caution in patients with moderate (CrCl 30-50 ml/min) 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 (see sections 4.3 and 5.2).

Paediatric population
There is no relevant use of Pirfenidone in the paediatric population for the indication of IPF.

Method of administration

Pirfenidone is 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 5.2).

4.4 Special warnings and precautions for use

Hepatic function

Elevated transaminases have been commonly reported in patients treated with Pirfenidone. Liver function tests (ALT, AST and bilirubin) should be performed 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).

If a patient exhibits an aminotransferase elevation >3 to <5 x ULN without bilirubin elevation and without symptoms or signs of drug-induced liver injury after starting pirfenidone 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 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.

Drug-induced liver injury

Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe drug-induced liver injury, including isolated cases with fatal outcome, have been reported post-marketing (see section 4.8).

In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

If a patient exhibits an aminotransferase elevation >3 to <5 x ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, pirfenidone should be permanently discontinued and the patient should not be rechallenged.

If a patient exhibits an aminotransferase elevation to ≥5 x ULN, pirfenidone should be permanently 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 must not be used in patients with severe hepatic impairment (see section 4.3).

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).

Severe skin reactions

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with pirfenidone treatment. If signs and symptoms suggestive of these reactions appear, pirfenidone should be withdrawn immediately. If the patient has developed SJS, TEN or DRESS with the use of pirfenidone, treatment with pirfenidone must not be restarted and should be permanently discontinued.

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 pirfenidone 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 Pirfenidone should immediately discontinue treatment. Patients with angioedema or severe allergic reactions should be managed according to standard of care. Pirfenidone must not be used in patients with a history of angioedema or hypersensitivity 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 patient's 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 Pirfenidone (see section 4.8). As the symptoms 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 nausea, headache or dizziness.

Information about excipients

Pirfenidone Sandoz 267 mg film-coated tablets contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Approximately 70–80% of pirfenidone is metabolised 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 (267 mg, 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 two times a day cannot be avoided, the dose of pirfenidone should be reduced to 1602 mg daily (534 mg, 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 two times a day.

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 (≥1,000 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.

Breast-feeding

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 breastfed infant 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 have a moderate influence on the ability to drive or use machines, therefore patients should exercise caution when driving or operating machinery if they experience these symptoms.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions during clinical study experience with Pirfenidone at a dose of 2,403 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%), decreased appetite (20.7%% versus 8.0%), headache (10.1% versus 7.7%), and photosensitivity reaction (9.3% versus 1.1%).

Tabulated list of adverse reactions

The safety of Pirfenidone has been evaluated in clinical studies including 1,650 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.

Table 1 shows the adverse reactions reported at a frequency of ≥2% in 623 patients receiving Pirfenidone at the recommended dose of 2,403 mg/day in three pooled 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), not known (cannot be estimated from the available data)] the adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions by SOC and MedDRA frequency	
Infections and infestations	
Very Common	Upper respiratory tract infection
Common	Urinary tract infection
Blood and lymphatic system disorders	
Uncommon	Agranulocytosis[1]
Immune system disorders	

Uncommon	Angioedema[1]
Not known	Anaphylaxis[1]
Metabolism and nutrition disorders	
Very Common	Weight decreased; decreased appetite
Uncommon	Hyponatraemia[1]
Psychiatric disorders	
Very Common	Insomnia
Nervous system disorders	
Very Common	Headache; dizziness
Common	Somnolence; dysgeusia; lethargy
Vascular disorders	
Common	Hot flush
Respiratory, thoracic and mediastinal disorders	
Very Common	Dyspnoea; cough;
Common	Productive cough
Gastrointestinal disorders	
Very Common	Dyspepsia; nausea; diarrhoea; gastroesophageal reflux disease; vomiting; constipation
Common	Abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; flatulence
Hepatobiliary disorders	
Common	ALT increased; AST increased; gamma glutamyl transferase increased
Uncommon	Total serum bilirubin increased in combination with increases of ALT and AST[1]; Drug-induced liver injury[2]
Skin and subcutaneous tissue disorders	
Very Common	Rash
Common	Photosensitivity reaction; pruritus; erythema; dry skin; rash
Not Known	Stevens-Johnson syndrome[1]; toxic epidermal necrolysis[1]; drug reaction with eosinophilia and systemic symptoms (DRESS)1
Musculoskeletal and connective tissue disorders	
Very Common	Arthralgia
Common	Myalgia
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 (see section 4.4)
2. Cases of severe drug-induced liver injury, including reports with fatal outcome have been identified through post-marketing surveillance (see section 4.3, 4.4).

Exposure-adjusted analyses of pooled clinical trials in IPF confirmed that

the safety and tolerability profile of pirfenidone in IPF patients with advanced disease (n=366) is consistent with that established in IPF patients with non-advanced disease (n=942).

Description of selected adverse reactions

Decreased appetite
During the pivotal clinical trials, cases of decreased appetite were readily manageable and generally not associated with significant sequelae. Uncommonly, cases of decreased appetite were associated with significant weight loss and required medical intervention.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

There is limited clinical experience with overdose. Multiple doses of pirfenidone up to a total dose of 4,806 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 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 (1,197 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 the combined PIPF-004 and PIPF-006 population treated with the dose of 2,403 mg/d comprising in total 692 patients, the median baseline percent predicted FVC values were 73.9% in the pirfenidone group and 72.0% in the placebo group (range: 50-123% and 48-138%, respectively), and the median baseline percent predicted Carbon Monoxide Diffusing Capacity (DLco) 45.1% in the pirfenidone group and 45.6% in the placebo group (range: 25-81% and 21-94%, respectively). In PIPF-004, 2.4% in the pirfenidone group and 2.1% in the placebo group had percent predicted FVC below 50% and/or percent predicted DLco below 35% at Baseline. In PIPF-006, 1.0% in the pirfenidone group and 1.4% in the placebo group had percent predicted FVC below 50% and/or percent predicted DLco below 35% at Baseline.

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 2,403 mg/day	**Placebo (N = 174)**
Decline of ≥10% or death or lung	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 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 2,403 mg/day	**Placebo (N = 173)**
Decline of ≥10% or death or lung	39 (23%)	46
Decline of less than 10%	88 (52%)	89
No decline (FVC change >0%)	44 (26%)	38

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 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 $\%DL_{CO}$ 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 2,403 mg/day	**Placebo (N =**
Decline of ≥10% or death	46 (17%)	88 (32%)
Decline of less than 10%	169	162
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).

IPF patients with advanced lung function impairment
In pooled post-hoc analyses of studies PIPF-004, PIPF-006 and PIPF-016, in the population of advanced IPF (n = 170) with FVC < 50% at baseline and/or DLco < 35% at baseline, the annual decline of FVC in patients receiving pirfenidone (n=90) compared with patients receiving placebo (n=80) was -150.9 mL and -277.6 mL, respectively.

In MA29957, a supportive 52-week Phase IIb, multicentre, randomised, double-blind, placebo-controlled clinical trial in IPF patients with advanced lung function impairment (DLco < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, 89 patients treated with pirfenidone monotherapy had a similar decline in FVC as pirfenidone-treated patients in the post-hoc analysis of the pooled phase 3 trials PIPF-004, PIPF-006, and PIPF-016.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with pirfenidone in all subsets of the paediatric population in IPF (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Administration of pirfenidone capsules with food results in a large reduction in Cmax (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. Compared to the fasted state, the oral administration of pirfenidone with food, reduced pirfenidone Cmax by 40% in tablet formulation. 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 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 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 metabolised via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1. *In vitro* data indicate some pharmacologically relevant activity of the major metabolite (5-carboxy-pirfenidone) at concentrations in excess of peak plasma concentrations in IPF patients. This may become clinically relevant in patients with moderate renal impairment where plasma exposure to 5-carboxy-pirfenidone is increased.

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 1,335 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 metabolised to 5-carboxy-pirfenidone. The mean (SD) $AUC_{0-\infty}$ 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; 100 (26.3) mg•h/L and 168 (67.4) mg•h/L compared to 28.7 (4.99) mg•h/L respectively.

Renal Impairment Group	**Statistics**	**$AUC_{0-\infty}$ (mg•hr/L)**	
		Pirfenidone	**5-Carboxy-Pirfenidone**
Normal n □ 6	Mean (SD) Median (25^{th}–75^{th})	42.6 (17.9) 42.0 (33.1–55.6)	28.7 (4.99) 30.8 (24.1–32.1)
Mild n □ 6	Mean (SD) Median (25^{th}–75^{th})	59.1 (21.5) 51.6 (43.7–80.3)	49.3[a] (14.6) 43.0 (38.8–56.8)
Moderate n □ 6	Mean (SD) Median (25^{th}–75^{th})	63.5 (19.5) 66.7 (47.7–76.7)	100[b] (26.3) 96.3 (75.2–123)
Severe n □ 6	Mean (SD) Median (25^{th}–75^{th})	46.7 (10.9) 49.4 (40.7–55.8)	168[c] (67.4) 150 (123–248)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity.

[a] p-value versus Normal = 1.00 (pair-wise comparison with Bonferroni)
[b] p-value versus Normal = 0.009 (pair-wise comparison with Bonferroni)
[c] p-value versus Normal < 0.0001 (pair-wise comparison with Bonferroni)

Exposure to 5-carboxy-pirfenidone increases 3.5-fold or more in patients with moderate renal impairment. Clinically relevant pharmacodynamic activity of the metabolite in patients with moderate renal impairment cannot be excluded. No dose adjustment is required in patients with mild renal impairment who are receiving pirfenidone. Pirfenidone should be used with caution in patients with moderate renal impairment. 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 1,500 mg/kg/day, 37 times the human dose of 2,403 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 (1,000 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 (≥1,000 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Pregelatinised starch
Croscarmellose sodium (E468)
Hydroxypropyl cellulose (E463)
Silicon dioxide (E551)
Magnesium stearate (E572)

Tablet coating
Opadry pink 85F240048:
Polyvinyl alcohol – Part. hydrolysed (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553B)
Iron oxide yellow (E172)

Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC-Alu blister

Pack sizes
Blister packs of 84 or 252 film-coated tablets

Unit-dose blister packs of 84x1 film-coated tablets

Continuation packs:
Blister multipack containing 252 (3 packs of 84) film-coated tablets or
Unit-dose blister multipack containing 252 (3 packs of 84x1) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

Park View, Riverside Way

Watchmoor Park

Camberley, Surrey

GU15 3YL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04416/1652

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/05/2022

10 DATE OF REVISION OF THE TEXT

11/11/2024