PACK INSERT FOR MALAYSIA

Esbriet®

Pirfenidone

1. NAME OF MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 267 mg pirfenidone.

Excipients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate, titanium dioxide, gelatin and brown ink (shellac glaze, n-butyl alcohol, isopropyl alcohol, iron oxide black, iron oxide red, propylene glycol, iron oxide yellow, ammonium hydroxide).

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Two piece capsules with a white- to off-white opaque body and white to off-white opaque cap imprinted with "PFD 267 mg" in brown ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with Esbriet 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 nine capsules per day over a 14-day period as follows:

- Days 1 to 7: one capsule, three times a day (801 mg/day)
- Days 8 to 14: two capsules, three times a day (1602 mg/day)
- Day 15 onward: three capsules, three times a day (2403 mg/day)

The recommended daily dose of Esbriet for patients with IPF is three 267 mg capsules three times a day with food for a total of 2403 mg/day.

Doses above 2403 mg/day are not recommended for any patient.

Patients who miss 14 consecutive days or more of Esbriet 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 side effects, patients should be reminded to take the medicinal product with food. If symptoms persist Esbriet may be reduced to 1-2 capsules (267 mg – 534 mg) 2-3 times/day with 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 Esbriet may be reduced to 3 capsules/day (1 capsule three times a day). If the rash persists after 7 days, Esbriet 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, Esbriet 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 Esbriet 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 Esbriet treatment in this population. 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). Esbriet 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 sections 4.3, 4.4 and 5.2). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment. Esbriet should be used with caution in patients with moderate (CrCl 30-50 ml/min) renal impairment. Esbriet 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 Esbriet in the paediatric population for the indication of IPF.

Method of administration

Esbriet is for oral use. The capsules 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 2.
- 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

Elevations in ALT and AST >3 × upper limit of normal (ULN) have been reported in patients receiving therapy with Esbriet. 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 Esbriet, 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 Esbriet 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 Esbriet therapy, confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. If clinically appropriate the dose of Esbriet should be reduced or interrupted. Once liver function tests are within normal limits Esbriet 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, Esbriet should be discontinued and the patient should not be rechallenged.

If a patient exhibits an aminotransferase elevation to >5 x ULN, Esbriet should be discontinued and the patient should not be rechallenged.

Hepatic impairment

In subjects with moderate hepatic impairment (i.e. Child-Pugh Class B), Esbriet exposure was increased by 60%. Esbriet 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 Esbriet 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). Esbriet has not been studied in individuals with severe hepatic impairment and Esbriet 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 Esbriet. 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 Esbriet in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of Esbriet should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. Esbriet should not be used in patients with a history of angioedema due to Esbriet (see section 4.3).

Dizziness

Dizziness has been reported in patients taking Esbriet. 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 Esbriet may be warranted.

Fatigue

Fatigue has been reported in patients taking Esbriet. 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 Esbriet (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.

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 Esbriet 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.

Esbriet is contraindicated in patients with concomitant use of fluvoxamine (see section 4.3). Fluvoxamine should be discontinued prior to the initiation of Esbriet therapy and avoided during Esbriet 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 Esbriet with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of Esbriet should be reduced to 801 mg daily (one capsule, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with Esbriet therapy. Discontinue Esbriet if necessary (see sections 4.2 and 4.4).

Co-administration of Esbriet 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 Esbriet should be reduced to 1602 mg daily (two capsules, three times a day). Esbriet should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily.

Esbriet 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 Esbriet. 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 Esbriet 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 wherever possible.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Esbriet 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 Esbriet 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 suckling child cannot be excluded.

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

Esbriet may cause dizziness and fatigue, which could influence the ability to drive or use machines.

4.8 Undesirable effects

The safety of Esbriet 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.

The most commonly reported adverse reactions during clinical study experience with Esbriet 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%), 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 2,403 mg/day of Esbriet and placebo in clinical studies.

Table 1 shows the adverse reactions reported at a frequency of ≥2% in 623 patients receiving Esbriet at the recommended dose of 2,403 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

4.9 Overdose

There is limited clinical experience with overdose. Multiple doses of pirfenidone up to a 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 Esbriet 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 Esbriet 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 study PIPF-004, the decline of percent predicted FVC from Baseline at Week 72 of treatment was significantly reduced in patients receiving Esbriet (N=174) compared with patients receiving placebo (N=174; p=0.001, rank ANCOVA). Treatment with Esbriet 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 Esbriet 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 (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 Esbriet 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 Esbriet 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 Esbriet (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 Esbriet 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 Esbriet 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 (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 Esbriet 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 Esbriet 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 Esbriet 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 Esbriet (N=278) compared with

patients receiving placebo (N=277; p<0.000001, rank ANCOVA). Treatment with Esbriet 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 Esbriet 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 (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 Esbriet compared with patients receiving placebo in PIPF-016 (p=0.036, rank ANCOVA); 26% of patients receiving Esbriet 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 Esbriet 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±0.02l versus -0.16±0.02 l respectively, p=0.042).

5.2 Pharmacokinetic properties

Absorption

Administration of Esbriet 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 Esbriet 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 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). Esbriet 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) AUC0-∞ 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**	**AUC0-∞ (mg•hr/L)**	
		Pirfenidone	**5-Carboxy-Pirfenidone**
Normal	Mean (SD)	42.6 (17.9)	28.7 (4.99)
n = 6	Median (25^{th}–75^{th})	42.0 (33.1–55.6)	30.8 (24.1–32.1)
Mild	Mean (SD)	59.1 (21.5)	49.3[a] (14.6)
n = 6	Median (25^{th}–75^{th})	51.6 (43.7–80.3)	43.0 (38.8–56.8)
Moderate	Mean (SD)	63.5 (19.5)	100[b] (26.3)
n = 6	Median (25^{th}–75^{th})	66.7 (47.7–76.7)	96.3 (75.2–123)
Severe	Mean (SD)	46.7 (10.9)	168[c] (67.4)
n = 6	Median (25^{th}–75^{th})	49.4 (40.7–55.8)	150 (123–248)

AUC0-∞ = 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) AUC0-∞ = area under the concentration-time curve from time zero to infinity

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 Esbriet. 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 Storage

Do not store above 30°C.

Shelf-life: Please refer to expiry date on outer carton.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.2 Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed via wastewater and disposal through household waste should be avoided. Use established "collection systems," if available in your location.

6.3 Packs

Hard capsules 267mg 270

Medicine: keep out of reach of children

MYEsbriet0118/CDS8.0

Roche

Revision date: January 2018
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Catalent Pharma Solutions LLC, Winchester (KY), USA.