ESBRIET®

Pirfenidone

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Pirfenidone belongs to the chemical class of pyridine

derivatives ATC code: L04AX05

1.2 TYPE OF DOSAGE FORM

Film-coated tablet

1.3 ROUTE OF ADMINISTRATION

For oral use

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: pirfenidone

Film-coated tablet containing 267 mg and 801 mg pirfenidone

Excipients:

Tablet core: Microcrystalline cellulose, Silica, Povidone K30, Croscarmellose sodium, Magnesium stearate

Tablet coat: Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Iron oxide red, Iron oxide black and Iron oxide yellow

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF)

2.2 DOSAGE AND ADMINISTRATION

Method of Administration

Esbriet is to be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness (see Sections 2.6 Undesirable Effects and 3.2 Pharmacokinetic Properties).

Posology

Adults

The recommended daily dose of Esbriet for patients with IPF is 801 mg three times a day with food, for a total of 2403 mg/day.

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 2.7 Overdose*).

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

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 Esbriet may be reduced 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 of the instruction to use a sunblock daily and to avoid exposure to the sun (see Section 2.4 Warnings and Precautions.). The dose of Esbriet may be reduced to 801 mg each day (267 mg, three times daily). 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 2.4 Warnings and Precautions). Once the rash has resolved, Esbriet may be reintroduced 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.

Recommendations in case of elevations in ALT, AST and serum bilirubin: If a patient exhibits an aminotransferase elevation >3 to ≤5 × 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 × ULN accompanied by symptoms or hyperbilirubinemia, Esbriet should be discontinued and the patient should not be rechallenged.

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

2.2.1 Special Dosage Instructions

Elderly

No dose adjustment is necessary in patients 65 years and older (see Section 3.2 Pharmacokinetic Properties).

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) to severe (CrCl < 30 mL/min) renal impairment (*see Section 3.2.5 Pharmacokinetics in Special Populations*). Esbriet has not been studied and is not recommended in patients with end-stage renal disease requiring dialysis.

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 concomitantly taking a known CYP1A2 inhibitor (see Sections 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction and 3.2 Pharmacokinetic Properties). Esbriet has not been studied and is not recommended in patients with severe hepatic impairment or end stage liver disease (*see Sections 2.4 Warnings and Precautions and 3.2 Pharmacokinetic Properties*). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (*see Sections 2.2 Dosage and Administration, 2.4 Warnings and Precautions and 3.2.5 Pharmacokinetics in Special Populations*).

2.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Concomitant use of fluvoxamine (see Section 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction)

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General 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 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. In the event of significant elevation of liver aminotransferases the dose of Esbriet should be adjusted or treatment discontinued according to the guidelines in *section 2.2 Dosage and Administration*. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments may be necessary (see Section 2.2 Dosage and Administration).

Photosensitivity Reaction and Rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with Esbriet. 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 2.2 Dosage and Administration).

2.4.2 Drug Abuse and Dependence

No text

2.4.3 Ability to Drive and Use Machines

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

2.4.4 Laboratory Tests

No text

2.4.5 Interactions with other Medicinal Products 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 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 2.3 Contraindications). Fluvoxamine should be discontinued prior to the initiation of Esbriet therapy and avoided during Esbriet 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 Esbriet with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of Esbriet 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 Esbriet therapy. Discontinue Esbriet if necessary (see Sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

Co-administration of Esbriet 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 Esbriet should be reduced to 1602 mg daily (534 mg, 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.

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 Esbriet treatment.

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 clearance and decrease exposure to Esbriet. 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 whenever possible.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Pregnancy

Teratogenic effects:

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 (≥1000 mg/kg/day) rats exhibited prolongation of gestation and reduction in fetal viability. As a precautionary measure, it is preferable to avoid the use of Esbriet during pregnancy.

Fertility

No adverse effects on fertility were observed in preclinical studies (see Section 3.3 Preclinical Safety).

2.5.2 Labor and Delivery

No text

2.5.3 Nursing Mothers

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 3.3 Preclinical Safety). A risk to the breastfeeding 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.

2.5.4 Pediatric Use

Safety and effectiveness of Esbriet in pediatric patients has not been established.

2.5.5 Geriatric Use

No dosage adjustment is required based upon age

2.5.6 Gender

No text

2.5.7 Renal Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.5.8 Hepatic Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations.

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

The safety of Esbriet has been evaluated in 623 patients from three Phase 3 clinical studies. Table 1 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Esbriet in clinical trials.

In this section, the following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10).

Table 1: Adverse Drug Reactions Occurring in Patients Treated with Esbriet in Clinical Trials

ADR (MedDRA)	Esbriet (n = 623)	
System Organ Class	All grades (%)	Frequency Category
Metabolism and Nutrition Disorders		
Anorexia	13.0%	Very common
Weight decreased	10.1%	Very common
Decreased appetite	8.0%	Common
Psychiatric Disorders		
Insomnia	10.4%	Very common
Nervous system Disorders		
Headache	22.0%	Very common

Dizziness	18.0%	Very common
Dysgeusia	5.8%	Common
Gastrointestinal Disorders		
Dyspepsia	18.5%	Very common
Nausea	36.1%	Very common
Diarrhea	25.8%	Very common
Abdominal pain	6.3%	Common
Vomiting	13.3%	Very common
Gastro-esophageal reflux disease	11.1%	Very common
Hepatobiliary Disorders		
ALT increased	3.2%	Common
AST increased	2.7%	Common
Skin and subcutaneous disorders		
Photosensitivity reaction	9.3%	Common
Rash	30.3%	Very common
Pruritus	7.9%	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	10.0%	Very Common
General disorders and administration site conditions		
Fatigue	26.0%	Very common
Asthenia	6.4%	Common

2.6.1.1 Laboratory Abnormalities

No text

2.6.2 Post-Marketing

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 may be 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

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

2.6.2.1 Laboratory Abnormalities

No text

2.7 OVERDOSE

There is limited clinical experience with overdose. Multiple doses of Esbriet 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 the most frequently reported adverse reactions for Esbriet.

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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

The mechanism of action of pirfenidone has not been fully established. However, existing data indicate that pirfenidone exerts both anti-fibrotic 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 tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and Esbriet has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Esbriet 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).

3.1.2 Clinical / Efficacy Studies

The clinical efficacy of Esbriet has been studied in three multinational, Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with IPF.

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 (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 Esbriet (N = 174) compared with patients receiving placebo (N = 174; $p = 0.001$, rank ANCOVA). Treatment with Esbriet 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 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 2403 mg/day (N = 174)	**Placebo (N = 174)**
Decline of ≥10% or death or lung transplant	35 (20%)	60 (35%)
Decline of less than 10%	97 (56%)	90 (52%)
No decline (FVC change >0%)	42 (24%)	24 (14%)

Although there was no difference between patients receiving 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 in percent predicted FVC from Baseline at Week 72 compared with placebo (N = 173; p = 0.501). However, treatment with Esbriet 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 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 2403 mg/day (N = 171)	**Placebo (N = 173)**
Decline of ≥10% or death or lung transplant	39 (23%)	46 (27%)
Decline of less than 10%	88 (52%)	89 (51%)
No decline (FVC change >0%)	44 (26%)	38 (22%)

The decline in 6MWT distance from baseline to Week 72 was significantly reduced compared with placebo in study PIPF-006 ($p < 0.001$, rank ANCOVA). Additionally, in an ad hoc analysis, 33% of patients receiving Esbriet showed a decline of ≥50 m in 6MWT distance, compared to 47% of patients receiving placebo in PIPF-016.

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 2403 mg/day to placebo. Treatment was administered three times daily for 52 weeks. The primary endpoint was the change from Baseline to Week 52 in percent predicted FVC.

In study PIPF-016, the decline in 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 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 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 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 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).

3.2 PHARMACOKINETIC PROPERTIES

3.2.1 Absorption

Administration of Esbriet capsules 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.

Bioequivalence 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 effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

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 absolute bioavailability of pirfenidone has not been determined in humans.

3.2.2 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.

3.2.3 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. In vitro and in vivo studies to date have not detected any activity of the major metabolite (5-carboxy-pirfenidone), even at concentrations or doses greatly above those associated with activity of pirfenidone itself.

3.2.4 Elimination

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

3.2.5 Pharmacokinetics in Special Populations

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 drug is predominantly metabolized to 5-carboxy-pirfenidone. 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.

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 × 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 concomitantly taking a known CYP1A2 inhibitor (see Sections 2.2 Dosage and Administration and 2.4 Warnings and Precautions).

3.3 PRECLINICAL SAFETY

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

3.3.1 Carcinogenicity

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 tumors 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 tumors was observed in female rats administered 1500 mg/kg/day, 37 times the human dose of 2403 mg/day. The results of mechanistic studies indicate that the occurrence of uterine tumors 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.

3.3.2 Mutagenicity

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.

3.3.3 Impairment of Fertility

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 estrous cycle and a high incidence of irregular cycles. At high doses (≥1000 mg/kg/day) rats exhibited a prolongation of gestation and reduction in fetal viability. Studies in lactating rats indicate that pirfenidone and/or its metabolites are excreted in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk.

3.3.4 Teratogenicity

Reproductive toxicology studies demonstrated no adverse effects on male and female fertility or postnatal development of offspring in rats and there was no evidence of teratogenicity in rats (1000 mg/kg/day) or rabbits (300 mg/kg/day).

3.3.5 Other

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 minimized by application of sunscreen.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Do not store above 30ºC

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

4.2 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.

4.3 PACKING

Film-coated tablet 267 mg	90
Film-coated tablet 801 mg	90

Medicine: keep out of reach of children

Current at March 2017

Import by Roche Thailand Ltd., Bangkok