ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets
Esbriet 534 mg film-coated tablets
Esbriet 801 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 267 mg pirfenidone.
Each film-coated tablet contains 534 mg pirfenidone.
Each film-coated tablet contains 801 mg pirfenidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Esbriet 267 mg film-coated tablets are yellow, oval, approximately 1.3 x 0.6. cm biconvex film-coated tablets, debossed with “PFD”.
Esbriet 534 mg film-coated tablets are orange, oval, approximately 1.6 x 0.8 cm biconvex film-coated tablets, debossed with “PFD”.
Esbriet 801 mg film-coated tablets are brown, oval, approximately 2 x 0.9 cm biconvex film-coated tablets, debossed with “PFD”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Esbriet is indicated in adults 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 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 Esbriet 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 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 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, 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 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 Esbriet treatment in this population. Esbriet 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. 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 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 Esbriet. Liver function tests (ALT, AST and bilirubin) should be performed 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).

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 Esbriet 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 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.

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, Esbriet should be permanently discontinued and the patient should not be rechallenged.

If a patient exhibits an aminotransferase elevation to ≥5 x ULN, Esbriet 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%. 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 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). Esbriet has not been studied in individuals with severe hepatic impairment and Esbriet 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 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).

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 Esbriet treatment. If signs and symptoms suggestive of these reactions appear, Esbriet should be withdrawn immediately. If the patient has developed SJS,

TEN or DRESS with the use of Esbriet, treatment with Esbriet 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 Esbriet 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 Esbriet should immediately discontinue treatment. Patients with angioedema or severe allergic reactions should be managed according to standard of care. Esbriet must not be used in patients with a history of angioedema or hypersensitivity 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 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 Esbriet (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.

Sodium

Esbriet contains less than 1 mmol sodium (23 mg) per 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 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 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 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 two times a day cannot be avoided, the dose of pirfenidone 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 two times a day.

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 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 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.

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 breastfed infant 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 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 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%), 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 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.

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 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 1Adverse 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

Table 1Adverse reactions by SOC and MedDRA frequency	
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 erythematous; rash macular; rash pruritic
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 Esbriet 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 national reporting system listed in Appendix V.

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 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 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 Esbriet 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 Esbriet group and 45.6% in the placebo group (range: 25-81% and 21-94%, respectively). In PIPF-004, 2.4% in the Esbriet 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 Esbriet 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 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 (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 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 4Categorical 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±0.02 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 Esbriet (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 Esbriet monotherapy had a similar decline in FVC as Esbriet-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 Esbriet 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 Esbriet 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. 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 Cmax (108.26% - 125.60%) slightly exceeded the upper bound of standard bioequivalence limit (90% CI: 80.00% - 125.00%). The effect of food on pirfenidone oral AUC was consistent between the tablet and capsule formulations. Compared to the fasted state, administration of either formulation with food reduced pirfenidone Cmax, with Esbriet tablet reducing the Cmax slightly less (by 40%) than Esbriet

capsules (by 50%). 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.

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) $AUC_{0-\infty}$ 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 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 List of excipients

Tablet core

Microcrystalline cellulose
Croscarmellose sodium
Povidone K30
Colloidal anhydrous silica
Magnesium stearate

Film coat

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol 3350
Talc
267 mg tablet
Iron oxide yellow (E172)
534 mg tablet
Iron oxide yellow (E172)
Iron oxide red (E172)
801 mg tablet
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

267 mg tablet and 801 mg tablet
3 years for blisters.
4 years for bottles.

534 mg tablet
2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-Density Polyethylene (HDPE) bottle with a child-resistant and tamper-evident screw cap

Pack sizes

267 mg film-coated tablets
1 bottle containing 90 film-coated tablets
2 bottles each containing 90 film-coated tablets (180 film-coated tablets in total)

534 mg film-coated tablets
1 bottle containing 21 film-coated tablets
1 bottle containing 90 film-coated tablets
801 mg film-coated tablets
1 bottle containing 90 film-coated tablets

PVC/Aclar (PCTFE) aluminium foil blister
Pack sizes

267 mg film-coated tablets

1 blister containing 21 film-coated tablets (21 in total)
2 blisters each containing 21 film-coated tablets (42 in total)
4 blisters each containing 21 film-coated tablets (84 in total)
8 blisters each containing 21 Film-coated tablets (168 in total)

2-week treatment initiation pack: multipack containing 63 (1 pack containing 1 blister of 21 and 1 pack containing 2 blisters of 21) film-coated tablets

Continuation pack: multipack containing 252 (3 packs each containing 4 blisters of 21) film-coated tablets

801 mg film-coated tablets

4 blisters each containing 21 film-coated tablets (84 in total)

Continuation pack: multipack containing 252 (3 packs each containing 4 blisters of 21) 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

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/007
EU/1/11/667/008
EU/1/11/667/009
EU/1/11/667/010
EU/1/11/667/011
EU/1/11/667/012
EU/1/11/667/013
EU/1/11/667/014
EU/1/11/667/015
EU/1/11/667/016
EU/1/11/667/017
EU/1/11/667/018
EU/1/11/667/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 February 2011
Date of latest renewal: 08 September 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil-Barell-Str. 1
D-79639 Grenzach-Wyhlen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH must ensure that at launch all physicians who are expected to prescribe Esbriet are provided with a physician information pack containing the following:

- Product information (SPC)
- Physician information (safety checklists)
- Patient information (PIL)

The safety checklist about Esbriet should contain the following key elements related to liver function, drug-induced liver injury and photosensitivity:

Liver function, drug-induced liver injury

- Esbriet is contraindicated in patients with severe hepatic impairment or end stage liver disease.
- Elevations of serum transaminases can occur during treatment with Esbriet.
- There is a need to monitor liver function tests prior to initiation of treatment with Esbriet and at regular intervals thereafter.
- Close monitoring is required of any patients who develop liver enzyme elevation with appropriate dose adjustment or discontinuation.
- Prompt clinical evaluation and liver function tests for patients who develop signs or symptoms of liver injury.

Photosensitivity

- Patients should be informed that Esbriet is known to be associated with photosensitivity reactions and that preventative measures have to be taken.
- Patients are advised to avoid or reduce exposure to direct sunlight (including sunlamps).
- Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medications known to cause photosensitivity.

The physician information should encourage the prescribers to report serious adverse reactions and clinically significant ADRs of special interest including:

- Photosensitivity reactions and skin rashes
- Abnormal liver function tests
- Drug-induced liver injury
- Any other clinically significant ADRs based on the judgment of the prescriber

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

90 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/007 90 tablets
EU/1/11/667/008 180 tablets (2 x 90)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 534 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 534 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

21 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/009 21 tablets
EU/1/11/667/010 90 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 534 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 801 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/011 90 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 801 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON Film-coated Tablets in Blisters

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

1 blister containing 21 film-coated tablets (21 in total)
2 blisters each containing 21 film-coated tablets (42 in total)
4 blisters each containing 21 film-coated tablets (84 in total)
8 blisters each containing 21 Film-coated tablets (168 in total)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/012 21 tablets
EU/1/11/667/013 42 tablets (2 x 21)
EU/1/11/667/014 84 tablets (4 x 21)
EU/1/11/667/015 168 tablets (8 x 21)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON Film-coated Tablets in Blisters Multi Pack 63 – (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack: 63 (1 pack containing 1 blister of 21 and 1 pack containing 2 blisters of 21) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/016 63 tablets (21 + 42)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON Film-coated Tablets in Blisters Multi Pack 252 – (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack containing 252 (3 packs each containing 4 blisters of 21) film-coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/017 252 tablets (3x84)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

P**ARTICULARS TO APPEAR ON THE OUTER PACKAGING**

CARTON Film-coated tablets in Blisters

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 801 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

4 blisters each containing 21 film-coated tablets (84 in total)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/018 84 tablets (4x21)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 801 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

P**ARTICULARS TO APPEAR ON THE OUTER PACKAGING**

CARTON Film-coated tablets in Blisters 252 Multipack (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 801 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

Multipack containing 252 (3 packs each containing 4 blisters of 21) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/019 252 tablets (3x84)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 801 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTERPACKAGING

LABEL – INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

21 film-coated tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/016 63 tablets (21+42)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL – INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

42 film-coated tablets. Component of a multipack, can’t be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/016 63 tablets (21 + 42)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL – INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

84 film-coated tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/017 252 tablets (3 x 84)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 267 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL – INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 801 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

84 film-coated tablets. Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
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Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/019 252 tablets (3 x 84)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

esbriet 801 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE 200 ML

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 267 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/007
EU/1/11/667/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE 70 ML

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 534 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 534 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

21 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE 200 ML

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 534 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 534 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/0010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL - BOTTLE 200 ML

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 801 mg pirfenidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/667/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTER STRIPS

BLISTER STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg film-coated tablets

pirfenidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTER STRIPS

BLISTER STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Esbriet 801 mg film-coated tablets

pirfenidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the user
Esbriet 267 mg film-coated tablets
Esbriet 534 mg film-coated tablets
Esbriet 801 mg film-coated tablets
pirfenidone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Esbriet is and what it is used for

Esbriet contains the active substance pirfenidone and it is used for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in adults.

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

2. What you need to know before you take Esbriet

Do not take Esbriet
- if you are allergic to pirfenidone or any of the other ingredients of this medicine (listed in section 6)
- if you have previously experienced angioedema with pirfenidone, including symptoms such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing
- if you are taking a medicine called fluvoxamine (used to treat depression and obsessive compulsive disorder [OCD])
- if you have severe or end stage liver disease
- if you have severe or end stage kidney disease requiring dialysis.

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Esbriet
- You may become more sensitive to sunlight (photosensitivity reaction) when taking Esbriet. Avoid the sun (including sunlamps) whilst taking Esbriet. Wear sunblock daily and cover your arms, legs and head to reduce exposure to sunlight (see section 4: Possible side effects).
- You should not take other medicines, such as tetracycline antibiotics (such as doxycycline), which may make you more sensitive to sunlight.
- You should tell your doctor if you suffer from kidney problems.
- You should tell your doctor if you suffer from mild to moderate liver problems.

- You should stop smoking before and during treatment with Esbriet. Cigarette smoking can reduce the effect of Esbriet.
- Esbriet may cause dizziness and tiredness. Be careful if you have to take part in activities where you have to be alert and co-ordinated.
- Esbriet can cause weight loss. Your doctor will monitor your weight whilst you are taking this medicine.
- Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with Esbriet treatment. Stop using Esbriet and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

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

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

Other medicines and Esbriet
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

This is especially important if you are taking the following medicines, as they may change the effect of Esbriet.

Medicines that may increase side effects of Esbriet:
- enoxacin (a type of antibiotic)
- ciprofloxacin (a type of antibiotic)
- amiodarone (used to treat some types of heart disease)
- propafenone (used to treat some types of heart disease)
- fluvoxamine (used to treat depression and obsessive compulsive disorder (OCD)).

Medicines that may reduce how well Esbriet works:
- omeprazole (used in the treatment of conditions such as indigestion, gastroesophageal reflux disease)
- rifampicin (a type of antibiotic).

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

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

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

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

Esbriet contains sodium
Esbriet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Esbriet

Treatment with Esbriet should be started and overseen by a specialist doctor experienced in the diagnosis and treatment of IPF.

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

Your medicine will usually be given to you in increasing doses as follows:
- for the first 7 days take a dose of 267 mg (1 yellow tablet), 3 times a day with food (a total of 801 mg/day)
- from day 8 to 14 take a dose of 534 mg (2 yellow tablets or 1 orange tablet), 3 times a day with food (a total of 1,602 mg/day)
- from day 15 onwards (maintenance), take a dose of 801 mg (3 yellow tablets or 1 brown tablet), 3 times a day with food (a total of 2,403 mg/day).

The recommended maintenance daily dose of Esbriet is 801 mg (3 yellow tablets or 1 brown tablet) three times a day with food, for a total of 2403 mg/day.

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

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

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

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

If you stop taking Esbriet
In some situations, your doctor may advise you to stop taking Esbriet. If for any reason you have to stop taking Esbriet for more than 14 consecutive days, your doctor will restart your treatment with a dose of 267 mg 3 times a day, gradually increasing this to a dose of 801 mg 3 times a day.

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

4. Possible side effects

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

Stop taking Esbriet and seek medical attention immediately if you notice any of the following symptoms or signs
- Swelling of the face, lips and/or tongue, itching, hives, difficulty breathing or wheezing, or feeling faint, which are signs of angioedema, a serious allergic reaction or anaphylaxis.
- Yellowing of the eyes or skin, or dark urine, potentially accompanied by itching of the skin, pain on the upper right side of your stomach area (abdomen), loss of appetite, bleeding or bruising more easily than normal, or feeling tired. These may be signs of abnormal liver function and could indicate liver injury, which is an uncommon side effect of Esbriet.
- Reddish non-elevated, or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals, and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, or toxic epidermal necrolysis).

- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

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

Very common side effects (may affect more than 1 in 10 people):
- infections of the throat or the airways going into the lungs and/or sinusitis
- feeling sick (nausea)
- stomach problems such as acid reflux, vomiting, and feeling constipated
- diarrhoea
- indigestion or stomach upset
- weight loss
- decreased appetite
- difficulty sleeping
- tiredness
- dizziness
- headache
- shortness of breath
- cough
- aching joints/joint pains.

Common side effects (may affect up to 1 in 10 people):
- bladder infections
- feeling sleepy
- changes in taste
- hot flushes
- stomach problems such as feeling bloated, abdominal pain and discomfort, heart burn and passing wind
- blood tests may show increased levels of liver enzymes
- skin reactions after going out in the sun or using sunlamps
- skin problems such as itchy skin, skin redness or red skin, dry skin, skin rash
- muscle pain
- feeling weak or feeling low in energy
- chest pain
- sunburn.

Uncommon side effects (may affect up to 1 in 100 people):
- Low levels of sodium in the blood. This may cause headache, dizziness, confusion, weakness, muscle cramps or nausea and vomiting.
- blood tests may show decrease in white blood cells.

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

5. How to store Esbriet

Keep this medicine out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Esbriet contains

267 mg tablet
The active substance is pirfenidone. Each film-coated tablet contains 267 mg of pirfenidone.
The other ingredients are: microcrystalline cellulose, croscarmellose sodium (see Section 2 'Esbriet contains sodium'), povidone K30, colloidal anhydrous silica, magnesium stearate
The film coat consists of: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172).

534 mg tablet
The active substance is pirfenidone. Each film-coated tablet contains 534 mg of pirfenidone.
The other ingredients are: microcrystalline cellulose, croscarmellose sodium (see Section 2 'Esbriet contains sodium'), povidone K30, colloidal anhydrous silica, magnesium stearate
The film coat consists of: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide yellow (E172) and iron oxide red (E172).

801 mg tablet
The active substance is pirfenidone. Each film-coated tablet contains 801 mg of pirfenidone.
The other ingredients are: microcrystalline cellulose, croscarmellose sodium (see Section 2 'Esbriet contains sodium'), povidone K30, colloidal anhydrous silica, magnesium stearate
The film coat consists of: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172) and iron oxide black (E172).

What Esbriet looks like and contents of the pack

267 mg tablet
Esbriet 267 mg film-coated tablets are yellow, oval, biconvex film-coated tablets, debossed with "PFD".
The bottle packs contain one bottle containing 90 tablets or two bottles each containing 90 tablets (180 tablets in total).
The blister packs contain 21, 42, 84 or 168 film-coated tablets and the multipacks contain 63 (2-week treatment initiation pack 21+42) or 252 (continuation pack 3x84) film-coated tablets.

534 mg tablet
Esbriet 534 mg film-coated tablets are orange, oval, biconvex film-coated tablets, debossed with "PFD".
The bottle packs contain either one bottle containing 21 tablets or one bottle containing 90 tablets.

801 mg tablet
Esbriet 801 mg film-coated tablets are brown, oval, biconvex film-coated tablets, debossed with "PFD".
The bottle pack contains one bottle containing 90 tablets.
The blisters pack contains 84 film-coated tablets and the multipack contains 252 (continuation pack 3x84) film-coated tablets.
The 801 mg blisters strips are each marked with the following symbols and abbreviated names of the day as a reminder to take a dose three times a day:

 (sunrise; morning dose)  (sun; daytime dose) and  (moon; evening dose).

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
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Manufacturer

Roche Pharma AG
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Germany

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

There are also links to other websites about rare diseases and treatments.