**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 267 mg pirfenidone.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Two piece capsules with a blue opaque body and gold opaque cap imprinted with "InterMune 267 mg" in brown ink and containing a white to pale yellow powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Esbriet is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).

### 4.2 Posology and method of administration

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

Posology

*Adults*
Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine capsules per day over a 14-day period as follows:

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

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

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

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

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

*Dose adjustments and other considerations for safe use*
*Gastrointestinal events:* In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist Esbriet may be reduced to 1-2 capsules (267 mg – 534 mg) 2-3 times/day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve.

*Photosensitivity reaction or rash:* Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sunblock daily and to avoid sun exposure (see section 4.4). The dose of Esbriet may be reduced to 3 capsules/day (1 capsule three times a day). If the rash persists after 7 days, Esbriet should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see section 4.4). Once the rash has resolved, Esbriet may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.

*Hepatic function:* In the event of significant elevation of alanine and /or aspartate aminotransferases (ALT/AST) with or without bilirubin elevation, the dose of Esbriet should be adjusted or treatment discontinued according to the guidelines listed in section 4.4.

Special populations

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

*Hepatic impairment*
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (ie. Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in some individuals with mild to moderate hepatic impairment, caution should be used with Esbriet treatment in this population. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see sections 4.5 and 5.2). Esbriet has not been studied in patients with severe hepatic impairment or end stage liver disease, and it should not be used in patients with these conditions (see sections 4.3, 4.4 and 5.2). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see sections 4.4 and 5.2).

*Renal impairment*
No dose adjustment is necessary in patients with mild to moderate 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 in the treatment of IPF.

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 4.8 and 5.2).

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients,
- 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 4.4).

## 4.4 Special warnings and precautions for use

Hepatic function

Elevations in ALT and AST >3 × upper limit of normal (ULN) have been reported in patients receiving therapy with Esbriet. Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with Esbriet, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter (see section 4.8). In the event of significant elevation of liver aminotransferases the dose of Esbriet should be adjusted or treatment discontinued according to

the guidelines listed below. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, the following dose adjustments may be necessary.

*Recommendations in case of ALT/AST elevations*
If a patient exhibits an aminotransferase elevation to >3 to ≤5 x ULN after starting Esbriet therapy, confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. If clinically appropriate the dose of Esbriet should be reduced or interrupted. Once liver function tests are within normal limits Esbriet may be re-escalated to the recommended daily dose if tolerated.

If a patient exhibits an aminotransferase elevation to ≤5 x ULN accompanied by symptoms or hyperbilirubinaemia, Esbriet should be discontinued and the patient should not be rechallenged.

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

*Hepatic impairment*
In subjects with moderate hepatic impairment (ie. Child-Pugh Class B), Esbriet exposure was increased by 60%. Esbriet should be used with caution in patients with pre-existing mild to moderate hepatic impairment (ie. Child-Pugh Class A and B) given the potential for increased Esbriet exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see sections 4.5 and 5.2). Esbriet has not been studied in individuals with severe hepatic impairment and Esbriet should not be used in patients with severe hepatic impairment.

Photosensitivity reaction and rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with Esbriet. Patients should be instructed to use a sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash (see section 4.2).

Dizziness

Dizziness has been reported in patients taking Esbriet. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination (see section 4.7). In clinical studies, most patients who experienced dizziness had a single event, and most events resolved, with a median duration of 22 days. If dizziness does not improve or if it worsens in severity, dose adjustment or even discontinuation of Esbriet may be warranted.

Fatigue

Fatigue has been reported in patients taking Esbriet. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination (see section 4.7).

Weight loss

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

## 4.5 Interaction with other medicinal products and other forms of interaction

Pirfenidone is primarily metabolised by CYP1A2. *In vitro* metabolism studies with hepatic microsomes indicate that approximately 48% of pirfenidone is metabolised via CYP1A2 with other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1 each contributing less than 13%. . 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.

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).

Esbriet should be used with caution in patients treated with other moderate or strong inhibitors of CYP1A2 (e.g. ciprofloxacin, amiodarone, propafenone).

Cigarette smoking and inducers of CYP1A2

A Phase 1 interaction study evaluated the effect of cigarette smoking (CYP1A2 inducer) on the pharmacokinetics of Esbriet. The exposure to pirfenidone in smokers was 50% of that observed in non-smokers. Smoking has the potential to induce hepatic enzyme production and thus increase medicinal product clearance and decrease exposure. Concomitant use of strong inducers of CYP1A2 including smoking should be avoided during Esbriet therapy based on the observed relationship between cigarette smoking and its potential to induce CYP1A2. Patients should be encouraged to discontinue use of strong inducers of CYP1A2 and to stop smoking before and during treatment with pirfenidone

In the case of moderate inducers of CYP1A2 (e.g. omeprazole), concomitant use may theoretically result in a lowering of pirfenidone plasma levels.

Co-administration of medicinal products that act as potent inducers of both CYP1A2 and the other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. rifampicin) may result in significant lowering of pirfenidone plasma levels. These medicinal products should be avoided 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 (≥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.

Breast-feeding

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (see section 5.3). A risk to the suckling child cannot be excluded.

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

Fertility

No adverse effects on fertility were observed in preclinical studies (see section 5.3).

## 4.7 Effects on ability to drive and use machines

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.

## 4.8 Undesirable effects

The safety of Esbriet has been evaluated in clinical studies including 1345 healthy volunteers and patients.

The most commonly reported (≥10%) adverse reactions during clinical study experience with Esbriet at a dose of 2403 mg/day compared to placebo, respectively, were nausea (32.8% versus 13.3%), rash (28.7% versus 8.6%), fatigue (22.3% versus 13.3%), diarrhoea (21.7% versus 13.5%), dyspepsia (16.8% versus 5.5%), and photosensitivity reaction (12.2% versus 1.7%).

Serious adverse reactions were recorded at similar frequencies among patients treated with 2403 mg/day of Esbriet and placebo in clinical studies.

Table 1 shows the adverse reactions reported at a frequency of ≥2% in 345 patients receiving Esbriet at the recommended dose of 2403 mg/day in two pivotal Phase 3 studies. Adverse reactions are listed by System Organ Class and within each frequency grouping [Very common (≥1/10), Common (≥1/100 to <1/10)] the adverse reactions are presented in order of decreasing seriousness.

| **Table 1 Adverse reactions by SOC and MedDRA frequency** | |
|---|---|
| **Infections and infestations** | |
| Common: | Upper respiratory tract infection; urinary tract infection |
| **Metabolism and nutrition disorders** | |
| Common: | Weight decreased; anorexia; decreased appetite |
| **Psychiatric disorders** | |
| Common: | Insomnia |
| **Nervous system disorders** | |
| Common: | Dizziness; headache; somnolence; dysgeusia |
| **Vascular disorders** | |
| Common: | Hot flush |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Dyspnoea; cough; productive cough |
| **Gastrointestinal disorders** | |
| Very Common: | Dyspepsia; nausea; diarrhoea |
| Common: | Gastroesophageal reflux disease; vomiting; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; constipation; flatulence |
| **Hepatobiliary disorders** | |
| Common: | ALT increased; AST increased; gamma glutamyl transferase increased |
| **Skin and subcutaneous tissue disorders** | |
| Very Common: | Photosensitivity reaction; rash |
| Common: | Pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic |
| | |

| Table 1 Adverse reactions by SOC and MedDRA frequency | |
|---|---|
| **Musculoskeletal and connective tissue disorders** | |
| Common: | Myalgia; arthralgia |
| **General disorders and administration site conditions** | |
| Very Common: | Fatigue |
| Common: | Asthenia; non-cardiac chest pain |
| **Injury poisoning and procedural complications** | |
| Common: | Sunburn |

### 4.9 Overdose

There is limited clinical experience with overdose. Multiple doses of pirfenidone up to a 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 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 three Phase 3, multicentre, randomised, double-blind, placebo-controlled studies in patients with IPF. Two of the Phase 3 studies (PIPF-004 and PIPF-006) were multinational, and the third (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 (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 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 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 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 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 this study (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 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]).

The third 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).

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 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. A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that Esbriet be administered with food to reduce the incidence of nausea and dizziness.

The bioavailability of pirfenidone has not been determined in humans.

Distribution

Pirfenidone binds to human plasma proteins, primarily to serum albumin. The overall mean binding ranged from 50% to 58% at concentrations observed in clinical studies (1 to 100 μg/ml). Mean apparent oral steady-state volume of distribution is approximately 70 l, indicating that pirfenidone distribution to tissues is modest.

Biotransformation

*In vitro* metabolism studies with hepatic microsomes indicate that approximately 48% of pirfenidone is metabolised via CYP1A2 with other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1 each contributing less than 13%. *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.

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.

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 drug is predominantly metabolised to 5-carboxy-pirfenidone, and the pharmacokinetics of this metabolite is altered in subjects with moderate to severe renal impairment. However, 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. No dose adjustment is required in patients with mild to moderate renal impairment who are receiving pirfenidone. 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 1500 mg/kg/day, 37 times the human dose of 2403 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 (1000 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 (≥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.

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 was 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.

Environmental Risk Assessment (ERA)

Pirfenidone is not considered to present a potential risk to surface water, microorganisms and ground water or to sediment-dwelling invertebrates.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content

Microcrystalline cellulose
Croscarmellose sodium
Povidone
Magnesium stearate

Capsule shell: body

Indigo carmine (E132)
Titanium dioxide (E171)
Gelatin

Capsule shell: cap

Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium Dioxide (E171)
Gelatin

Imprinting Ink

Brown S-1-16530 ink containing:
Shellac
Iron oxide black (E172)
Iron oxide red (E172)
Iron oxide yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Pack sizes

*2-week treatment initiation pack*
1 x PVC/PE/PCTFE aluminium foil blister card containing 21 capsules, packaged together with 1 x PVC/PE/PCTFE aluminium foil blister card containing 42 capsules, for a total of 63 capsules per pack.

*4-week treatment maintenance pack*
4 x 1-week treatment packs of PVC/PE/PCTFE aluminium foil blister cards each containing 63 capsules for a total of 252 capsules per pack.

250 ml white HDPE bottle with child-resistant closure containing 270 capsules.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal <and other handling>

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

InterMune Europe Ltd
Wellesley House
Duke of Wellington Avenue

Royal Arsenal
London
SE18 6SS
UK
Tel.: +44 (0) 208 317 6460
Fax.: +44 (0) 208 317 6461

## 8. MARKETING AUTHORISATION NUMBER(S)

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

## A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

## B. CONDITIONS OF THE MARKETING AUTHORISATION

## A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

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

Catalent UK Packaging Limited (trading as Catalent Pharma Solutions),
Sedge Close,
Headway,
Great Oakley,
Corby,
Northamptonshire,
NN18 8HS, United Kingdom.

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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

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

The MAH shall set up a post-authorisation safety study (PASS) in the form of an observational registry in order to collect information on demographics of patients prescribed Esbriet and suspected adverse drug reactions. This is in order to further characterise the long term safety profile of pirfenidone based on the important identified, potential risks and missing information as detailed in the Esbriet Risk Management Plan.

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 and photosensitivity:

*Liver function*
- 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.

*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
- Any other clinically significant ADRs based on the judgment of the prescriber

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 01 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.
In particular a PASS Registry will be used to collect additional data regarding all identified and potential safety concerns, and for important missing information.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON - BOTTLE 250 ML**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

270 capsules

## 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

## 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

InterMune Europe Ltd.
Wellesley House
Duke of Wellington Avenue
Royal Arsenal
London
SE18 6SS
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Esbriet

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON –2-WEEK TREATMENT INITIATION PACK**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Initiation Pack
2-week treatment initiation pack containing a total of 63 capsules:

Week 1 – 21 capsules
Week 2 – 42 capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet inside the pouch before use.
Oral use.

OPENING INSTRUCTIONS
Press and hold 1
Pull and slide blister card out 2

Lift
Here

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

## 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

InterMune Europe Ltd.
Wellesley House
Duke of Wellington Avenue
Royal Arsenal
London
SE18 6SS
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Esbriet

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 1-WEEK TREATMENT PACK OF 63 CAPSULES**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

1-week treatment pack of 63 capsules

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet inside the pouch before use.
Oral use.

OPENING INSTRUCTIONS
Press and hold 1
Pull and slide blister card out 2

Lift
Here

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

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

## 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

InterMune Europe Ltd.
Wellesley House
Duke of Wellington Avenue
Royal Arsenal
London
SE18 6SS
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Esbriet

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – 4-WEEK TREATMENT MAINTENANCE PACK CONTAINING 4 X 1-WEEK TREATMENT PACKS OF 63 CAPSULES**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

4-week treatment pack of 252 capsules
63 capsules per week

## 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

## 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

InterMune Europe Ltd.
Wellesley House
Duke of Wellington Avenue
Royal Arsenal
London
SE18 6SS
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Esbriet

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**LABEL - BOTTLE 250 ML**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg hard capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
270 capsules

## 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

## 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

InterMune
London SE18 6SS, United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER CARD – 2-WEEK TREATMENT INITIATION PACK**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. NAME OF THE MARKETING AUTHORISATION HOLDER

InterMune Europe Ltd.

## 4. EXPIRY DATE

EXP

## 5. BATCH NUMBER

Lot

## 6. OTHER

2-week pack
WEEK 1
WEEK 2
AM, Noon, PM

Day 1, Day 2, Day 3, Day 4, Day 5 Day 6, Day 7, Day 8, Day 9, Day 10, Day 11, Day 12, Day 13, Day 14

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER CARD – 1-WEEK TREATMENT PACK OF 63 CAPSULES**

## 1. NAME OF THE MEDICINAL PRODUCT

Esbriet 267 mg capsules

Pirfenidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 267 mg pirfenidone.

## 3. NAME OF THE MARKETING AUTHORISATION HOLDER

InterMune Europe Ltd.

## 4 EXPIRY DATE

EXP

## 5 BATCH NUMBER

Lot

## 6. OTHER

1-week pack

AM, Noon, PM

Day 1, Day 2, Day 3, Day 4, Day 5 Day 6, Day 7

**B. PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Esbriet 267 mg hard capsules**
Pirfenidone

**Read all of this leaflet carefully before you start taking this medicine.**
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**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 mild to moderate 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. Before you take Esbriet

**Do not take Esbriet**
- if you are allergic (hypersensitive) to the active substance pirfenidone or any of the other ingredients in this medicine (for the full list of ingredients see section 6: Further information)
- 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.

**Take special care with 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 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.

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.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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:
- ciprofloxacin (a type of antibiotic)
- amiodarone (used to treat some types of heart disease)
- propafenone (used to treat some types of heart disease).

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).

Ask your doctor or pharmacist for advice before taking any medicine.

**Taking Esbriet with food and drink**
Take this medicine during or after a meal to reduce the risk of side effects such as nausea (feeling sick) and dizziness (see section 4: Possible side effects).

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

**Pregnancy and breastfeeding**
Do not take this medicine if you are pregnant, planning to become pregnant or think you might be pregnant. The risk to the unborn child is unknown.

If you are breastfeeding, speak to your doctor or pharmacist before taking Esbriet. It is not known if Esbriet passes into breast milk. If you are breastfeeding and you need to take Esbriet, your doctor will discuss the risks and benefits of taking this medicine while breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicine.

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

## 3. How to take Esbriet

Always take Esbriet exactly as your doctor has told you. You should 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 1 capsule 3 times a day with food (a total of 801 mg/day)
- from day 8 to 14 take 2 capsules, 3 times a day with food (a total of 1602 mg/day)
- from day 15 onwards, take 3 capsules 3 times a day with food (a total of 2403 mg/day).

Swallow the capsules 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 capsules 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, but separate each dose by at least 3 hours. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Esbriet**
Do not stop taking Esbriet unless your doctor tells you to. If for any reason you have to stop taking Esbriet for more than 14 consecutive days, your doctor will restart your treatment with 1 capsule 3 times a day, gradually increasing this to 3 capsules 3 times a day.

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

## 4. Possible side effects

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

The frequency of possible side effects listed below is defined using the following convention:
- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1000).

Stop taking Esbriet and tell your doctor immediately
- If you experience a serious allergic (hypersensitivity) reaction such as swelling of the face, lips and/or tongue, difficulty breathing or wheezing y.
- If you experience a severe skin reaction to sunlight or sunlamps such as blistering and/or marked peeling of the skin. Severe photosensitivity reactions are uncommon. Avoid the sun (including sunlamps) whilst taking Esbriet, wear sunblock daily and cover your arms, legs and head to reduce exposure to sunlight to limit this reaction.

**Other side effects may include**
Tell your doctor or pharmacist as soon as possible if you notice any of the following side effects listed below.

**Very common side effects** (affects more than 1 user in 10):
- skin reactions after going out in the sun or using sunlamps
- feeling sick (nausea)
- tiredness
- diarrhoea
- indigestion or stomach upset.

**Common side effects** (affects 1 to 10 users in 100):
- infections of the throat or the airways going into the lungs and/or sinusitis
- bladder infections
- weight loss
- loss of appetite
- difficulty sleeping

- dizziness, headache
- feeling sleepy
- changes in taste
- hot flushes
- shortness of breath
- cough
- stomach problems such as acid reflux, vomiting, feeling bloated, abdominal pain and discomfort, heart burn, feeling constipated and passing wind
- blood tests may show increased levels of liver enzymes
- skin problems such as itchy skin, skin redness or red skin, dry skin, skin rash
- muscle pain, aching joints/joint pains
- feeling weak or feeling low in energy
- chest pain
- sunburn.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Esbriet

Keep out of the reach and sight of children.

Do not use Esbriet 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.

Do not store this medicine above 30ºC.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. Further information

**What Esbriet contains**
The active substance is pirfenidone. Each capsule contains 267 mg of pirfenidone.
The other ingredients are:
- Capsule filling: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate
- Capsule shell (body): gelatin, indigo carmine (E132), titanium dioxide (E171)
- Capsule shell (cap): gelatin, red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171)
- Capsule brown printing ink: shellac, iron oxide black (E172), iron oxide red (E172), , iron oxide yellow (E172).

**What Esbriet looks like and contents of the pack**
Esbriet hard capsules (capsules) have a blue opaque body and a gold opaque cap with ‘InterMune 267 mg’ printed in brown ink. The capsules contain a white to pale yellow powder.

Your medicine is provided in either a 2-week treatment initiation pack, a 4-week treatment pack or in a bottle.

The 2-week treatment initiation pack contains a total of 63 capsules - a Week-1 blister card containing 21 capsules (1 capsule per pocket) and a Week-2 blister card containing 42 capsules (2 capsules per pocket).

The 4-week treatment pack contains 4 x 1-week blister cards each containing 63 capsules (3 capsules per pocket) for a total of 252 capsules.

The bottle pack contains 270 capsules.

Not all pack sizes may be marketed.

**Marketing Authorisation holder and Manufacturer**

Marketing Authorisation holderInterMune Europe Ltd., Wellesley House, Duke of Wellington Avenue, Royal Arsenal, London,
SE18 6SS, United Kingdom.

Manufacturer
Catalent UK Packaging Limited (trading as Catalent Pharma Solutions), Sedge Close, Headway, Great Oakley, Corby, Northamptonshire, NN18 8HS, United Kingdom.

**This leaflet was last approved in**

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

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