Esbriet®

Pirfenidone

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Pirfenidone belongs to the chemical class of pyridine derivative.

ATC code: L04AX05.

1.2 Type of Dosage Form

Film-coated tablet.

Esbriet 267 mg tablets are yellowish white to pale yellow, oval, approximately 1.3 x 0.6. cm biconvex film-coated tablets, debossed on one side with “PFD”.
Esbriet 801 mg tablets are greyish brown to brownish red, oval, approximately 2 x 0.9 cm biconvex film-coated tablets, debossed on one side with “PFD”.

1.3 Route of Administration

For oral use.

1.4 Sterile/Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: pirfenidone.
Film-coated tablets containing 267 mg and 801 mg pirfenidone.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication

Esbriet is indicated to slow the progression of idiopathic pulmonary fibrosis (IPF) in adult patients with mild to moderate IPF.
The studies beyond 48 weeks of treatment showed inconsistent efficacy result.

2.2 Dosage and Administration

Method of Administration

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

Testing Prior to Esbriet Administration

Conduct liver function tests prior to initiating treatment with Esbriet.

Posology

Adults

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

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14 day period as follows:

- Days 1 to 7: a dose of 267 mg administered three times a day (801 mg/day)
- Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg/day)
- Day 15 onward: a dose of 801 mg administered three times a day (2403 mg/day)

Doses above 2403 mg/day are not recommended for any patient (see section *2.7 Overdose).*

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

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

Dose Adjustments and Other Considerations

Gastrointestinal events: In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist, the dose of Esbriet may be reduced to 1–2 tablets (267 mg – 534 mg) 2–3 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 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 to use a sunblock daily and to avoid exposure to the sun (see section *2.4 Warnings and Precautions*). The dose of Esbriet may be reduced to 801 mg each day (267 mg, three times daily). If the rash persists after 7 days, Esbriet should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period.

Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice (see section *2.4 Warnings and Precautions*). Once the rash has resolved, Esbriet may be reintroduced and re-escalated up to the recommended daily dose at the discretion of the physician.

Hepatic function: If a patient exhibits an aminotransferase elevation > 3 to < 5 × ULN without bilirubin elevation after starting Esbriet therapy, confounding medicinal products should be discontinued, 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.

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

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

2.2.1 Special Dosage Instructions

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

Renal impairment
No dose adjustment is necessary in patients with mild renal impairment. Esbriet should be used with caution in patients with moderate (CrCl 30–50 mL/min) renal impairment (see section *3.2.5 Pharmacokinetics in Special Populations*). Esbriet is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min) or end stage renal disease requiring dialysis (see section *2.3 Contraindications*).

Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in some individuals with mild to moderate hepatic impairment, caution should be used with Esbriet treatment in this population. Patients should be monitored closely for signs of toxicity especially if concomitantly taking a known CYP1A2 inhibitor (see sections *2.4.5 Interactions with Other Medicinal Products and Other Forms of Interaction* and *3.2 Pharmacokinetic Properties*). Esbriet has not been studied and is contraindicated in patients with severe hepatic impairment or end-stage liver disease (see sections *2.3 Contraindications, 2.4 Warnings and Precautions,* and *3.2 Pharmacokinetic Properties*). It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see sections *2.2 Dosage and Administration, 2.4 Warnings and Precautions,* and *3.2.5 Pharmacokinetics in Special Populations*).

2.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- History of angioedema with pirfenidone.
- Concomitant use of fluvoxamine.
- Severe hepatic impairment or end stage liver disease.
- Severe renal impairment (CrCl < 30 mL/min) or end stage renal disease requiring dialysis.

2.4 Warnings and Precautions

2.4.1 General

Hepatic Function

Drug-Induced Liver Injury (DILI) in the form of transient and clinically silent elevations in transaminases, has been commonly reported in patients treated with Esbriet. Uncommonly, these elevations were associated with concomitant bilirubin increases, and serious clinical consequences including isolated cases with fatal outcome have been reported postmarketing.

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. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of significant elevation of liver aminotransferases or clinical signs and symptoms of liver injury, the dose of Esbriet should be adjusted or treatment discontinued according to the guidelines in section *2.2 Dosage and Administration*. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments may be necessary (see section *2.2 Dosage and Administration*).

Photosensitivity Reaction and Rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimized during treatment with Esbriet. Patients should be instructed to use an effective sunblock daily, to wear clothing that protects against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Dose adjustments or temporary treatment discontinuation may be necessary for photosensitivity reaction or rash (see section *2.2 Dosage and Administration*).

Angioedema

Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of Esbriet in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of Esbriet should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care.

Esbriet is contraindicated in patients with a history of angioedema due to Esbriet (see section *2.3 Contraindications*).

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. 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.

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

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with the use of Esbriet in the postmarketing setting. If signs or symptoms of SCAR occur, interrupt Esbriet treatment until the aetiology of the reaction has been determined. Consultation with a dermatologist is recommended. If a SCAR is confirmed, permanently discontinue Esbriet.

2.4.2 Drug Abuse and Dependence
No text.

2.4.3 Ability to Drive and Use Machines
Esbriet may cause dizziness and fatigue, which could influence the ability to drive or use machines.

2.4.4 Laboratory Tests
No text.

2.4.5 Interactions with Other Medicinal Products and Other Forms of Interaction
Pirfenidone is metabolized primarily via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Fluvoxamine and Inhibitors of CYP1A2
In a Phase 1 study, the co-administration of Esbriet and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes [CYP2C9, 2C19, and 2D6]) resulted in a 4-fold increase in exposure to pirfenidone in non-smokers.

Esbriet is contraindicated in patients with concomitant use of fluvoxamine (see section *2.3 Contraindications*). Fluvoxamine should be discontinued prior to the initiation of Esbriet therapy and avoided during Esbriet therapy due to the reduced clearance of pirfenidone.

In vitro-in vivo extrapolations indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold. If concomitant use of Esbriet with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of Esbriet should be reduced to 801 mg daily (267 mg, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with Esbriet therapy. Discontinue Esbriet if necessary (see sections *2.2 Dosage and Administration* and *2.4 Warnings and Precautions*).

Co-administration of Esbriet and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily cannot be avoided, the dose of Esbriet should be reduced to 1602 mg daily (two tablets of 267 mg, three times a day). Esbriet should be used with caution when ciprofloxacin is used at a dose of 250 mg or 500 mg once or twice daily.

Esbriet should be used with caution in patients treated with other moderate inhibitors of CYP1A2.

Agents or combinations of agents that are moderate or strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e. CYP2C9, 2C19, 2D6, and 2E1) should be avoided during Esbriet treatment.

Cigarette Smoking and Inducers of CYP1A2

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

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

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

Consumption of grapefruit juice is associated with inhibition of CYPIA2 and should be avoided during treatment with pirfenidone.

2.5 Use in Special Populations

2.5.1 Pregnancy

Teratogenic effects

There are no data from the use of Esbriet in pregnant women.

In animals, placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid.

At high doses (≥ 1000 mg/kg/day) rats exhibited prolongation of gestation and reduction in fetal viability.

As a precautionary measure, it is preferable to avoid the use of Esbriet during pregnancy.

Fertility

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

2.5.2 Labor and Delivery
No text.

2.5.3 Nursing Mothers
It is unknown whether pirfenidone or its metabolites are excreted in human milk.
Available pharmacokinetic data in animals have shown excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (see section *3.3 Preclinical Safety*). A risk to the breastfeeding child cannot be excluded.

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

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

2.5.5 Geriatric Use
No dosage adjustment is required based upon age.

2.5.6 Gender
No text.

2.5.7 Renal Impairment
Esbriet should be used with caution in patients with mild and moderate renal impairment (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*). Use of Esbriet in patients with severe renal impairment and end stage renal disease requiring dialysis is contraindicated (see section *2.3 Contraindications*).

2.5.8 Hepatic Impairment
In subjects with moderate hepatic impairment (i.e. Child-Pugh Class B), Esbriet exposure was increased by 60%. Esbriet should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B) given the potential for increased Esbriet exposure (see sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*). Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYPIA2 inhibitor. Esbriet has not been studied in individuals with severe hepatic impairment and Esbriet is contraindicated in patients with severe hepatic impairment (see sections *2.3 Contraindications* and *2.4 Warnings and Precautions*).

2.6 Undesirable Effects

2.6.1 Clinical Trials

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 (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), not known (cannot be estimated from the available data)] the adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions by SOC and MedDRA frequency

Infections and infestations	
Common	Upper respiratory tract infection; urinary tract infection
Blood and lymphatic system disorders	
Rare	Agranulocytosis[1]
Immune system disorders	
Uncommon	Angioedema[1]
Metabolism and nutrition disorders	
Very Common	Decreased appetite; weight decreased
Psychiatric disorders	
Very Common	Insomnia
Nervous system disorders	
Very Common	Headache; dizziness
Common	Somnolence; dysgeusia; lethargy
Vascular disorders	
Common	Hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea; cough; 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 (SJS); toxic epidermal necrolysis (TEN); 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 post-marketing surveillance

[2] Cases of severe drug-induced liver injury, including reports with fatal outcome have been identified through post-marketing surveillance (see sections *2.3 Contraindications*, *2.4 Warnings and Precautions*).

2.6.1.1 Laboratory Abnormalities

No text.

2.6.2 Post-Marketing

In addition to adverse reactions identified from clinical trials, the following adverse reactions have been identified during post-approval use of pirfenidone. Because these reactions may be reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Table 2. Adverse Drug Reactions Identified from Post-Marketing Experience

System Organ Class	Incidence (%)	Frequency Category
Blood and Lymphatic System Disorders		
Agranulocytosis	N/A	Uncommon[2]
Immune System Disorders		
Angioedema	N/A	Uncommon[2]
Hepatobiliary Disorders		
Bilirubin increased in combination with increases of ALT and AST	0.2%[1]	Uncommon
Clinically relevant Drug-Induced Liver Injury including isolated reports with fatal outcome	0.5%[2]	Uncommon

[1] Highest incidence observed during the pivotal IPF clinical trials

[2] The incidence and frequency category for ADRs observed only in the post-marketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Esbriet in the IPF pivotal trials

2.6.2.1 Laboratory Abnormalities

No text.

2.7 Overdose

There is limited clinical experience with overdose. Multiple doses of Esbriet up to a total dose of 4806 mg/day were administered as six 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation period. Adverse reactions were mild, transient, and consistent with the most frequently reported adverse reactions for Esbriet.

In the event of a suspected overdose, supportive medical care should be provided including monitoring of vital signs and close observation of the clinical status of the patient.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

The mechanism of action of pirfenidone has not been fully established. However, existing data indicate that pirfenidone exerts both anti-fibrotic and anti-inflammatory properties in a variety of *in vitro* systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis).

IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and Esbriet has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Esbriet attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

3.1.2 Clinical/Efficacy Studies

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

PIPF-004 and PIPF-006 compared treatment with Esbriet 2403 mg/day to placebo. The studies were nearly identical in design, with few exceptions including an intermediate dose group (1197 mg/day) in PIPF-004. In both studies, treatment was administered three times daily for a minimum of 72 weeks. The primary endpoint in both studies was the change from Baseline to Week 72 in percent-predicted Forced Vital Capacity (FVC).

In study PIPF-004, the decline in percent-predicted FVC from Baseline at Week 72 of treatment was significantly reduced in patients receiving Esbriet (n=174) compared with patients receiving placebo (n=174; p=0.001, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent-predicted FVC from Baseline at Week 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 3).

Table 3. 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 (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 in percent predicted FVC from Baseline at Week 72 compared with placebo (n=173; $p = 0.501$). However, treatment with Esbriet reduced the decline in percent-predicted FVC from Baseline at Week 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 4).

Table 4. Categorical Assessment of Change from Baseline to Week 72 in Percent-Predicted FVC in Study PIPF-006

	Pirfenidone 2403 mg/day (n=171)	**Placebo (n=173)**
Decline of ≥ 10% or death or lung transplant	39 (23%)	46 (27%)
Decline of less than 10%	88 (52%)	89 (51%)
No decline (FVC change > 0%)	44 (26%)	38 (22%)

The decline in 6MWT distance from Baseline to Week 72 was significantly reduced compared with placebo in study PIPF-006 ($p < 0.001$, rank ANCOVA). Additionally, in an ad hoc analysis, 33% of patients receiving Esbriet showed a decline of ≥ 50 m in 6MWT distance, compared to 47% of patients receiving placebo in PIPF-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 2403 mg/day to placebo. Treatment was administered three times daily for 52 weeks. The primary endpoint was the change from Baseline to Week 52 in percent-predicted FVC.

In study PIPF-016, the decline in percent-predicted FVC from Baseline at Week 52 of treatment was significantly reduced in patients receiving Esbriet (n=278) compared with patients receiving placebo (n=277; $p < 0.000001$, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent-predicted FVC from Baseline at Week 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 5).

Table 5. Categorical Assessment of Change from Baseline to Week 52 in Percent Predicted FVC in Study PIPF-016

	Pirfenidone 2403 mg/day (n=278)	**Placebo (n=277)**
Decline of ≥ 10% or death	46 (17%)	88 (32%)
Decline of less than 10%	169 (61%)	162 (58%)
No decline (FVC change > 0%)	63 (23%)	27 (10%)

The decline in distance walked during a 6MWT from Baseline to Week 52 was significantly reduced in patients receiving Esbriet compared with patients receiving placebo in PIPF-016 ($p=0.036$, rank ANCOVA); 26% of patients receiving Esbriet showed a decline of ≥ 50 m in 6MWT distance compared to 36% of patients receiving placebo.

In a pre-specified pooled analysis of studies PIPF-016, PIPF-004, and PIPF-006 at Month 12, all-cause mortality was significantly lower in Esbriet 2403 mg/day group (3.5%, 22 of 623 patients) compared with

placebo (6.7%, 42 of 624 patients), resulting in a 48% reduction in the risk of all-cause mortality within the first 12 months (HR 0.52 [95% CI, 0.31–0.87], p = 0.0107, log-rank test).

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Administration of Esbriet capsules with food results in a large reduction in C_{max} (by 50%) and a smaller effect on AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50–66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80–85% of the AUC observed in the fasted state.

Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. In the fed state, the 801 mg tablet met bioequivalence criteria based on the AUC measurements compared to the capsules, while the 90% confidence intervals for C_{max} (108.26%-125.60%) slightly exceeded the upper bound of standard bioequivalence limit. The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

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

The absolute bioavailability of pirfenidone has not been determined in humans.

3.2.2 Distribution

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

3.2.3 Metabolism

In vitro metabolism studies with hepatic microsomes indicate that pirfenidone is metabolized primarily via CYP1A2 with lesser contribution from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1. *In vitro* and *in vivo* studies to date have not detected any activity of the major metabolite (5-carboxy-pirfenidone), even at concentrations or doses greatly above those associated with activity of pirfenidone itself.

3.2.4 Elimination

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

3.2.5 Pharmacokinetics in Special Populations

Renal Impairment
No clinically relevant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild renal impairment compared to subjects with normal renal function. The parent drug is predominantly metabolized to 5-carboxy-pirfenidone. The $AUC_{0-\infty}$ of 5-carboxy-pirfenidone was significantly higher in the moderate ($p = 0.009$) and severe ($p < 0.0001$) renal impairment groups than in the group with normal renal function.

Esbriet is contraindicated in patients with severe renal impairment or end stage renal disease requiring dialysis (see section *2.3 Contraindications*).

Hepatic Impairment
The pharmacokinetics of pirfenidone and the 5-carboxy-pirfenidone metabolite were compared in subjects with moderate hepatic impairment (Child-Pugh Class B) and in subjects with normal hepatic function. Results showed that there was a mean increase of 60% in pirfenidone exposure after a single dose of 801 mg pirfenidone (3 × 267 mg capsule) in patients with moderate hepatic impairment. Pirfenidone should be used with caution in patients with mild to moderate hepatic impairment and patients should be monitored closely for signs of toxicity especially if concomitantly taking a known CYP1A2 inhibitor (see sections *2.2 Dosage and Administration* and *2.4 Warnings and Precautions*).

Esbriet is contraindicated in severe hepatic impairment and end stage liver disease (see sections *2.3 Contraindications* and *2.4 Warnings and Precautions*).

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

3.3.1 Carcinogenicity
In repeated dose toxicity studies increases in liver weight were observed in mice, rats and dogs; this was often accompanied by hepatic centrilobular hypertrophy. Reversibility was observed after cessation of treatment. An increased incidence of liver tumors was observed in carcinogenicity studies conducted in rats and mice. These hepatic findings are consistent with an induction of hepatic microsomal enzymes, an effect which has not been observed in patients receiving Esbriet. These findings are not considered relevant to humans.

A statistically significant increase in uterine tumors was observed in female rats administered 1500 mg/kg/day, 37 times the human dose of 2403 mg/day. The results of mechanistic studies indicate that the occurrence of uterine tumors is probably related to a chronic dopamine-mediated sex hormone imbalance involving a species-specific endocrine mechanism in the rat which is not present in humans.

3.3.2 Mutagenicity

Pirfenidone showed no indication of mutagenic or genotoxic activity in a standard battery of tests and when tested under UV exposure was not mutagenic. When tested under UV exposure pirfenidone was positive in a photoclastogenic assay in Chinese hamster lung cells.

3.3.3 Impairment of Fertility

In animals placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid. At high doses (≥ 450 mg/kg/day) rats exhibited a prolongation of estrous cycle and a high incidence of irregular cycles. At high doses (≥ 1000 mg/kg/day) rats exhibited a prolongation of gestation and reduction in fetal viability. Studies in lactating rats indicate that pirfenidone and/or its metabolites are excreted in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk.

3.3.4 Teratogenicity

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

3.3.5 Other

Phototoxicity and irritation were noted in guinea pigs after oral administration of pirfenidone and with exposure to UVA/UVB light. The severity of phototoxic lesions was minimized by application of sunscreen.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Do not store above 30ºC.

This medicine should not be used after the expiry date (EXP) shown on the pack. After the bottle is opened, can be used up to 6 months

4.2 Special Instruction for Use, Handling and Disposal

Disposal of unused/expired medicines

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

4.3 Packs

Film-coated Tablet 267 mg

Box, 1 bottle @ 90 film-coated tablets — Reg.No.: DKIXXXXXXXXXX

Film-coated Tablet 801 mg

Box, 1 bottle @ 90 film-coated tablets — Reg.No.: DKIXXXXXXXXXX

Medicine: keep out of reach and sight of children

Jauhkan dari pandangan dan jangkauan anak-anak

On medical prescription only

Harus dengan resep dokter

4.4 List of Excipients

Tablet core:
Microcrystalline cellulose, croscarmellose sodium, povidone K30, silica colloidal anhydrous, magnesium stearate.
Film coat:
Polyvinyl alcohol, titanium dioxide E171, macrogol 3350, talc
267 mg tablet: Iron oxide yellow E172
801 mg tablet: Iron oxide red E172, Iron oxide black E172

Manufactured by:
Delpharm Milano S.r.l., Segrate, Italy
For:
F. Hoffmann-La Roche Ltd., Basel, Switzerland

Imported by:
PT Menarini Indria Laboratories, Bekasi, Indonesia

Distributed by:
PT Roche Indonesia, Jakarta, Indonesia

(This PI has been reviewed and approved by Deny and Renata on 06 February 2024)

INFORMASI PRODUK UNTUK PASIEN

ESBRIET
Pirfenidone
Tablet Salut Selaput
267 mg dan 801 mg

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai mengonsumsi obat ini karena brosur ini berisi informasi penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Jika Anda mengalami efek samping, diskusikan dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat bagian 4: Efek samping yang mungkin terjadi.

Apa yang terdapat di dalam brosur ini

1. Apa itu Esbriet dan kegunaannya

Esbriet mengandung zat aktif pirfenidone dan digunakan untuk memperlambat perkembangan *Idiopathic Pulmonary Fibrosis (IPF)* ringan hingga sedang pada orang dewasa.
Studi pada penggunaan di atas 48 minggu menunjukkan hasil yang tidak konsisten.

IPF adalah suatu kondisi dimana jaringan dalam paru-paru menjadi bengkak dan luka dari waktu ke waktu, sehingga membuat sulit untuk bernapas. Kondisi ini menyulitkan paru-paru untuk berfungsi dengan baik. Esbriet membantu mengurangi bengkak dan luka pada paru-paru, sehingga membantu Anda bernapas dengan lebih baik.

2. Apa yang perlu Anda ketahui sebelum mengonsumsi Esbriet

Jangan mengonsumsi Esbriet

- jika Anda alergi terhadap pirfenidone atau salah satu bahan lain dari obat ini (tercantum di bagian 6: Isi kemasan dan informasi lainnya).
- jika Anda sebelumnya mengalami angioedema dengan pirfenidone, termasuk gejala seperti pembengkakan wajah, bibir, dan/atau lidah yang mungkin berkaitan dengan kesulitan bernapas atau mengi.
- jika Anda mengonsumsi obat yang disebut fluvoxamine (digunakan untuk mengobati depresi dan gangguan obsesif kompulsif [OCD]).
- jika Anda menderita penyakit hati parah atau stadium akhir.
- jika Anda menderita penyakit ginjal parah (CrCl < 30 mL/min) atau stadium akhir yang memerlukan dialisis.

Jangan mengonsumsi Esbriet jika salah satu kondisi di atas terjadi pada Anda. Jika Anda tidak yakin, tanyakan kepada dokter, apoteker atau perawat Anda.

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Peringatan dan perhatian
Konsultasikan dengan dokter, apoteker atau perawat Anda sebelum mengonsumsi Esbriet

- Anda mungkin menjadi lebih sensitif terhadap sinar matahari (reaksi fotosensitivitas) ketika mengonsumsi Esbriet.
  Hindari sinar matahari (termasuk *sunlamp* (lampu yang menghasilkan radiasi ultraviolet)) saat mengonsumsi Esbriet. Kenakan tabir surya setiap hari dan tutupi lengan, kaki, dan kepala Anda untuk mengurangi paparan sinar matahari (lihat bagian 4: Efek samping yang mungkin terjadi).
- Anda tidak boleh mengonsumsi obat lain, seperti antibiotik tetrasiklin (seperti *doxycycline*), yang dapat membuat Anda lebih sensitif terhadap sinar matahari.
- Anda harus memberi tahu dokter Anda jika Anda menderita gangguan hati ringan sampai sedang.
- Pengobatan harus dihentikan jika Anda mempunyai riwayat angioedema dengan pirfenidone, termasuk gejala seperti pembengkakan wajah, bibir, dan/atau lidah yang mungkin berkaitan dengan kesulitan bernapas atau mengi.
- Anda harus berhenti merokok sebelum dan selama pengobatan dengan Esbriet. Merokok dapat mengurangi efek dari Esbriet.
- Esbriet dapat menyebabkan pusing dan kelelahan. Hati-hati jika Anda harus ikut serta dalam kegiatan dimana Anda harus siaga dan terkoordinasi.
- Esbriet dapat menyebabkan penurunan berat badan. Dokter akan memantau berat badan Anda selama Anda mengonsumsi obat ini.
- Sindrom Stevens-Johnson, reaksi obat dengan gejala sistemik dan eosinophilia (DRESS) serta nekrolisis epidermal toksik (TEN) telah dilaporkan berhubungan dengan pengobatan Esbriet. Hentikan penggunaan Esbriet dan segera dapatkan bantuan medis jika Anda mengalami salah satu gejala yang terkait dengan reaksi kulit serius yang dijelaskan di bagian 4.

Esbriet bisa menyebabkan gangguan hati serius dan pada beberapa kasus bisa berakibat fatal. Anda akan membutuhkan tes darah sebelum memulai mengonsumsi Esbriet dan pada interval bulanan selama 6 bulan pertama dan kemudian setiap 3 bulan setelahnya selama Anda mengonsumsi obat ini untuk memastikan apakah hati Anda bekerja dengan baik. Penting bagi Anda untuk melakukan tes darah rutin selama Anda mengonsumsi Esbriet.

Anak-anak dan remaja
Jangan berikan Esbriet ke anak-anak dan remaja di bawah usia 18 tahun.

Obat-obatan lain dan Esbriet
Beri tahu dokter, apoteker atau perawat Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi, atau akan mengonsumsi obat-obatan lain.
Hal ini penting terutama jika Anda mengonsumsi obat-obatan berikut, karena dapat memengaruhi efek dari Esbriet.

Obat-obatan yang dapat meningkatkan efek samping dari Esbriet:
- Enoksasin (sejenis antibiotik)
- Siprofloksasin (sejenis antibiotik)
- Amiodaron (digunakan untuk mengobati beberapa jenis penyakit jantung)
- Propafenon (digunakan untuk mengobati beberapa jenis penyakit jantung)
- Fluvoksamin (digunakan untuk mengobati depresi dan gangguan obsesif kompulsif)

Obat-obatan yang dapat mengurangi kemanjuran Esbriet:
- Omeprazol (digunakan dalam pengobatan kondisi seperti gangguan pencernaan, penyakit asamlambung)
- Rifampisin (sejenis antibiotik)

Tanyakan kepada dokter, apoteker atau perawat Anda untuk saran sebelum mengonsumsi obat apa pun.

Esbriet dengan makanan dan minuman
Minum obat ini selama atau setelah makan untuk mengurangi risiko efek samping seperti mual (tidak enak badan) dan pusing (lihat bagian 4: Efek samping yang mungkin terjadi).
Jangan minum jus *grapefruit* saat mengonsumsi obat ini. *Grapefruit* dapat mencegah Esbriet bekerja dengan baik.

Kehamilan, menyusui, dan kesuburan
Jangan mengonsumsi obat ini jika Anda sedang hamil, berencana untuk hamil, atau merasa Anda mungkin hamil. Risiko pada janin belum diketahui.
Jika Anda sedang menyusui atau berencana untuk menyusui, konsultasikan dengan dokter, apoteker atau perawat Anda sebelum mengonsumsi Esbriet. Belum diketahui apakah Esbriet diekskresikan ke dalam ASI. Jika Anda sedang menyusui dan Anda perlu mengonsumsi Esbriet, dokter Anda akan memberi tahu risiko dan manfaat dari mengonsumsi obat ini saat menyusui.

Mengemudi dan menggunakan mesin
Jangan mengemudi atau menggunakan mesin jika Anda merasa pusing atau lelah setelah mengonsumsi Esbriet.

3. Cara penggunaan Esbriet
Selalu minum obat ini dengan cara yang sama persis dengan apa yang telah diberitahukan dokter, apoteker atau perawat Anda. Periksa dengan dokter, apoteker atau perawat Anda jika Anda tidak yakin.

Obat Anda biasanya akan diberikan kepada Anda dalam dosis meningkat sebagai berikut:
- untuk 7 hari pertama, minum 1 tablet kuning, 3 kali sehari dengan makanan (total 801 mg/hari)
- dari hari 8 sampai 14, minum 2 tablet kuning, 3 kali sehari dengan makanan (total 1602 mg/hari)
- dari hari 15 dan seterusnya, minum 3 tablet kuning atau 1 tablet cokelat, 3 kali sehari dengan makanan (total 2403 mg/hari).

Telan tablet secara keseluruhan dengan minum air, selama atau setelah makan untuk mengurangi risiko efek samping seperti mual (tidak enak badan) dan pusing. Jika gejala terus berlanjut, periksakan diri ke dokter Anda.

Pengurangan dosis akibat efek samping
Dokter mungkin mengurangi dosis Anda jika Anda mengalami efek samping seperti gangguan perut, reaksi kulit terhadap sinar matahari atau *sunlamp*, atau perubahan signifikan pada enzim hati Anda.

Jika Anda mengonsumsi Esbriet lebih banyak dari yang seharusnya
Segera hubungi dokter, apoteker atau perawat Anda, atau UGD rumah sakit terdekat jika Anda telah mengonsumsi lebih banyak tablet dari yang seharusnya, dan bawa serta obat Anda.

Jika Anda lupa minum Esbriet
Jika Anda lupa mengonsumsi, minum segera setelah Anda ingat. Jangan minum dosis ganda untuk mengganti dosis yang terlupakan. Tiap dosis harus dipisahkan setidaknya dengan rentang waktu 3 jam. Jangan minum lebih banyak tablet setiap hari dari dosis harian Anda yang telah diresepkan.

Jika Anda berhenti mengonsumsi Esbriet
Jangan berhenti mengonsumsi Esbriet kecuali jika dokter Anda meminta Anda demikian. Jika untuk alasan apa pun Anda harus berhenti mengonsumsi Esbriet selama lebih dari 14 hari berturut-turut, dokter akan memulai ulang pengobatan Anda dengan 1 tablet kuning 3 kali sehari, meningkat secara bertahap menjadi 3 tablet kuning atau 1 tablet cokelat, 3 kali sehari.

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Jika ada pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya**.**

Berhenti mengonsumsi Esbriet dan segera beri tahu dokter Anda:

- Jika Anda mengalami reaksi alergi serius (hipersensitivitas) seperti pembengkakan wajah, bibir, dan/atau lidah, kesulitan bernapas atau mengi.
- Jika Anda mengalami reaksi kulit yang parah terhadap sinar matahari atau *sunlamp* seperti kulit melepuh dan/atau mengelupas. Reaksi fotosensitivitas yang berat jarang terjadi. Hindari sinar matahari (termasuk *sunlamp*) selama mengonsumsi Esbriet, kenakan tabir surya setiap hari dan tutupi lengan, kaki, dan kepala untuk mengurangi paparan sinar matahari guna membatasi reaksi ini.
- Jika Anda merasa mata atau kulit menguning, atau urin berwarna gelap, kemungkinan disertai dengan rasa gatal pada kulit, rasa sakit di sisi kanan atas area perut Anda (abdomen), pendarahan atau mudah memar atau merasa cepat lelah. Ini mungkin tanda-tanda fungsi hati yang abnormal dan dapat mengindikasikan kerusakan pada hati. Ini merupakan efek samping yang tidak umum terjadi.
- Jika Anda melihat munculnya bercak kemerahan pada area tubuh seperti dada, punggung dan pinggang, disertai tanda-tanda infeksi seperti kulit mengelupas, sakit pada tenggorokan, demam, sariawan, atau gejala seperti flu. Anda mungkin perlu melakukan tes darah untuk memastikan apakah gejala Anda berkaitan dengan Obat Anda. Tanda dan gejala ini mungkin mengindikasikan sindrom Stevens-Johnson, reaksi obat dengan gejala sistemik dan eosinophilia (DRESS) atau nekrolisis epidermal toksik (TEN).

Sangat umum terjadi: Kemungkinan terjadi ≥ 1 dari 10 pasien.

- Infeksi saluran napas bagian atas
- Mual
- Muntah
- Penyakit *gastroesophageal reflux*
- Konstipasi (susah buang air besar)
- Diare
- Dispepsia
- Penurunan berat badan
- Selera makan menurun
- Insomnia
- Kelelahan
- Pusing
- Sakit kepala
- *Dyspnoea* (sesak napas)
- Ruam
- Batuk
- Batuk berdahak
- Nyeri sendi dan otot

Umum terjadi: kemungkinan terjadi ≥ 1 dari 100 pasien sampai < 1 dari 10 pasien.

- Infeksi saluran kemih
- *Somnolence* (mengantuk)
- *Dysgeusia* (gangguan pada indera pengecap)

- *Hot flush* (kemerahan atau rasa panas yang muncul secara tiba-tiba disebabkan oleh pelebaran kapiler pada kulit)
- Perut kembung
- Rasa tidak nyaman pada perut
- Nyeri perut
- Nyeri perut bagian atas
- Rasa tidak nyaman pada lambung
- Gastritis
- Flatulensi
- Peningkatan enzim hati (ALT, AST)
- Peningkatan *gamma glutamyl transferase*
- Gatal
- Eritema (bintik merah)
- Kulit kering
- Ruam merah
- Ruam *macular*
- Ruam gatal
- Reaksi fotosensitivitas
- Lesu
- Lemas
- *Non-cardiac chest pain*
- *Sunburn*

Tidak umum terjadi: kemungkinan terjadi ≥ 1 dari 1000 pasien sampai < 1 dari 100 pasien.
- Angioedema
- Cedera hati yang diinduksi obat, termasuk laporan yang terisolasi dengan hasil yang fatal
- Agranulasitosis
- Total serum bilirubin meningkat bersamaan dengan peningkatan ALT dan AST

Pelaporan efek samping
Jika Anda mengalami efek samping apa pun, beri tahu dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin tidak tercantum dalam brosur ini.

Anda juga dapat melaporkan efek samping melalui:

PT Roche Indonesia – Local Safety Unit
Email: indonesia.safety@roche.com
Tel: 0-800-140-1579 (bebas pulsa)

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. Cara penyimpanan Esbriet
Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada botol dan karton setelah "EXP", baik sebelum maupun setelah penggunaan pertama. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan itu. Setelah kemasan botol dibuka, dapat digunakan sampai dengan 6 bulan.

Jangan simpan obat ini di atas suhu 30ºC.

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Jangan membuang obat apa pun melalui air limbah atau sampah rumah tangga. Tanyakan kepada apoteker Anda cara membuang obat-obatan yang tidak lagi digunakan. Tindakan ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan Esbriet

Zat aktifnya adalah pirfenidone.
Tiap tablet kuning mengandung 267 mg pirfenidone.
Tiap tablet cokelat mengandung 801 mg pirfenidone.
Komposisi lain adalah:

- Isi tablet: *Microcrystalline cellulose, croscarmellose sodium, povidone K30, silica colloidal anhydrous, magnesium stearate.*
- Isi salut selaput: *Polyvinyl alcohol, titanium dioxide E171, macrogol 3350, talc*
  tablet 267 mg: pewarna *Iron oxide yellow E172*
  tablet 801 mg: pewarna *Iron oxide red E172, Iron oxide black E172*

Bentuk Esbriet dan isi kemasan

Tablet salut selaput 267 mg

- Tablet salut selaput Esbriet 267 mg berwarna kuning, berbentuk oval, cembung pada kedua sisinya, tercetak dengan tulisan "PFD".
- Kemasan dus berisi 1 botol yang berisi 90 tablet salut selaput.

Tablet salut selaput 801 mg

- Tablet salut selaput Esbriet 801 mg berwarna cokelat, berbentuk oval, cembung pada kedua sisinya, tercetak dengan tulisan "PFD".
- Kemasan dus berisi 1 botol yang berisi 90 tablet salut selaput.

Tablet salut selaput 267 mg
Dus, 1 botol @ 90 tablet salut selaput — Reg.No.: DKIXXXXXXXXXX
Tablet salut selaput 801 mg
Dus, 1 botol @ 90 tablet salut selaput — Reg.No.: DKIXXXXXXXXXX

Obat: Jauhkan dari pandangan dan jangkauan anak-anak

Harus dengan resep dokter

Diproduksi oleh:
Delpharm Milano S.r.l., Segrate, Italia
Untuk:
F. Hoffmann-La Roche Ltd., Basel, Swiss

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PT Menarini Indria Laboratories, Bekasi, Indonesia

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