PRODUCT MONOGRAPH

Pr ESBRIET®

pirfenidone capsules

267 mg

Anti-fibrotic/Anti-inflammatory Agent

Hoffmann-La Roche Limited
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L5N 5M8

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[Pr]ESBRIET®

pirfenidone capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsules, 267 mg	Capsule content: Microcrystalline cellulose Croscarmellose sodium Povidone Magnesium stearate Capsule shell: body Titanium dioxide Gelatin Capsule shell: cap Titanium dioxide Gelatin Imprinting Inks Brown S-1-16530 or 03A2 inks containing: Shellac Iron oxide black Iron oxide red Iron oxide yellow Propylene glycol Ammonium hydroxide

INDICATIONS AND CLINICAL USE

ESBRIET® (pirfenidone) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF) in adults.

Geriatrics (≥65 years of age):
No dose adjustment is necessary in patients 65 years and older (see ACTION AND CLINICAL PHARMACOLOGY).

Paediatrics (<18 years of age):
The safety and effectiveness of ESBRIET in paediatric patients have not been established.

CONTRAINDICATIONS

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- History of angioedema with pirfenidone (see WARNINGS AND PRECAUTIONS).
- Concomitant use of fluvoxamine (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- Severe hepatic impairment or end-stage liver disease (see WARNINGS AND PRECAUTIONS).
- Severe renal impairment (CrCl <30 mL/min) or end stage renal disease requiring dialysis (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General

Drug-Interactions with Inhibitors of CYP1A2 and Other CYP Isoenzymes

Fluvoxamine
ESBRIET is contraindicated in patients with concomitant use of fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on CYP2C9, 2C19, and 2D6). Fluvoxamine should be discontinued prior to the initiation of treatment with ESBRIET and avoided during ESBRIET therapy due to the potential for reduced clearance of pirfenidone (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ciprofloxacin
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 (a total daily dose of 1500 mg) cannot be avoided, the dose of ESBRIET should be reduced to 1602 mg daily (two capsules, three times a day). ESBRIET should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Strong and Selective Inhibitors of CYP1A2
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 (one capsule, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with ESBRIET therapy. Discontinue ESBRIET if necessary (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Other CYP1A2 Inhibitors
Agents or combinations of agents that are moderate to 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. ESBRIET should be used with caution in patients treated with moderate inhibitors of CYP1A2 that do not inhibit other CYP isoenzymes (see DRUG INTERACTIONS).

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

ESBRIET should be taken with food to reduce the incidence of dizziness or nausea.

Physicians should monitor patients as frequently as clinically indicated for toxicities and according to the instructions of "DOSAGE AND ADMINISTRATION" and "DRUG INTERACTIONS" in the product monograph for any additional medication used to treat the patient. For significant side effects, the treatment of symptoms and dose reduction or discontinuation of ESBRIET should be considered.

Fatigue
Fatigue has been reported in patients treated with ESBRIET. Therefore, patients should know how they react to ESBRIET before they engage in activities requiring mental alertness or coordination (e.g., driving or using machinery). If fatigue does not improve or if it worsens in severity, dose reduction or discontinuation of pirfenidone may be warranted.

Endocrine and Metabolism

Weight Loss
Anorexia and weight loss have 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.

Gastrointestinal

Gastrointestinal events (e.g., nausea, diarrhoea, dyspepsia, vomiting) have been reported in patients treated with ESBRIET. Patients who experience gastrointestinal side effects should be reminded to take ESBRIET with food. If gastrointestinal events do not improve or worsen in severity, dose reduction or discontinuation of ESBRIET may be warranted.

Hepatic/Biliary/Pancreatic

Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) have been reported in patients treated with ESBRIET. In some cases, these have been associated with concomitant elevations in bilirubin. Liver chemistry tests (ALT, AST, and bilirubin) should be conducted prior to the initiation of treatment with ESBRIET, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In

the event of elevations of ALT and/or AST the dose of ESBRIET may need to be reduced or treatment discontinued (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

In patients with moderate hepatic impairment (i.e., Child-Pugh Class B), ESBRIET exposure was increased by 60%. ESBRIET should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased ESBRIET exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY). ESBRIET has not been studied in individuals with severe hepatic impairment. ESBRIET should not be used in patients with severe hepatic impairment or end-stage liver disease (see CONTRAINDICATIONS).

Immune System

Angioedema
Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of ESBRIET in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of ESBRIET should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. ESBRIET should not be used in patients with a history of angioedema due to ESBRIET (see CONTRAINDICATIONS).

Neurologic

Dizziness
Dizziness has been reported in patients treated with ESBRIET. Therefore, patients should know how they react to ESBRIET before they engage in activities requiring mental alertness or coordination (e.g., driving or using machinery). Patients who experience intolerance to therapy due to dizziness should be reminded to take ESBRIET with food to reduce dizziness. If dizziness does not improve or worsens in severity, dose adjustment or discontinuation of ESBRIET may be warranted.

Renal

ESBRIET should not be used in patients with severe renal impairment, or end-stage renal disease requiring dialysis (CrCl <30 mL/min, per Cockcroft-Gault equation) (see CONTRAINDICATIONS). No dose adjustment is necessary in patients with mild to moderate renal impairment.

Skin

Photosensitivity Reaction and Rash
Photosensitivity reaction and rash have been reported in patients treated with ESBRIET. Patients treated with ESBRIET should be advised to avoid or minimize exposure to direct and

indirect sunlight, including through windows and from sunlamps, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to use daily an effective sun block (at least SPF 50 against UVA and UVB), and to wear clothing that protects against sun exposure such as wide-brimmed hats and long sleeves. Patients should be instructed to report promptly to their physician symptoms of photosensitivity reaction or rash. Severe photosensitivity reactions are uncommon. Dose reduction and temporary treatment discontinuation may be necessary in the event of photosensitivity reaction or rash. ESBRIET may be reintroduced with re-escalation to the tolerated dose in the same manner as the dose-escalation period (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women
ESBRIET has not been studied in pregnant women. In animals, placental transfer of pirfenidone and/or its metabolites to the foetus 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 foetal viability.

The use of ESBRIET should be avoided during pregnancy.

Nursing Women
It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown rapid excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (see TOXICOLOGY). A risk to the breast-fed child cannot be excluded.

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

Fertility
No adverse effects on fertility were observed in preclinical studies (see TOXICOLOGY).

Paediatrics (<18 years of age)
The safety and effectiveness of ESBRIET in paediatric patients have not been established.

Geriatrics (≥65 years of age)
No dose adjustment is necessary in patients 65 years and older (see ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Liver chemistry tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with ESBRIET, and subsequently at monthly intervals for the first 6 months and then

every 3 months thereafter. In the event of elevation in ALT, AST and/or bilirubin, the dose of ESBRIET may need to be reduced or treatment discontinued (see DOSAGE AND ADMINISTRATION: *Recommendations in case of elevations in ALT, AST, bilirubin*).

If a patient exhibits any ALT and/or AST elevation accompanied by symptoms (e.g. jaundice) or accompanied by hyperbilirubinaemia, ESBRIET should be discontinued promptly. The patient should be monitored closely until resolution of elevated ALT, AST and bilirubin and symptoms. The patient should NOT be re-challenged with ESBRIET.

If a patient exhibits ALT and/or AST elevation to >5 × ULN regardless of the level of serum bilirubin, ESBRIET should be discontinued promptly and the patient monitored closely until resolution of ALT and AST. The patient should NOT be re-challenged with ESBRIET.

ADVERSE REACTIONS

Adverse Drug Reaction

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

At the recommended dosage of 2403 mg/day, 14.6% of patients on ESBRIET compared to 9.6% on placebo permanently discontinued treatment because of an adverse event and 42.7% of patients on ESBRIET compared to 16.2% on placebo had a dose interruption or reduction because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies PIPF-016, PIPF-004 and PIPF-006) in which a total of 623 patients received 2403 mg/day of ESBRIET and 624 patients received placebo. Subjects ages ranged from 40 to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to ESBRIET was 62 weeks (range: 2 to 118 weeks) in these 3 trials. Patients in these

studies could elect to participate in an open-label extension study to examine the long-term safety of ESBRIET (Study PIPF 012).

Table 1 Adverse Drug Reactions Occurring in ≥3% Patients on ESBRIET and with Greater Frequency than Placebo in Studies PIPF-004, and PIPF-006, and PIPF-016

Adverse Drug Reactions	Number of Patients, n (%)	
	Randomized Patient Subset Updated	
	Pirfenidone (N = 623)	Placebo (N = 624)
Gastrointestinal Disorders		
Nausea	225 (36.1)	97 (15.5)
Abdominal pain[a]	165 (26.5)	103 (16.5)
Diarrhoea	161 (25.8)	127 (20.4)
Dyspepsia	115 (18.5)	43 (6.9)
Vomiting	83 (13.3)	39 (6.3)
Gastro-oesophageal reflux disease	69 (11.1)	44 (7.1)
Dry mouth	19 (3.0)	17 (2.7)
General Disorders and Administration Site Conditions		
Fatigue	162 (26.0)	119 (19.1)
Asthenia	40 (6.4)	24 (3.8)
Non-cardiac chest pain	32 (5.1)	25 (4.0)
Infections and Infestations		
Upper respiratory tract infection	167 (26.8)	158 (25.3)
Sinusitis	68 (10.9)	64 (10.3)
Influenza	41 (6.6)	38 (6.1)
Gastroenteritis viral	29 (4.7)	17 (2.7)
Rhinitis	20 (3.2)	19 (3.0)
Injury, Poisoning And Procedural Complications		
Sunburn	23 (3.7)	11 (1.8)
Investigations		
Weight decreased	63 (10.1)	34 (5.4)
Gamma-Glutamyltransferase increased	24 (3.9)	11 (1.8)
Alanine Aminotransferase increased	20 (3.2)	9 (1.4)
Metabolism and Nutrition Disorders		
Anorexia	81 (13.0)	31 (5.0)
Decreased appetite	50 (8.0)	20 (3.2)
Musculoskeletal and Connective Tissue Disorders		

Adverse Drug Reactions	Number of Patients, n (%)	
	Randomized Patient Subset Updated	
	Pirfenidone (N = 623)	Placebo (N = 624)
Arthralgia	62 (10.0)	44 (7.1)
Musculoskeletal Pain	24 (3.9)	22 (3.5)
Musculoskeletal Chest Pain	19 (3.0)	7 (1.1)
Nervous System Disorders		
Headache	137 (22.0)	120 (19.2)
Dizziness	112 (18.0)	71 (11.4)
Dysgeusia	36 (5.8)	14 (2.2)
Somnolence	22 (3.5)	18 (2.9)
Psychiatric Disorders		
Insomnia	65 (10.4)	41 (6.6)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal Pain	38 (6.1)	36 (5.8)
Epistaxis	22 (3.5)	21 (3.4)
Respiratory Tract Congestion	21 (3.4)	12 (1.9)
Skin and Subcutaneous Tissue Disorders		
Rash	189 (30.3)	64 (10.3)
Photosensitivity Reaction	58 (9.3)	7 (1.1)
Pruritus	49 (7.9)	33 (5.3)
Erythema	25 (4.0)	16 (2.6)
Dry Skin	21 (3.4)	11 (1.8)
Vascular Disorders		
Hot Flush	25 (4.0)	14 (2.2)
Hypertension	20 (3.2)	17 (2.7)

[a] Includes abdominal pain, upper abdominal pain, abdominal distension, abdominal discomfort, and stomach discomfort.

Abnormal Haematological and Clinical Chemistry Findings

In studies PIPF 004 and PIPF 006, haematology and urinalysis parameters were similar between patients taking ESBRIET and placebo. Serum chemistry parameters were also similar across the groups with the exception of gamma glutamyl transferase (GGT) and creatinine. A mean increase at 72 weeks from Baseline in GGT level of 7.6 U/L was observed in the ESBRIET group while no change was seen in the placebo group. A mean decrease at 72 weeks from Baseline of 5.6 µmol/L in serum creatinine was observed in the ESBRIET group, compared with a mean decrease of 1.1 µmol/L in the placebo group. Few patients experienced shifts from Grade 0, 1, or 2 to Grade 3 or 4 in laboratory tests in the studies and across treatment groups. There was an imbalance between ESBRIET and placebo groups for shifts in hyponatraemia, hypophosphataemia and lymphopaenia, which were more frequent in the ESBRIET group.

Marked laboratory abnormalities in pooled data from studies PIPF-004, PIPF-006, and PIPF-016 occurred infrequently (≤1% per treatment group) and with no greater frequency in the ESBRIET group than in the placebo group, with the following exceptions in liver tests, lymphocytes, and hyponatremia. Patients treated with ESBRIET 2403 mg/day had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the ESBRIET 2403 mg/day group and in 0.2% of patients in the placebo group. Grade 0 to 3 reductions in lymphocyte count were seen in 6 ESBRIET patients (1.0%) and in 1 placebo patient (0.2%). One ESBRIET patient (0.2%) had a post-Baseline Grade 4 lymphocyte abnormality at Week 4, which was resolved at Week 6, Grade 2 at Weeks 12, 24, and 36, and resolved thereafter. Lymphocyte abnormalities were not associated with AEs. Grade 0 to 3 sodium (hyponatremia) abnormalities were reported in 9 ESBRIET patients (1.5%) and 1 placebo patient (0.2%).

Demographic Factors

No effect was seen between adverse events and sex (male versus female), age (<65 versus ≥65 years), or Baseline IPF severity (FVC <70% predicted versus FVC 70% to 80% predicted versus FVC ≥80% predicted) within the ESBRIET group. No effect also was seen for race (white *versus* non-white); however, there were only 65 non-white patients in the three predominantly North American Phase III studies combined

Dose-Response Relationship (PIPF-004 and PIPF-006)

Study PIPF-004 included a group receiving a lower dose of ESBRIET (1197 mg/day) than the marketed dose of 2403 mg/day. Adverse drug reaction rates in the lower dose ESBRIET group were intermediate to the ESBRIET 2403 mg/day and placebo groups for a number of the more frequently occurring adverse drug reactions including nausea, dyspepsia, abdominal pain, decreased appetite, dizziness, headache, photosensitivity reaction and rash.

Adverse Drug Reactions in SP3

The safety analysis in the randomized, double-blind Phase III study (SP3) conducted in Japan included 109 patients who were treated with 1800 mg/day pirfenidone. This dose is comparable to the 2403 mg/day dose administered in studies PIPF-004 and PIPF-006 on a weight-normalized basis to account for the heavier body weight of the mostly North American patients in PIPF-004 and PIPF-006. In study SP3, 107 patients received placebo, and 55 patients received pirfenidone 1200 mg/day, for approximately 52 weeks. The adverse drug reaction profile for pirfenidone in the Japanese study, SP3, was generally similar to that observed with ESBRIET in studies PIPF-004 and PIPF-006 (primarily North American patients), with the exception of a higher incidence of photosensitivity reaction (51.4%) and a lower incidence of rash (9.2%) in patients on 1800 mg/day in the Japanese study. However, no photosensitivity reaction or rash was serious, severe, or life-threatening. The incidence of serious adverse drug reactions was 9.2% in the pirfenidone 1800 mg/day group and 5.6% in the placebo group.

Adverse Drug Reactions in Long-Term Studies

Study PIPF-012 was an uncontrolled, open-label extension, long-term, safety study which allowed patients who completed PIPF-004 and PIPF-006 to continue on pirfenidone treatment at 2403 mg/day or switch to pirfenidone 2403 mg/day from placebo treatment. A total of 603 patients were enrolled in Study PIPF-012. The mean duration of pirfenidone 2403 mg/day treatment in Study PIPF-012 was 27.5 weeks. The adverse drug reaction profile resulting from an interim analysis was similar to that observed in the Phase III trials and previous trials. No new safety signals or trends were observed.

Post-Market Adverse Drug Reactions

Because post-marketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In post-marketing experience in Japan many of the adverse reactions reported during post-approval use of pirfenidone (marketed as Pirespa) are consistent with the clinical trial experience with ESBRIET. These events include: abdominal discomfort, constipation, diarrhoea, dyspepsia, nausea, vomiting, ALT increased, AST increased, GGT increased, decreased appetite, dizziness, dysgeusia, somnolence, photosensitivity reaction, pruritus, rash.

The serious and unexpected adverse drug reactions include, but are not limited to, the following:

Blood and Lymphatic Disorders: Agranulocytosis, febrile neutropaenia, anaemia

Cardiac Disorders: Atrial fibrillation, palpitations, angina pectoris, ventricular tachycardia

Gastrointestinal Disorders: Gastric ulcer haemorrhage, gastritis, ileus

Metabolism and Nutrition Disorders: Dehydration, hyperkalaemia

General Disorders and Administration Site Condition: Pyrexia

Hepatobiliary Disorders: Bilirubin increased in combination with increases of ALT and AST, hepatic function abnormal, liver disorder

Immune System: Angioedema

Infections and Infestations: Bronchopulmonary aspergillosis, pneumonia, pneumonia bacterial, urinary tract infection

Investigations: C-reactive protein increased, hepatic enzyme increased, platelet count decreased, blood urea increased, renal impairment

Respiratory, Thoracic and Mediastinal Disorders: Lung disorder, pneumonitis, pneumothorax

DRUG INTERACTIONS

Overview

Drug-Interactions with Inhibitors of CYP1A2 and Other CYP Isoenzymes

Fluvoxamine
ESBRIET is contraindicated in patients with concomitant use of fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on CYP2C9, 2C19, and 2D6). Fluvoxamine should be discontinued prior to the initiation of treatment with ESBRIET and avoided during ESBRIET therapy due to the potential for reduced clearance of pirfenidone (see CONTRAINDICATIONS).

Ciprofloxacin
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 (a total daily dose of 1500 mg) cannot be avoided, the dose of ESBRIET should be reduced to 1602 mg daily (two capsules, three times a day). ESBRIET should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Strong and Selective Inhibitors of CYP1A2
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 (one capsule, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with ESBRIET therapy. Discontinue ESBRIET if necessary (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Other CYP1A2 Inhibitors
Agents or combinations of agents that are moderate to 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. ESBRIET should be used with caution in patients treated with moderate inhibitors of CYP1A2 that do not inhibit other CYP isoenzymes.

Pirfenidone is primarily metabolized via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.

Patients should discontinue and avoid use of strong inhibitors of CYP1A2 due to the potential for reduced clearance of pirfenidone (see Table 2).

Patients should discontinue and avoid use of strong inducers of CYP1A2 to avoid reduced exposure to pirfenidone (see Table 2).

Drug-Drug Interactions

In a Phase I 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 an approximately 4-fold increase in exposure to pirfenidone in non-smokers.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated)

Table 2 Established or Potential Drug-Drug Interactions

	Ref.	Effect	Clinical Comment
CYP1A2 Inhibitors			
CYP1A2, 2C9, 2C19, 2D6: Fluvoxamine	CT	↑4× $AUC_{0-\infty}$, ↑2× C_{max} Increased exposure (and reduced clearance)	Concomitant therapy is contraindicated (see WARNINGS AND PRECAUTIONS).
CYP1A2: Ciprofloxacin	CT	↑81% $AUC_{0-\infty}$, ↑23% C_{max} Increased exposure (and reduced clearance)	Concomitant therapy should be used with caution. Dose reductions may be needed (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).
CYP1A2: Methoxsalen Mexiletine Oral contraceptives	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy should be used with caution.
Inhibitors of Other CYPs when Administered with CYP1A2 Inhibitors			
CYP2C9: Amiodarone Miconazole	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.
CYP2C19: Fluconazole Esomeprazole Moclobemide Omeprazole Voriconazole	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.

	Ref.	Effect	Clinical Comment
CYP2D6: Bupropion Fluoxetine Paroxetine Quinidine Cinacalcet Duloxetine Terbinafine	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.
CYP Inducers			
CYP1A2: Phenytoin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
CYP2C9: Carbamazepine Rifampin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
CYP2C9, 2C19: Rifampin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
Legend: CT = Clinical Trial; T = Theoretical			

Drug-Food Interactions

Administration of ESBRIET with food results in a large reduction in C_{max} (by approximately 50%) and a smaller reduction in 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 to 85% of the AUC observed in the fasted state. Less nausea and dizziness were observed in fed when compared with fasted subjects. Therefore, ESBRIET should be administered with food to reduce the incidence of dizziness or nausea (see DOSAGE AND ADMINISTRATION: Dosing Considerations).

Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with ESBRIET to prevent increased exposure to ESBRIET.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Cigarette Smoking and Inducers of CYP1A2: Cigarette smoking induces hepatic enzyme production, including CYP1A2, and thus may increase clearance of ESBRIET leading to reduced exposure. Patients should stop smoking before, and not smoke during ESBRIET therapy to avoid reduced exposure to pirfenidone. In a Phase I study the exposure to pirfenidone in smokers was significantly less than in non-smokers. Cigarette smoking should be avoided during ESBRIET therapy to prevent reduced exposure to pirfenidone.

Effects on Ability to Drive and Use Machines: No studies on the effects on 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. Patients should be reminded to take ESBRIET with food to reduce the incidence of dizziness.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Treatment with ESBRIET should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.
- ESBRIET should be taken with food (see DRUG INTERACTIONS).
- ESBRIET should not be taken concomitantly with fluvoxamine (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- Reduction of the ESBRIET dose may be required for ciprofloxacin and strong but selective inhibitors of CYP1A2 (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Adults

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

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

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.

Dose Adjustments

Gastrointestinal Events: In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take ESBRIET with food. If gastrointestinal events do not improve, or worsen in severity, dose reduction or discontinuation of ESBRIET may be warranted.

Photosensitivity Reaction or Rash: Patients who experience severe photosensitivity reaction or rash should be instructed to discontinue ESBRIET promptly and to seek medical advice without delay (see WARNINGS AND PRECAUTIONS). 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.

Ciprofloxacin: 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 (a total daily dose of 1500 mg) cannot be avoided, the dose of ESBRIET should be reduced to 1602 mg daily (two capsules, three times a day). ESBRIET should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Elderly: No dose adjustment is necessary in patients 65 years and older.

Paediatric: ESBRIET has not been studied in paediatric patients, and is not recommended for use in this patient population.

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 individuals with moderate hepatic impairment (around 60% increase in Child-Pugh Class B), patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see DRUG INTERACTIONS). ESBRIET should not be used in patients with severe hepatic impairment or end-stage liver disease (see CONTRAINDICATIONS). Liver chemistry tests (ALT, AST, bilirubin) should be monitored before and during treatment with ESBRIET. Dose adjustments, including discontinuation, may be necessary in the event of elevations in ALT, AST, and/or bilirubin (see WARNINGS AND PRECAUTIONS, and see below for dose adjustments).

Recommendations in Case of ALT, AST, Bilirubin Elevations

For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments, including discontinuation, may be necessary. Confounding medicinal products should be discontinued promptly, other causes excluded and close monitoring of the patient is advised.

If a patient exhibits a Grade 2 ALT and/or AST elevation to >3 to ≤5 × ULN without hyperbilirubinaemia after starting treatment with ESBRIET at the recommended dose of 2403 mg/day, or any time after starting therapy, confounding medicinal products should be

discontinued, other causes excluded, and the patient monitored closely. As clinically appropriate, ESBRIET can be continued at the recommended dose of 2403 mg/day, reduced or temporarily discontinued. Once ALT and AST levels have resolved, ESBRIET may be re-escalated to the recommended daily dose and continued, if tolerated and the patient should be monitored closely.

If a patient exhibits any ALT and/or AST elevation accompanied by symptoms or accompanied by hyperbilirubinaemia (excluding patients with known predominantly unconjugated hyperbilirubinaemia, e.g., Gilbert's syndrome), ESBRIET should be discontinued promptly. The patient should be monitored closely until resolution of elevated ALT, AST, bilirubin, and symptoms. The patient should NOT be re-challenged with ESBRIET.

If a patient exhibits ALT and/or AST elevation to >5 × ULN regardless of the level of serum bilirubin, ESBRIET should be discontinued promptly and the patient monitored closely until resolution of elevated ALT, AST, and bilirubin. The patient should NOT be re-challenged with ESBRIET.

Renal Impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment. ESBRIET should not be used in patients with severe renal impairment or end-stage renal disease requiring dialysis (CrCl <30mL/min, per Cockcroft-Gault equation) (see CONTRAINDICATIONS).

Missed Dose

If a dose is missed, the next capsule(s) should be taken as originally planned. Double doses should not be taken to make up for forgotten capsules or doses.

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.

If treatment is missed for less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Administration

ESBRIET is to be swallowed whole with water and taken with food to reduce the possibility of nausea or dizziness.

OVERDOSAGE

In studies PIPF-004 and PIPF-006, an overdose was defined as any study drug exposure of greater than 15 capsules (>4005 mg) in any given day or greater than 5 capsules (>1335 mg) in any single dose. No patients met the definition of overdose in these studies. There is therefore, limited clinical experience with overdose. Multiple doses of pirfenidone up to 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 generally consistent with the most frequently reported adverse reactions for pirfenidone.

There is no specific antidote. 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanisms of action of pirfenidone have not been fully established. However, existing data suggest that pirfenidone exerts anti-fibrotic and anti-inflammatory properties in a variety of *in vitro* systems and animal models of pulmonary fibrosis (e.g., 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). 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). Pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Pharmacodynamics

An observed dose-response relationship favouring a dose of 2403 mg/day pirfenidone compared with 1197 mg/day pirfenidone was observed in a Phase III randomized, double-blind, placebo-controlled study (PIPF-004). A PK-PD evaluation of a subset of these patients showed a weak positive relationship between pirfenidone plasma exposure and the primary endpoint of FVC change.

A double-blind, randomized, placebo- and active-controlled parallel arm study was performed to determine the impact of two doses of pirfenidone (2403 mg/day & 4005 mg/day) on QT interval in healthy human volunteers (40/treatment arm). ECG assessments were performed at baseline and on day 10 of treatment. There was no evidence of a treatment-related effect on the QTc interval at either of the tested doses. Statistically significant increases in heart rate were observed, with maximum increases of 3.8 bpm (90% CI 1.7, 5.9) in the pirfenidone 2403 mg/day group and 4.9 bpm (90% CI 2.5, 7.4) in the pirfenidone 4005 mg/day group.

Pharmacokinetics

Table 3 Arithmetic Mean (Range) Pirfenidone Pharmacokinetic Parameters in Patients with IPF

	N	C_{max} (µg/mL)	AUC[a] (mg•h/L)	T_{max} (h)
IPF patients (PIPF-004)	57	14.7 (6.48–33.6)	180 (85.6–544)	not measured

a: AUC_{0-24} estimates reflect three doses of 801 mg administered over the 24 hour period at steady-state

Absorption: The bioavailability of pirfenidone has not been determined in humans.

Administration of pirfenidone with food results in a large reduction in C_{max} (by around 50%) and a smaller reduction of AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50 to 66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80 to 85% of the AUC observed in the fasted state. Reduced incidences of adverse events (in particular nausea and dizziness) were observed in fed subjects when compared to the fasted group. Therefore, ESBRIET should be administered with food to reduce the incidence of dizziness or nausea.

Distribution: Pirfenidone binds to human plasma proteins, primarily to 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.

Metabolism: Pirfenidone is primarily metabolized via CYP1A2 (approximately 70–80%) with minor contributions 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.

The clearance of oral 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. The concentration-dependence of pirfenidone clearance did not appear to translate into a lack of dose proportionality in the Phase III trial and is not likely to be clinically relevant.

Excretion: 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 and Conditions

Population pharmacokinetic analyses were conducted, using data collected from four studies in healthy subjects or patients with renal impairment and one study in patients with IPF. Results showed no clinically relevant effects of age, gender or body size on the pharmacokinetics of pirfenidone.

Paediatrics: The safety and effectiveness of ESBRIET in paediatric patients have not been established.

Geriatrics: The independent effect of patient age on the PK of pirfenidone is relatively small (the predicted AUC for pirfenidone was approximately 23% higher in 80 year old compared to 50 year old patients) and unlikely to be clinically significant.

Gender: No clinically relevant effect of gender on the pharmacokinetics of pirfenidone has been observed. The C_{max} of pirfenidone in females was approximately 10% higher than in males.

Race: No clinically relevant effect of race on the pharmacokinetics of pirfenidone has been observed. The predicted AUC_{0-24} of pirfenidone was found to be 21% lower in Caucasian compared with African-American subjects. However, there were only a small number of non-Caucasian patients included in controlled clinical trials.

Body Size: No clinically relevant effect of body size on the pharmacokinetics of pirfenidone has been observed. Obese subjects were observed to have higher exposure than either normal or overweight subjects but the former were older and had worse renal function.

Hepatic Insufficiency: The pharmacokinetics of pirfenidone were compared in subjects with moderate hepatic impairment (Child-Pugh Class B) and 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 they are concomitantly taking a known CYP enzyme inhibitor (in particular a CYP1A2 inhibitor). ESBRIET is contraindicated in severe hepatic impairment and end stage liver disease (see CONTRAINDICATIONS).

Renal Insufficiency: No significant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild renal impairment (CrCl of 51–80 mL/min; Cockcroft-Gault equation) to severe renal impairment (CrCl <30 mL/min) compared with subjects with normal renal function (CrCl >80 mL/min). However, the parent drug is predominantly metabolized to 5-carboxy-pirfenidone, and the pharmacokinetics of this metabolite are altered in subjects with moderate to severe renal impairment. 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; 100 (26.3) and 168 (67.4) mg•h/L compared to 28.7 (4.99) mg•h/L respectively. However, the predicted amount of metabolite accumulation at steady state is minimal as 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. ESBRIET is contraindicated in patients with severe renal impairment (CrCl <30 mL/min) or end stage renal disease requiring dialysis (see CONTRAINDICATIONS).

Japanese Patients:
Study SP3: a phase III study conducted in Japanese patients, compared pirfenidone 1800 mg/day (tablets, a comparable dose to 2403 mg/day in the North American and European populations of PIPF-004/006 on a weight-normalized basis) with placebo (N = 110, N = 109, respectively). Treatment with pirfenidone 1800 mg/day statistically 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, relative difference 43.8%, p = 0.042). There was also a statistically significant prolongation in progression free survival compared with placebo (HR: 0.64 [0.43–0.96], p = 0.028).

STORAGE AND STABILITY
Store at room temperature (15 - 30°C).

SPECIAL HANDLING INSTRUCTIONS
There are no special handling instructions for ESBRIET.

DOSAGE FORMS, COMPOSITION AND PACKAGING
ESBRIET is supplied as hard gelatin two-piece capsule, with a white opaque body and white opaque cap imprinted with "PFD 267 mg" in brown ink and containing a white to pale yellow powder.

Each capsule contains 267 mg pirfenidone.

In addition, each capsule contains the following nonmedicinal ingredients:
Capsule content:
- Microcrystalline cellulose
- Croscarmellose sodium
- Povidone
- Magnesium stearate

Capsule shell: body
- Titanium dioxide
- Gelatin

Capsule shell: cap
- Titanium dioxide
- Gelatin

Imprinting Inks
Brown S-1-16530 or 03A2 inks containing:
- Shellac
- Iron oxide black
- Iron oxide red
- Iron oxide yellow

Propylene glycol
Ammonium hydroxide

ESBRIET is supplied in 250 mL white HDPE bottle with child-resistant closure containing 270 capsules, or in treatment packs as follows:

2-week treatment initiation pack
7 x PVC/PE/PCTFE aluminium foil blister strips, each containing 3 capsules (for the Week 1 dosing), packaged together with 7 x PVC/PE/PCTFE aluminium foil blister strips, each containing 6 capsules (for the Week 2 dosing), for a total of 63 capsules per pack.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

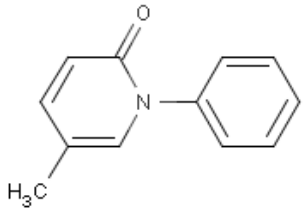
Proper name: pirfenidone

Chemical name: 5-Methyl-1-phenyl-2-*(*1H)-pyridone

Molecular formula: $C_{12}H_{11}NO$

Molecular mass: 185.22

Structural formula:



Physicochemical properties:

Description: White to pale yellow crystalline powder

Solubility: Freely soluble in methanol, ethyl alcohol, acetone, and chloroform. Sparingly soluble in 1.0 N hydrochloric acid, water and 1.0 N sodium hydroxide.

Melting point: Between 106°C and 112°C

pKa 0.2 ± 0.6

CLINICAL TRIALS

Study Demographics and Trial Design

The clinical efficacy of ESBRIET (pirfenidone capsules 267 mg) has been studied in three Phase III, multicentre, randomized, double-blind, placebo-controlled studies in patients with IPF (PIPF-004, PIPF-006 and PIPF-016).

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 final follow-up visit was held 3 to 4 weeks after the treatment completion visit. The primary endpoint in both studies was the change from Baseline to Week 72 in percent predicted Forced Vital Capacity (FVC).

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.

Table 4 Summary of Patient Demographics for Phase III Clinical Trials in Patients with IPF

Study #	Trial design	Dosage, route of administration and duration	Study patients (n) Esbriet/ Control	Mean age (Range)		Gender	
				Esbriet	Control	Esbriet	Control
PIPF-004	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of ESBRIET in patients with IPF	2403 mg/day (three 267 mg capsules TID) ESBRIET vs. placebo, administered orally for 72 weeks.	174/174	65.7 years (45–80 years)	66.3 years (40–79 years)	32.2% female	26.4% female
PIPF-006	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of ESBRIET in patients with IPF	2403 mg/day (three 267 mg capsules TID) ESBRIET vs. placebo, administered orally for 72 weeks.	171/173	66.8 years (45–80 years)	67.0 years (42–80 years)	28.1% female	28.3% female

Study #	Trial design	Dosage, route of administration and duration	Study patients (n) Esbriet/ Control	Mean age (Range)		Gender	
				Esbriet	Control	Esbriet	Control
PIPF-016	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of ESBRIET in patients with IPF	2403 mg/day (three 267 mg capsules TID) ESBRIET vs. placebo, administered orally for 52 weeks.	278/277	68.4 years (47–80 years)	67.8 years (41–80 years)	20.1% female	23.1% female

Study Results

Forced Vital Capacity

In study PIPF-004, the decline in lung function, as measured by 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). The absolute difference in the mean change in percent predicted FVC was 4.4% between treatment groups, representing a relative difference of 35.5%. 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 5).

In study PIPF-006, there was no statistically significant difference between treatment with ESBRIET (N = 171) and placebo (N = 173) in the reduction of the decline of percent predicted FVC from Baseline at Week 72 (p = 0.501, rank ANCOVA). However, treatment with ESBRIET reduced the decline in lung function, as measured by 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 5).

The primary endpoint analysis of the pooled population also showed an ESBRIET treatment effect on percent predicted FVC at week 72 (p = 0.005, rank ANCOVA). The absolute difference in the mean change in percent predicted FVC was 2.5% between two treatment groups, representing a relative difference of 22.8%. At Week 72, a decline from Baseline in percent predicted FVC of ≥10% was seen in 21.4% of patients receiving ESBRIET compared to 30.5% receiving placebo (Table 4).

Table 5 Categorical Assessment of Change from Baseline to Week 72 in Percent Predicted FVC

	Number (% of Patients)					
	PIPF-004		PIPF-006		Pooled	
	ESBRIET 2403 mg/d (n = 174)	Placebo (n = 174)	ESBRIET 2403 mg/d (n = 171)	Placebo (n = 173)	ESBRIET 2403 mg/d (n = 345)	Placebo (n = 347)
Decline of ≥10% or death or lung transplant	35 (20%)	60 (35%)	39 (23%)	46 (27%)	74 (21%)	106 (30%)
Decline of <10% but ≥0%	97 (56%)	90 (52%)	88 (52%)	89 (51%)	185 (54%)	179 (52%)
Improvement of >0%	42 (24%)	24 (14%)	44 (26%)	38 (22%)	86 (25%)	62 (18%)

In study PIPF 016, the decline of percent predicted FVC from Baseline at Week 52 of treatment, was significantly reduced in patients receiving ESBRIET (N = 278) compared with patients receiving placebo (N = 277; $p < 0.000001$, rank ANCOVA). Treatment with ESBRIET also significantly reduced the decline of percent predicted FVC from Baseline at Weeks 13 ($p < 0.000001$), 26 ($p < 0.000001$), and 39 ($p = 0.00002$).

Progression Free Survival (PFS)

In the analysis of PFS in study PIPF-004, treatment with ESBRIET significantly reduced the combined risk of death or disease progression by 36% compared to placebo (HR 0.64 [0.44–0.95]; $p = 0.023$). Disease progression was defined as ≥10% decline in percent predicted FVC or ≥15% decline in percent predicted diffusing capacity of the lungs for carbon monoxide (DL_{CO}).

The reduction in risk was primarily due to differences in disease progression due to decline in percent predicted FVC. In study PIPF-006, there was no difference in PFS between the two treatment arms (HR 0.84 [0.58–1.22]; $p = 0.355$). In the pooled analysis, treatment with ESBRIET 2403 mg/day resulted in a 26% reduction in the risk of death or progression of disease compared with placebo (HR 0.74 [95% CI, 0.57–0.96]; $p = 0.025$).

In the analysis of PFS in study PIPF-016, treatment with ESBRIET significantly reduced the combined risk of death or disease progression by 43% compared to placebo (HR 0.57 [0.43–0.77]; $p = 0.0001$). Disease progression was defined as death, ≥10% decline in percent predicted FVC or ≥ 50 meters decline in six minute walk test (6MWT) distance.

Six Minute Walk Test Distance

In study PIPF-004, 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 ($p = 0.171$). The difference in the mean decline in the 6MWT distance between the treatment groups at Week 72 was 16.4 meters, representing a relative difference of 21.3%.

In study PIPF-006, the decline in 6MWT distance from baseline to Week 72 was significantly reduced compared with placebo in this study ($p < 0.001$, rank ANCOVA). The difference in the mean decline in the 6MWT distance between the treatment groups at Week 72 was 31.8 meters, representing a relative difference of 41.3%.

In study PIPF-016, the decline in 6MWT distance from baseline to Week 52 was significantly reduced compared with placebo ($p = 0.036$, rank ANCOVA). The difference in the mean decline in the 6MWT distance between the treatment groups was 26.7 meters, representing a relative difference of 44.2%.

Mortality

The overall survival was captured as an exploratory efficacy endpoint in pivotal studies. The cause of death was not adjudicated and the effect of ESBRIET on all-cause mortality is inconclusive.

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]).

In Study PIPF-016, the mortality rate with Esbriet 2403 mg/ day group was 4.0 % compared with 7.2% with placebo (HR 0.55 [95% CI, 0.26–1.15]).

DETAILED PHARMACOLOGY

Animal Pharmacology

The findings from a range of *in vitro* and *in vivo* primary pharmacodynamic studies suggested the anti-fibrotic and anti-inflammatory properties of pirfenidone. Bleomycin-induced pulmonary fibrosis has become an established model for human IPF and studies with pirfenidone in this model using mice, hamsters and rats demonstrated its activity in inhibiting the development and progression of fibrosis at exposures lower than that associated with the recommended human dose. *In vitro* and *in vivo* studies to date have not detected any activity of the major human metabolite, 5-caboxy-pirfenidone.

At concentrations higher than the C_{max} seen in humans, pirfenidone may cause transient CNS depressant effects. Inhibitory effects on gastric emptying and small intestinal transport were observed in rats. An additional pharmacological effect was an arrhythmogenic effects in mice, rats and dogs.

Pirfenidone decreased "general activity and behavior" and "the central nervous system" in mice at an oral dose of 100 mg/kg or above. Pirfenidone had effects on "the respiratory and cardiovascular systems" in anesthetized rats at an intraduodenal dose of 30 mg/kg or above. Studies in mice and rats caused transient general activity and behavior effects (marked sedation and abnormal posture at oral doses of 100 mg/kg or above; at 300 mg/kg staggering gait, ptosis

and a decrease in the body temperature), decreased the spontaneous motor activity and the body temperature at an oral dose of 100 mg/kg or above. At 300 mg/kg, significant potentiating effects of anesthesia, anticonvulsive effects (electroshock or PTZ-induced convulsions) and analgesic effects were observed and significantly reduced the blood pressure and significantly increased the respiratory volume and arterial blood flow in anesthetized rats at an intraduodenal dose of 30 mg/kg or above. At 100 mg/kg or above, pirfenidone caused a decrease in the respiratory rate, an increase in the heart rate, and occurrence of a premature beat.

In anesthetized rats, pirfenidone caused a transient increase in heart rate immediately after administration at 100 mg/kg. 300 mg/kg of pirfenidone caused a decrease in blood pressure and increase in heart rate lasting approximately 30 minutes. Pirfenidone caused premature ventricular contracts (PVC) and atrioventricular block at 100 mg/kg or above. Continuous PVC was also observed at 300 mg/kg.

Studies in anesthetized dogs demonstrated that an intraduodenal administration of pirfenidone at 100 mg/kg or more causes a decrease in blood pressure and an increase in heart rate.

Human Pharmacology

Pirfenidone was converted to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by NADPH-fortified human liver microsomes. The result of experiments with human recombinant CYP enzymes implicated several CYP enzymes such as CYP1A2, 2C9, 2C19, 2D6, and 2E1 in the metabolism of pirfenidone. However, the results of the antibody inhibition experiments and correlation analysis suggest that CYP1A2 is the major CYP enzyme responsible for the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone in human liver microsomes. The overall results indicate CYP1A2 as the major CYP involved in the metabolism, however, results from experiments with human recombinant CYP enzymes and correlation analysis indicate that other CYP enzymes participate in the overall metabolism of pirfenidone.

Pirfenidone was found not to significantly inhibit CYP or MAO enzymes. However under one experimental condition examined using human liver microsomes, pirfenidone caused direct inhibition of CYP1A2, CYP2A6, CYP2D6 and CYP2E1, as approximately 34%, 27%, 21% and 27% inhibition was observed at 1000 μM. As well, CYP enzymes are not influenced by 5-carboxy-pirfenidone and only mildly influenced by pirfenidone (at 250 μM).

TOXICOLOGY

With the exception of phototoxicity, nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction. Phototoxicity and irritation were noted in guinea pigs and mice after oral administration of pirfenidone and with exposure to UVA light.

Acute Toxicity

In mice and rats the clinical signs observed at the maximum non-lethal doses included hypoactivity and abnormal gait. These clinical signs were observed in dogs in addition to vomiting, mydriasis and tremors. In a study with rats, the toxicity of pirfenidone was reduced when administered with food. Pirfenidone was more toxic to female rats and female dogs in which higher systemic exposures compared to males was observed.

Table 6 Acute Toxicity

Species	Route	Maximum Non-Lethal Dose (mg/kg)	Minimum Lethal Dose (mg/kg)
Mouse	Oral, gavage	1000	2000
Rat	Oral, gavage	500 (fasted); 1000 (fed)	1000 (fasted)
Dog	Oral, capsule	1000	Not determined

Chronic toxicity

In repeated dose studies, decreased body weight was observed in mice, rats and dogs administered oral pirfenidone. Increased liver weights were observed with hepatic centrilobular hypertrophy and increased CYP content in all species. In dogs, transient vomiting, abnormal gait, tremors, limb weakness, rigidity and hypoactivity were observed at doses 10-fold higher (C_{max}) than the clinical dose. The toxic signs observed in these studies were reversible after pirfenidone administration was stopped.

Table 7 Chronic Toxicity

Species	Route	Duration	Doses (mg/kg/day)	Results
Mouse, $B6C3F_1$	Oral, diet	13 weeks	0, 200, 600, 2000	↓ Body weight at the highest dose. ↑ Red blood cell indices, reticulocyte ratio and platelet count in males. ↓ Albumin (both sexes), A/G ratio (males), total protein (females) and cholesterol; ↑ BUN (males). Dose-related ↑ liver weight with centrilobular hepatocyte hypertrophy, and splenic extramedullary hematopoiesis in males at 2000 mg/kg/day. NOAEL: 600 mg/kg/day
Rat, F344	Oral, diet	13 weeks	0, 500, 1000, 1500	↓ Body weight and body weight gain, ↓ erythrocytes (RBC), haemoglobin, and hematocrit and ↑ MCV, platelets and reticulocytes in both sexes. ↑Total protein, albumin, glucose, BUN, cholesterol, calcium, and inorganic phosphorous; ↓ A/G ratio, triglycerides and chloride. ↑ Liver, kidney, adrenal, and testes weights. Dose-dependent centrilobular hepatocyte hypertrophy, kidney tubular epithelial regeneration (males only), and adrenal gland zone fasciculata hypertrophy (males only at 1500 mg/kg/day).
Rat, SD	Oral, gavage	6 months	0, 20, 100, 500, 1000	Salivation, ↓ activity, and respiratory rate at 500 and 1000 mg/kg/day during the first 6 weeks of treatment. ↓ Food consumption and body weight gain in high-dose males. ↓ RBC, haemoglobin, and hematocrit in females, and ↑ MCV and MCH in males, together with ↓ prothrombin time in males and ↑ activated partial thromboplastin time in females. ↑ Total protein, albumin, A/G ratio, creatinine kinase, amylase, cholesterol, calcium, and inorganic phosphorous; ↓ creatinine, triglycerides, and chloride. ↑ Liver weight (both sexes) and centrilobular hypertrophy in 2/12 males at 1000 mg/kg/day. ↑ CYP content and selected isoenzymes at 500 and 1000 mg/kg/day. NOAEL: 100 mg/kg/day

Species	Route	Duration	Doses (mg/kg/day)	Results
Rat, SD	Intravenous	4 weeks	0, 500, 1000, 1625	Ten deaths by Day 4 of treatment (1 female at 1000 mg/kg/day and 9 females at 1625 mg/kg/day). ↑ Absolute liver and kidney weights and hepatic centrilobular hypertrophy at 1625 mg/kg/day. NOAEL: 500 mg/kg/day
Dog, Beagle	Oral, capsule	3 months	0, 20, 70, 200	Mucous in faeces, salivation, vomiting, abnormal gait, difficulty in standing, rigidity, limb weakness, head shakes, vocalization and hypoactivity at the higher doses. ↑ Platelet counts at 200 mg/kg/day. ↑ Alkaline phosphatase at 70 and 200 mg/kg/day. ↑ Liver weight and reversible hepatocellular hypertrophy at 200 mg/kg/day. ↑ Submaxillary gland weight and acinar hypertrophy at 200 mg/kg/day. ↑ CYP content and microsomal enzyme activities at all doses. NOAEL: 70 mg/kg/day
Dog, Beagle	Oral, capsule	9 months	0, 20, 70, 200	Mucous in faeces (all doses), salivation, vomiting, abnormal gait, difficulty standing, rigidity, limb weakness, head shakes, vocalization and hypoactivity at the higher doses. ↓ Body weight (females), ↑ platelet counts, ↑ alkaline phosphatase, ↑ liver weight with reversible hepatocellular hypertrophy, ↑ submaxillary gland weight and acinar hypertrophy at 200 mg/kg/day. ↑ CYP content and microsomal enzyme activities at all doses. NOAEL: 70 mg/kg/day
Dog, Beagle	Oral, capsule	9 months	0, 20, 70, 200 (given as b.i.d.)	Excessive salivation and reddening of the inner ear skin. And ↑ alkaline phosphatase at the higher doses. NOAEL: 200 mg/kg/day

A/G = albumin/globulin; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; BUN = blood urea nitrogen; RBC = red blood cells; SD = Sprague Dawley; NOAEL = no observed adverse effect level.

Reproductive Toxicity

Reproductive toxicology studies demonstrated no adverse effects of pirfenidone on male and female fertility or postnatal development of offspring in rats. Rats exhibited prolongation of the estrus cycle and an increased incidence of irregular cycles at higher doses (≥450 mg/kg/day). Prolonged gestation and reduced fetal viability were observed in rats at high doses (≥1000 mg/kg/day). The placental transfer of pirfenidone and/or its metabolites occurred in animals with the potential for their accumulation in amniotic fluid. Dose-related increases in fetal incidences of soft tissue variations and skeletal variations were observed but were considered related to lower maternal food consumption and body weight. There was no evidence of teratogenicity in rats or rabbits at doses up to 4-fold higher than the clinical dose. Pirfenidone and/or its metabolites were also excreted in milk in lactating rats.

Table 8 Reproductive Toxicity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Rat, SD	Oral, diet	50–69 days: Premating (28 days M and 14 days F) to Gestation Day 20	0, 450, 900	↓ Body weight and food consumption at both dose levels. ↓ Gravid uterine weights and foetal body weights. NOAEL (fertility and foetal development): 900 mg/kg/day.
Rat, SD	Oral, gavage	50–69 days: Premating (28 days M and 14 days F) to Gestation Day 17	0, 50, 150, 450, 1000	Transient hypoactivity, ptosis, limb weakness, abnormal gait, and hypopnea (both sexes) at 150, 450, and 1000 mg/kg/day. Dose-related prolongation of estrus cycle and high incidence of irregular cycles at 450 and 1000 mg/kg/day. NOAEL (reproductive toxicity, males): 1000 mg/kg/day NOAEL (reproductive toxicity, females): 150 mg/kg/day NOAEL (foetal development): 1000 mg/kg/day
Rabbit, Japanese white	Oral, gavage	Gestation Days 6 to 18	0, 30, 100, 300	Transient accelerated respiration, prone position, dilation of auricular blood vessels, sluggish startle reaction, ear drop, scant feces, salivation, and ptosis at 100 and 300 mg/kg/day. ↓ Food consumption and ↓ body weight gain. One animal at 100 mg/kg/day delivered prematurely on Day 28 and two animals aborted (Day 24 and Day 26) and another died (Day 27) at 300 mg/kg/day. NOAEL (reproductive toxicity): 30 mg/kg/day NOAEL (foetal development): 300 mg/kg/day
Rat, SD	Oral, gavage	Gestation Day 7 to Lactation Day 20 (postpartum)	0, 100, 300, 1000	F_0: ↓ activity, respiratory inhibition, salivation, and lacrimation at all doses. Prolongation of gestation period at 1000 mg/kg/day (22.7 days versus 22.2 days in control) and decreased foetal viability. F_1: ↓ Body weights during pre-weaning period at 300 and 1000 mg/kg/day. F_2: no effect on litter size.

SD = Sprague Dawley; NOAEL = no observed adverse effect level.

Genotoxicity and Photogenotoxicity

Pirfenidone showed no genotoxic potential in standard *in vitro* and *in vivo* genotoxicity assays. However, under UV exposure, pirfenidone was positive in a photoclastogenic assay in Chinese hamster lung cells but was not mutagenic in the Ames test. The metabolite 5-carboxy-pirfenidone was not photomutagenic or photoclastogenic in similar assays.

Table 9 Genotoxicity and Photogenotoxicity

Type of Study	Test System	Method of admin.	Doses	Results
Ames	*S. typhimurium*, *E. coli*	*In vitro*	100–5000 µg/plate	Negative
Chromosome Aberration	Chinese hamster ovary cells	*In vitro*	1000–2800 µg/mL (no activation) 500–1400 µg/mL (with activation)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	231–1850 µg/mL (with and without activation) 116–925 µg/mL (without activation, 48 hr exposure)	Negative
Bone marrow micronucleus	Mouse, ICR	Oral, gavage (single dose)	200, 400, 800 mg/kg	Negative
Liver UDS	Rat, F344	Oral, gavage (single dose)	1000, 2000 mg/kg	Negative
Ames	*S typhimurium* strains TA102 and TA98, *E coli* strain WP2/pKM101	*In vitro*	39.1–5000 µg/plate (without activation, with UV exposure)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	560–1900 µg/mL (without activation, in the absence of UV exposure)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	1–120 µg/mL (without activation, with UV exposure)	Positive

UDS = Unscheduled DNA synthesis

Carcinogenicity

In long term studies, an increased incidence of liver tumours (hepatocellular adenoma) was observed in mice (≥800 mg/kg/day) and rats (≥750 mg/kg/day). At a pirfenidone dose of 1500 mg/kg/day (4-fold higher than the clinical dose), a statistically significant increase in uterine adenocarcinoma was observed in female rats. The results of mechanistic studies indicated that the occurrence of uterine tumours may be related to a chronic dopamine-mediated sex hormone imbalance involving a species specific endocrine mechanism in the rat which is not present in humans. The relevance of these findings to humans is unknown.

Table 10 Carcinogenicity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Mouse, $B6C3F_1$	Oral, diet	104 weeks	0, 800, 2000, 5000	↑ Liver tumours at all doses (both sexes): considered to be a rodent species-specific non-genotoxic effect due to hepatic CYP induction.
Rat, F344	Oral, diet	104 weeks	0, 375, 750, 1500	↑ Liver tumours at all doses (both sexes): considered to be rodent species-specific non-genotoxic effect due to hepatic CYP induction. ↑ uterine tumours at 1500 mg/kg/day: considered to be rodent species-specific due to chronic dopamine-mediated sex hormone imbalance.

Phototoxicity

Pirfenidone was phototoxic in guinea pigs and mice inducing transient erythema at doses 4-fold higher than the clinical dose (based on C_{max}). Sunscreens with SPF 50+ prevented pirfenidone induced phototoxicity in guinea pigs.

Table 11 Phototoxicity and Photosensitivity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Guinea pig, Hartley	Oral, gavage / topical	1 day/ 2 weeks	0, 40, 160 (oral); 0%, 1%, 5% (topical)	No phototoxicity or photosensitivity
Guinea pig, Hartley	Oral, gavage	3 days	0, 2.5, 10, 40, 160	Reversible phototoxic effects.
Guinea pig, Hartley	Oral, gavage	Single dose	0, 160	Severity of phototoxic lesions ↓ over time after UV exposure and was minimal at 6 hours post-dose.
Guinea pig, Hartley	Oral, gavage	Single dose	0, 160	Severity of phototoxic lesions ↓ with ↑ grade of sunscreen. SPF 50 cream and SPF 50 lotion decreased the total toxicity score by 100% and 74%, respectively.
Mouse, HR-1 Hairless	Oral, gavage	28 days	0, 500	Local toxicity of skin: mild acanthosis and mild single cell necrosis in the epidermis of the auricle and the dorsal skin. These changes were not apparent after a 1-month recovery period.

UV = ultraviolet; SPF = sun protection factor

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PART III: CONSUMER INFORMATION

PrESBRIET®

pirfenidone capsules

This leaflet is part III of a three-part "Product Monograph" published when ESBRIET® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ESBRIET®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ESBRIET is used for the treatment of idiopathic pulmonary fibrosis (IPF) in adults.

What it does:
How ESBRIET works is not yet fully understood. It may reduce inflammation and fibrosis in your lungs. It may slow down worsening of your IPF.

When it should not be used:
- If you are allergic to pirfenidone or any of the other ingredients in this medicine.
- If you have previously experienced angioedema with pirfenidone, including symptoms such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing.
- If you have severe or end-stage liver disease.
- If you have severe or end-stage kidney disease or you require dialysis.
- If you are taking:
  - fluvoxamine to treat depression and obsessive compulsive disorder (OCD)

  Tell your doctor or pharmacist if you are taking fluvoxamine. A different medication should be prescribed for you before you begin taking ESBRIET.

What the medicinal ingredient is:
Pirfenidone

What the non-medicinal ingredients are:
Ammonium hydroxide, black iron oxide, croscarmellose sodium, gelatin, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, red iron oxide, shellac, titanium dioxide, yellow iron oxide

What dosage form it comes in:
267 mg capsules

What Esbriet looks like and contents of the pack:
Esbriet hard capsules (capsules) have a white opaque body and a white opaque cap with 'PFD 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 or in a bottle.

The 2-week treatment initiation pack contains a total of 63 capsules. There are 7 blister strips with 3 capsules per strip (1 capsule per pocket for Week 1) and 7 blister strips with 6 capsules per strip (2 capsules per pocket for Week 2).

The blisters strips are each marked with the following symbols:

 (sunrise; morning)  (sun; afternoon) and  (moon; evening).

The bottle pack contains 270 capsules.

WARNINGS AND PRECAUTIONS

BEFORE you use ESBRIET talk to your doctor or pharmacist if you:
- Are taking fluvoxamine. Do not take ESBRIET with fluvoxamine.
- Are taking ciprofloxacin. A dose adjustment may be required if you take ciprofloxacin with ESBRIET.
- Are taking any other medications, obtained with or without a prescription, drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.
- Are normally exposed to direct or indirect sunlight.
- Have liver or kidney problems or disease.
- Are pregnant or planning to become pregnant. It is not known whether taking ESBRIET may be harmful to an unborn baby.
- Are breastfeeding or planning to do so. It is not known if ESBRIET passes into breast milk.

Driving and using machines:
Before you perform tasks which may require you to be alert and coordinated, wait until you know how you will respond to ESBRIET. Dizziness and tiredness can occur when you take ESBRIET. Taking ESBRIET with food may decrease dizziness. Be careful when driving or using machines.

Increased sensitivity to sunlight:
You may become more sensitive to sunlight when taking ESBRIET.
You should:
- Avoid (not take) other medicines which may make you more sensitive to sunlight. Ask your pharmacist if you are not sure.
- Avoid or minimize exposure to direct or indirect sunlight, including through windows and from sunlamps.
- Wear an effective sunblock daily (at least SPF 50, against UVA and UVB).
- Wear clothing that protects against sun exposure such as a wide-brimmed hat and long sleeves.
- Seek shade.

ESBRIET can cause weight loss. Your doctor will monitor your weight while you are taking this medicine.

Do not drink grapefruit juice during the time that you are taking ESBRIET. Grapefruit juice may prevent ESBRIET from working properly.

Do not smoke before and during treatment with ESBRIET. Cigarette smoking may reduce the effect of ESBRIET.

INTERACTIONS WITH THIS MEDICATION

Severe Drug Interactions can occur if ESBRIET is taken in combination with some other medications. In particular, do not take ESBRIET with **fluvoxamine.**

If you currently take fluvoxamine, a different medication should be prescribed for you before you begin taking ESBRIET.

Be sure to tell your doctor or pharmacist about **all** the medicines you take (including medicines obtained without a prescription, drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines), especially the medicines listed below.

- Amiodarone, mexiletine or quinidine to treat abnormal heart rhythm
- Bupropion, duloxetine, fluoxetine, moclobemide, or paroxetine to treat depression and/or anxiety
- Carbamazepine or phenytoin to treat seizure
- Cinacalcet to treat parathyroid condition
- Ciprofloxacin to treat bacterial infection
- Esomeprazole or omeprazole to treat heartburn
- Fluconazole, miconazole, terbinafine, or voriconazole to treat fungal infections
- Methoxsalen to treat skin conditions such as psoriasis
- Oral contraceptives (The Pill for birth control)
- Rifampin, a type of antibiotic, to treat bacterial infection

Ask your doctor or pharmacist for advice before taking any medications while you are taking ESBRIET.

PROPER USE OF THIS MEDICATION

ESBRIET should only be prescribed and monitored by physicians with the appropriate training and experience in the diagnosis and treatment of IPF.

Always take ESBRIET exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the capsules:

- Whole
- With a drink of water
- With food or during or after a meal to reduce the risk of side effects such as persistent stomach problems and dizziness (see **Serious Side Effects, How Often They Happen and What to Do About Them**).

Usual adult dose:

ESBRIET is usually prescribed in increasing doses as follows:

- For the first 7 days take 1 capsule 3 times a day with food (a total of 3 capsules a day or 801 mg/day)
- From Day 8 to 14 take 2 capsules, 3 times a day with food (a total of 6 capsules a day or 1602 mg/day)
- From Day 15 onwards, take 3 capsules 3 times a day with food (a total of 9 capsules a day or 2403 mg/day)

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

If a dose is missed, the next capsule(s) should be taken as originally planned. Double doses should not be taken to make up for forgotten capsules or doses. If you miss taking ESBRIET for 14 days in a row or more, you should talk to your doctor. You will need to re-start your ESBRIET therapy in increasing doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- **Increased Sensitivity to Sunlight:** skin reactions after going out in the sun or using sunlamps, sunburn
- Skin problems such as **rash**, itchy skin, skin redness, dry skin
- Tiredness, feeling weak or feeling low in energy
- Indigestion, heartburn, acid reflux, loss of appetite, anorexia, changes in taste, bloating, abdominal pain and discomfort
- Infections of the throat or the airways going into the lungs and/or sinusitis, influenza and/or common cold
- Difficulty sleeping, feeling sleepy
- Headache
- Muscle pain, aching joints/joint pains
- Weight loss

If any of these affects you severely, tell your doctor or pharmacist.

ESBRIET may cause liver problems and other abnormal blood test results. To check whether your liver is working properly and your other blood levels you will need blood tests. Blood tests should be done before you start taking ESBRIET, at monthly intervals for the first 6 months and then every three months while you are taking this medicine. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Common	**Increased Sensitivity to Sunlight:** skin reaction/**rash** to sunlight, blistering and/or marked peeling of the skin	✓		
	Diarrhoea	✓		
	Fatigue	✓		
	Persistent Stomach Problems: such as nausea, vomiting	✓		
Common	**Dizziness**		✓	
Uncommon	**Liver Problems (abnormal blood test results related to your liver):** yellow skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			✓
	Angioedema: swelling of the face, lips and/or tongue, difficulty breathing or wheezing			✓
Rare	**Allergic Reaction: rash,** hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Unknown	**Chest pain (angina),** slow, fast or irregular heart beats			

This is not a complete list of side effects. For any unexpected effects while taking ESBRIET, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store at room temperature (15 – 30°C).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.rochecanada.com
or by contacting the sponsor, Hoffmann-La Roche Limited, at:
1-888-762-4388.

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