ORAL-ESB-2021 01-0

ESBRIET®

Pirfenidone Capsules
Pirfenidone Film-Coated Tablets

1. INDICATIONS AND USAGE

ESBRIET is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

2. DOSAGE AND ADMINISTRATION

2.1. Testing Prior to ESBRIET Administration

Conduct liver function tests prior to initiating treatment with ESBRIET *[see Warnings and Precautions (5.1)]*.

2.2. Recommended Dosage

The recommended daily maintenance dosage of ESBRIET is 801 mg three times daily for a total of 2403 mg/day. Doses should be taken with food at the same time each day.

Upon initiation of treatment, titrate to the full dosage of 2403 mg/day over a 14-day period as follows:

Table 1 Dosage Titration for ESBRIET in Patients with IPF

Treatment days	Dosage
Days 1 through 7	267 mg three times daily (801 mg/day)
Days 8 through 14	534 mg three times daily (1602 mg/day)
Days 15 onward	801 mg three times daily (2403 mg/day)

Dosages above 2403 mg/day are not recommended for any patient [*see Overdosage (9)]*.

2.3. Dosage Modifications due to Adverse Reactions

Patients who miss 14 or more days of ESBRIET should re-initiate treatment by undergoing the initial 2-week titration regimen up to the full maintenance dosage *[see Dosage and Administration (2.2)]*. For treatment interruption of less than 14 days, the dosage prior to the interruption can be resumed.

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 267 mg – 534 mg two to three times a day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for one to two weeks to allow symptoms to resolve.

Photosensitivity reaction or rash

Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun (see section 5.2). 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 5.2). 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.

Dosage Modification due to Elevated Liver Enzymes

If a patient exhibits an aminotransferase elevation >3 to <5 × ULN without bilirubin elevation after starting ESBRIET therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of Esbriet should be reduced or interrupted. Once liver function tests are within normal limits Esbriet may be re-escalated to the recommended daily dose if tolerated.

If a patient exhibits an aminotransferase elevation >3 to <5 × ULN accompanied by hyperbilirubinemia or clinical 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.

2.4. Dosage Modification due to Drug Interactions

Strong CYP1A2 Inhibitors (e.g. fluvoxamine, enoxacin)
Reduce ESBRIET to 267 mg three times a day (801 mg/day).

Moderate CYP1A2 Inhibitors (e.g., ciprofloxacin)
With use of ciprofloxacin at a dosage of 750 mg twice daily, reduce ESBRIET to 534 mg three times a day (1602 mg/day).

3. DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg, white to off-white, hard gelatin capsules of size #1 with white opaque body and white opaque cap. The capsule is imprinted with "PFD 267 mg" in brown ink.

Film-coated tablets: oval, biconvex, debossed with "PFD", containing 267 mg (yellow) and 801 mg (brown) pirfenidone.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Elevated Liver Enzymes

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 post-marketing.

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials 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. Increases in ALT and AST ≥3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to ESBRIET have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury, that could lead to death or the need for liver transplants in some patients.

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 2.1, 2.3 Dosage and Administration*. For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments may be necessary *[see Dosage and Administration (2.1, 2.3)]*.

5.2. Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash *[see Dosage and Administration (2.3)]*.

5.3. Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common (>2%) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions *[see Dosage and Administration (2.3)]*.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Liver Enzyme Elevations *[see Warnings and Precautions (5.1)]*
- Photosensitivity Reaction or Rash *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Disorders *[see Warnings and Precautions (5.3)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

ESBRIET was studied in 3 randomized, double-blind, placebo-controlled trials (Studies 1, 2, and 3) 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.

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. 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.

Table 2 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Esbriet in clinical trials.

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

Table 2 Adverse Reactions Occurring in Patients Treated with Esbriet in Clinical Trials

ADR (MedDRA)	Idiopathic Pulmonary Fibrosis (n = 623)	
Study Duration	52-72 weeks	
System Organ Class	**All grades (%)**	**Frequency Category**
Metabolism and Nutrition Disorders		
Weight decreased	10.1 %	Very common
Decreased appetite	20.7%	Very Common
Psychiatric Disorders		
Insomnia	10.4 %	Very Common
Nervous System Disorders		
Headache	22.0 %	Very Common
Dizziness	18.0 %	Very Common
Dysgeusia	5.8 %	Common
Gastrointestinal Disorders		
Dyspepsia	18.5 %	Very Common
Nausea	36.1 %	Very Common
Diarrhea	25.8 %	Very Common
Abdominal pain	6.3 %	Common
Vomiting	13.3 %	Very Common
Gastro-esophageal reflux disease	11.1 %	Very Common
Hepatobiliary Disorders		
ALT increased	3.2 %	Common
AST increased	2.7 %	Common
Skin and Subcutaneous Disorders		
Photosensitivity reaction	9.3 %	Common
Rash	30.3 %	Very Common
Pruritus	7.9 %	Common
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	10.0 %	Very Common
Respiratory, Thoracic and Mediastinal Disorders		
Upper respiratory tract infections	27 %	Very Common
Sinusitis	11 %	Very Common
General Disorders and Administration Site Conditions		
Fatigue	26.0 %	Very Common
Asthenia	6.4 %	Common
Non-cardiac chest pain	5 %	Common

6.2. Postmarketing Experience

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 are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Table 3: 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.

7. DRUG INTERACTIONS

7.1. CYP1A2 Inhibitors

Pirfenidone is metabolized primarily (70 to 80%) via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6 and 2E1.

Strong CYP1A2 Inhibitors

The concomitant administration of ESBRIET and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to ESBRIET *[see Clinical Pharmacology (11)]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of ESBRIET and avoided during ESBRIET treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of ESBRIET as needed *[see Dosage and Administration (2.4)]*.

Moderate CYP1A2 Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET *[see Clinical Pharmacology (11)]*. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, dosage reductions are recommended *[see Dosage and Administration (2.4)]*. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

Concomitant CYP1A2 and other CYP Inhibitors

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 ESBRIET (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be discontinued prior to and avoided during ESBRIET treatment.

7.2. CYP1A2 Inducers

The concomitant use of ESBRIET and a CYP1A2 inducer may decrease the exposure of ESBRIET and this may lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to ESBRIET treatment and avoid the concomitant use of ESBRIET and a strong CYP1A2 inducer *[see Clinical Pharmacology (11)]*.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Teratogenic Effects: **Pregnancy Category C**.

There are no adequate and well-controlled studies of ESBRIET in pregnant women. Pirfenidone was not teratogenic in rats and rabbits. Because animal reproduction studies are not always predictive of human response, ESBRIET should be used during pregnancy only if the benefit outweighs the risk to the patient.

A fertility and embryo-fetal development study with rats and an embryo-fetal development study with rabbits that received oral doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (on mg/m^2 basis at maternal doses up to 1000 and 300 mg/kg/day, respectively) revealed no evidence of impaired fertility or harm to the fetus due to pirfenidone. In the presence of maternal toxicity, acyclic/irregular cycles (e.g., prolonged estrous cycle) were seen in rats at doses approximately equal to and higher than the MRDD in adults (on a mg/m^2 basis at maternal doses of 450 mg/kg/day and higher). In a pre- and post-natal development study, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dosage approximately 3 times the MRDD in adults (on a mg/m^2 basis at a maternal dose of 1000 mg/kg/day).

8.2. Nursing Mothers

A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. It is not known whether ESBRIET is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ESBRIET, taking into account the importance of the drug to the mother.

8.3. Pediatric Use

Safety and effectiveness of ESBRIET in pediatric patients have not been established.

8.4. Geriatric Use

Of the total number of subjects in the clinical studies receiving ESBRIET, 714 (67%) were 65 years old and over, while 231 (22%) were 75 years old and over. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

8.5. Hepatic Impairment

ESBRIET should be used with caution in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration (2.2)]*.

The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe (Child Pugh Class C) hepatic impairment *[see Clinical Pharmacology (11)]*.

8.6. Renal Impairment

ESBRIET should be used with caution in patients with mild (CL_{cr} 50–80 mL/min), moderate (CL_{cr} 30–50 mL/min), or severe (CL_{cr} less than 30 mL/min) renal impairment *[see Clinical Pharmacology (11)]*. Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed *[see Dosage and Administration (2.3)]*. The safety, efficacy, and pharmacokinetics of ESBRIET have not been studied in patients with end-stage renal disease requiring dialysis. Use of ESBRIET in patients with end-stage renal diseases requiring dialysis is not recommended.

8.7. Smokers

Smoking causes decreased exposure to ESBRIET *[see Clinical Pharmacology (11)]*, which may alter the efficacy profile of ESBRIET. Instruct patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using ESBRIET.

9. OVERDOSAGE

There is limited clinical experience with overdosage. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4806 mg per day were administered as six 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

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

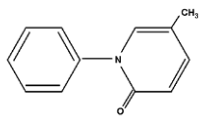
10. DESCRIPTION

ESBRIET belongs to the chemical class of pyridone. ESBRIET is available as a white to off-white hard gelatin capsule containing 267 mg of pirfenidone for oral administration.

ESBRIET is available as film-coated tablets containing 267 mg (yellow) and 801 mg (brown) pirfenidone.

The chemical name of pirfenidone is 5-methyl-1-phenyl-2-1(H)-pyridone. It has a

molecular formula of $C_{12}H_{11}NO$ and a molecular weight of 185.23. The structural formula of pirfenidone is:



Pirfenidone is a white to pale yellow, non-hygroscopic powder. It is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The melting point is approximately 109°C.

ESBRIET capsule contains pirfenidone and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate.

In addition, the capsule shell contains gelatin and titanium dioxide. The capsule brown printing ink includes shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide.

ESBRIET tablets contain pirfenidone and the following inactive ingredients: Microcrystalline cellulose, colloidal anhydrous silica, povidone, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol (polyethylene glycol), talc, and iron oxide.

11. CLINICAL PHARMACOLOGY

11.1. Mechanism of Action

The mechanism of action of pirfenidone in the treatment of IPF has not been established.

11.2. Pharmacodynamics

Cardiac Electrophysiology:

The effect of ESBRIET on QT interval was evaluated in a randomized, placebo, and positive controlled parallel study in 160 healthy adult volunteers. Volunteers received ESBRIET 2403 mg/day (recommended dosage) and 4005 mg/day (1.6 times recommended dose) or placebo for 10 days or a single dose of 400 mg moxifloxacin (active control).

Relative to placebo, the maximum mean change from baseline in study-specific QT interval was 3.2 milliseconds (ms) and 2.2 ms for ESBRIET 2403 mg/day and 4005 mg/day, respectively. No volunteer had a QTc interval greater than 480 ms or change from baseline greater than 60 ms. Although there was no evidence that ESBRIET prolonged the QTc interval in this study, a definitive conclusion may not be drawn as the positive control (moxifloxacin) did not perform as expected in this study, and ESBRIET at 4005 mg/day (1.7 times the maximum recommended dose) did not cover the maximum pirfenidone exposure increase with co-administration of fluvoxamine, a strong CYP1A2 inhibitor.

11.3. Pharmacokinetics

Absorption:

After single oral-dose administration of 801 mg ESBRIET (three 267 mg capsules), the maximum observed plasma concentration (C_{max}) was achieved between 30 minutes and 4 hours (median time of 0.5 hours). Food decrease the rate and extent of absorption. Median T_{max} increased from 0.5 hours to 3 hours with food. Maximum plasma concentrations (C_{max}) and $AUC_{0\text{-}inf}$ decreased by approximately 49% and 16% with food, respectively. A reduced incidence of adverse reactions was observed in the fed group when compared to the fasted group. In controlled studies with IPF patients, ESBRIET was taken with food *[see Dosage and Administration (2) and Clinical Efficacy (13)]*.

Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations.

A reduced incidence of adverse reactions was observed in the fed group when compared to the fasted group. In controlled studies with IPF patients, ESBRIET was taken with food [*see Dosage and Administration (2) and Clinical Efficacy(13)*].

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

Distribution:

ESBRIET binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner over the range of concentrations observed in clinical trials. The overall mean binding was 58% at concentrations observed in clinical studies (1 to 10 µg/mL). Mean apparent oral volume of distribution is approximately 59 to 71 liters.

Metabolism:

In vitro profiling studies in hepatocytes and liver microsomes have shown that ESBRIET is primarily metabolized in the liver by CYP1A2 and multiple other CYPs (CYP2C9, 2C19, 2D6, and 2E1). Oral administration of ESBRIET results in the formation of four metabolites. In humans, only pirfenidone and 5-carboxy-pirfenidone are present in plasma in significant quantities. The mean metabolite-to-parent ratio ranged from approximately 0.6 to 0.7.

No formal radiolabeled studies have assessed the metabolism of pirfenidone in humans. *In vitro* data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination:

The mean terminal half-life is approximately 3 hours in healthy subjects. Pirfenidone is excreted predominantly as metabolite 5-carboxy-pirfenidone, mainly in the urine (approximately 80% of the dose). The majority of ESBRIET was excreted as the 5-carboxy metabolite (approximately 99.6% of that recovered).

Specific Populations:

Hepatic Impairment

The pharmacokinetics of ESBRIET and the 5-carboxy-pirfenidone metabolite were studied in 12 subjects with moderate hepatic impairment (Child Pugh Class B) and in 12 subjects with normal hepatic function. Results showed that the mean exposure, $AUC_{0\text{-}inf}$ and C_{max} of pirfenidone increased approximately 1.6- and approximately 1.4-fold in subjects with moderate hepatic impairment, respectively. The exposure of 5-carboxy-pirfenidone did not change significantly in subjects with moderate hepatic impairment.

Renal Impairment

No clinically relevant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild to severe renal impairment compared with subjects with normal renal function. The parent drug is predominantly metabolized to 5-carboxy-pirfenidone, for which pharmacodynamics and safety margins were not established. The AUC0-∞ of 5-carboxy-pirfenidone was significantly higher in the moderate ($p = 0.009$) and severe ($p < 0.0001$) renal impairment groups than in the group with normal renal function. The predicted amount of metabolite accumulation at steady state is not pharmacodynamically important because the terminal elimination half-life is only 1–2 hours in these subjects and there is no or minimal pharmacologic activity of the metabolite as measured by TNF inhibitory effects.

The pharmacokinetics and safety of ESBRIET has not been studied in patients with end-stage renal disease requiring dialysis and is not recommended in these patients.

Geriatric

Results of population pharmacokinetic analysis suggest that no dosage adjustment is needed in geriatric patients.

Gender

Results of population pharmacokinetic analysis of ESBRIET showed no significant differences in pharmacokinetics between males and females.

Obesity

Results of population pharmacokinetic analysis showed that obesity (Body Mass Index [BMI] greater than or equal to 30 kg/m^2) has no significant effect on the pharmacokinetics of ESBRIET.

Race

Population pharmacokinetic analysis showed that race has no significant effect on the pharmacokinetics of pirfenidone.

Drug Interaction Studies:

Cytochrome P450 1A2 Inhibitors

Pirfenidone is a substrate of cytochrome P450 1A2. In a single-dose drug interaction study in 25 healthy nonsmokers and 25 smokers, ESBRIET was coadministered with fluvoxamine (50 mg at bedtime for 3 days; 50 mg twice a day for 3 days, and 50 mg in the morning and 100 mg at bedtime for 4 days). An approximately 4-fold increase in exposure to pirfenidone in nonsmokers and approximately 7-fold increase in exposure in smokers was observed.

In a single-dose drug interaction study in 27 healthy subjects, coadministration of 801 mg of ESBRIET and 750 mg of ciprofloxacin (a moderate inhibitor of CYP1A2) on Day 6 (ciprofloxacin was dosed at 750 mg twice daily from Day 2 to Day 7) increased the exposure to pirfenidone by 81%.

Cytochrome P450 1A2 Inducers

Following a single oral dose of 801 mg ESBRIET in 25 smokers and 25 healthy nonsmokers, the systemic exposure in smokers was significantly lower compared to nonsmokers. $AUC_{0\text{-}inf}$ and C_{max} of pirfenidone in smokers were 46% and 68% of those in nonsmokers, respectively.

Inhibitory Effect of Pirfenidone on P-glycoprotein (Pgp)

The potential for pirfenidone to inhibit Pgp mediated transport of digoxin (5.0 µM) was evaluated in the absence and presence of pirfenidone at concentrations ranging from 1 to 1000 µM in *in vitro* system. Pirfenidone showed weak inhibition (10 to 30%) of Pgp facilitated digoxin B-A efflux at concentrations of 100 µM and above. Effect of pirfenidone upon Pgp substrate pharmacokinetics and safety has not been evaluated in humans.

Inhibitory Effect of Pirfenidone on CYP2C9, 2C19 or 1A2, 2D6, 3A4

The potential for pirfenidone to inhibit CYP2C9, 2C19 or 1A2 was evaluated *in vitro* at concentrations up to 1000 µM (approximately 10-fold the mean human C_{max}). Pirfenidone showed a concentration-dependent inhibition on CYP2C9, 2C19 or 1A2, 2D6, and 3A4. At 1000 µM, pirfenidone inhibits the activity of these enzymes by 30.4%, 27.5%, 34.1%, 21%, and 9.6%, respectively. Effect of pirfenidone upon pharmacokinetics and safety of CYP2C9, 2C19, 1A2, 2D6, and 3A4 substrates has not been evaluated in humans.

12. NONCLINICAL TOXICOLOGY

12.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies were conducted in mice and rats with admixture of pirfenidone to the diet to evaluate its carcinogenic potential.

In a 24-month carcinogenicity study in B6C3F1 mice, pirfenidone caused statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma and hepatoblastoma in male mice at doses of 800 mg/kg and above (AUC exposure approximately 0.4 times adult exposure at the MRDD). There were statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma in female mice at doses of 2000 mg/kg and above (AUC exposure approximately 0.7 times adult exposure at the MRDD).

In a 24-month carcinogenicity study in Fischer rats, pirfenidone caused statistically significant dose-related increases of the combination of hepatocellular adenoma and carcinoma in male rats at doses of 750 mg/kg and above (AUC exposure approximately 1.9 times adult exposure at the MRDD). There were statistically significant increases of the combination of hepatocellular adenoma and carcinoma and the combination of uterine adenocarcinoma and adenoma at a dose of 1500 mg/kg/day (AUC exposure approximately 3.0 times adult exposure at the MRDD).

The relevance of these tumor findings in rodents to humans is unknown.

Mutagenesis

Pirfenidone was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacteria, a chromosomal aberration test in Chinese hamster lung cells, and a micronucleus test in mice.

Impairment of Fertility

Pirfenidone had no effects on fertility and reproductive performance in rats at dosages up to 1000 mg/kg/day (approximately 3 times the MRDD in adults on a mg/m^2 basis).

13. CLINICAL EFFICACY

The clinical efficacy of Esbriet has been studied in three multinational, Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with IPF. Three of the Phase 3 studies (PIPF-004, PIPF-006, and PIPF-016) were multinational, and one (SP3) was conducted in Japan.

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

In study PIPF-004, the decline in percent predicted FVC from Baseline at Week 72 of treatment was significantly reduced in patients receiving Esbriet (N = 174) compared with patients receiving placebo (N = 174; $p = 0.001$, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent predicted FVC from Baseline at Weeks 24 ($p = 0.014$), 36 ($p < 0.001$), 48 ($p < 0.001$), and 60 ($p < 0.001$). At Week 72, a decline from Baseline in percent predicted FVC of ≥ 10% (a threshold indicative of the risk of mortality in IPF) was seen in 20% of patients receiving Esbriet compared to 35% receiving placebo (Table 4).

Table 4 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 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).

Table 5 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 a total of 555 patients, the median baseline percent predicted FVC and %DLCO were 68% (range: 48–91%) and 42% (range: 27–170%), respectively. Two percent of patients had percent predicted FVC below 50% and 21% of patients had a percent predicted DLCO below 35% at Baseline.

In study PIPF-016, the decline in percent predicted FVC from Baseline at Week 52 of treatment was significantly reduced in patients receiving Esbriet (N = 278) compared with patients receiving placebo (N = 277; $p < 0.000001$, rank ANCOVA). Treatment with Esbriet also significantly reduced the decline in percent predicted FVC from Baseline at Weeks 13 ($p < 0.000001$), 26 ($p < 0.000001$), and 39 ($p = 0.000002$). At Week 52, a decline from Baseline in percent predicted FVC of ≥ 10% or death was seen in 17% of patients receiving Esbriet compared to 32% receiving placebo (Table 6).

Table 6 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).

The study (SP3) in Japanese patients compared pirfenidone 1800 mg/day (comparable to 2403 mg/day in the US and European populations of PIPF-004/006 on a weight-normalised basis) with placebo (N=110, N=109, respectively). Treatment with pirfenidone significantly reduced mean decline in vital capacity (VC) at Week 52 (the primary endpoint) compared with placebo (-0.09±0.02 l versus -0.16±0.02 l respectively, p=0.042).

14. HOW SUPPLIED/STORAGE AND HANDLING

Do not store above 30°C.

Keep the bottle tightly closed. Do not use if the seal over the bottle opening is broken or missing.

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

15. SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Disposal of unused/expired medicines

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

16. NATURE AND CONTENTS OF CONTAINER

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

PACK SIZES

267 mg capsules

1 bottle containing 270 capsules

267 mg film-coated tablets

1 bottle containing 90 film-coated tablets

801 mg film-coated tablets

1 bottle containing 90 film-coated tablets

Medicine: Keep out of reach of children

Current at Jan 2021

F. Hoffmann-La Roche Ltd, Basel, Switzerland