

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022535Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ESBRIET safely and effectively. See full prescribing information for ESBRIET.

ESBRIET® (pirfenidone) capsules, for oral use

Initial U.S. Approval: 2014

INDICATIONS AND USAGE

ESBRIET is a pyridone indicated for the treatment of idiopathic pulmonary fibrosis (IPF). (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 801 mg (three capsules) three times daily taken with food. (2)
- Upon initiation of treatment, the daily dosage should be titrated to the full dosage of nine capsules per day over a 14-day period as follows:

Treatment days	Dosage
Days 1 through 7	1 capsule three times a day with meals
Days 8 through 14	2 capsules three times a day with meals
Days 15 onward	3 capsules three times a day with meals

- Consider temporary dosage reduction, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.1, 5.2, 5.3)
- Prior to treatment, conduct liver function tests. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Elevated liver enzymes: ALT, AST, and bilirubin elevations have occurred with ESBRIET. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reductions or discontinuations may be required. (2.1, 5.1)
- Photosensitivity and rash: Photosensitivity and rash have been noted with ESBRIET. Avoid exposure to sunlight and sunlamps. Wear sunscreen and

protective clothing daily. Temporary dosage reductions or discontinuations may be required. (5.2)

- Gastrointestinal disorders: Nausea, vomiting, diarrhea, dyspepsia, gastro-esophageal reflux disease, and abdominal pain have occurred with ESBRIET. Temporary dosage reductions or discontinuations may be required. (5.3)

ADVERSE REACTIONS

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact InterMune at 1-888-486-6411 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g., fluvoxamine) increase systemic exposure of ESBRIET and may alter the adverse reaction profile of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET or reduce to one capsule three times a day. Consider dosage reduction with use of ciprofloxacin. (7.1)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with severe hepatic impairment. (8.6, 12.3)
- Renal Impairment: Monitor for adverse reactions and consider dosage modification or discontinuation of ESBRIET as needed. ESBRIET is not recommended for use in patients with end stage renal disease on dialysis. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of ESBRIET. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October/2014

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FULL PRESCRIBING INFORMATION

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 267 mg capsules) three times a day with food for a total of 2403 mg/day. Doses should be taken at the same time each day.

Upon initiation of treatment, titrate to the full dosage of nine capsules per 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	1 capsule three times a day with food
Days 8 through 14	2 capsules three times a day with food
Days 15 onward	3 capsules three times a day with food

Dosages above 2403 mg/day (9 capsules per day) are not recommended for any patient.

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.

If patients experience significant adverse reactions (i.e., gastrointestinal, photosensitivity reaction or rash), consider temporary dosage reductions or interruptions of ESBRIET to allow for resolution of symptoms *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Dosage Modification due to Elevated Liver Enzymes

Dosage modifications or interruptions may also be necessary when liver enzyme and bilirubin elevations are exhibited. For liver enzyme elevations, modify the dosage as follows:

If a patient exhibits >3 but $\leq 5 \times$ the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting ESBRIET therapy:

- Discontinue confounding medications, exclude other causes, and monitor the patient closely.
- Repeat liver chemistry tests as clinically indicated.
- The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re-titration to the full dosage as tolerated.

If a patient exhibits >3 but $\leq 5 \times$ ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

If a patient exhibits $>5 \times$ ULN ALT and/or AST:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

2.4 Dosage Modification due to Drug Interactions

Strong CYP1A2 Inhibitors (e.g., fluvoxamine, enoxacin)

Reduce ESBRIET to one capsule three times a day.

Moderate CYP1A2 Inhibitors (e.g., ciprofloxacin)

With use of ciprofloxacin at a dosage of 750 mg twice daily, reduce ESBRIET to two capsules three times a day.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 267 mg, white, hard gelatin capsules printed with “InterMune[®]” and “267 mg” on the cap of the capsule in brown ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Enzymes

Increases in ALT and AST $>3 \times$ ULN have been reported in patients treated with ESBRIET. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with ESBRIET 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST $\geq 3 \times$ ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations $\geq 10 \times$ 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 $\geq 3 \times$ 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. Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with ESBRIET in all patients, then monthly for the first 6 months and every 3 months thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations [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.

The most common adverse reactions with an incidence of $\geq 10\%$ and more frequent in the ESBRIET than placebo treatment group are listed in Table 2.

Table 2. Adverse Reactions Occurring in $\geq 10\%$ of ESBRIET-Treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	% of Patients (0 to 118 Weeks)	
	ESBRIET 2403 mg/day (N = 623)	Placebo (N = 624)
Nausea	36%	16%
Rash	30%	10%
Abdominal Pain ¹	24%	15%
Upper Respiratory Tract Infection	27%	25%
Diarrhea	26%	20%
Fatigue	26%	19%
Headache	22%	19%
Dyspepsia	19%	7%
Dizziness	18%	11%
Vomiting	13%	6%
Anorexia	13%	5%
Gastro-esophageal Reflux Disease	11%	7%
Sinusitis	11%	10%
Insomnia	10%	7%
Weight Decreased	10%	5%
Arthralgia	10%	7%

¹ Includes abdominal pain, upper abdominal pain, abdominal distension, and stomach discomfort.

Adverse reactions occurring in ≥ 5 to $< 10\%$ of ESBRIET-treated patients and more commonly than placebo are photosensitivity reaction (9% vs. 1%), decreased appetite (8% vs. 3%), pruritus (8% vs. 5%), asthenia (6% vs. 4%), dysgeusia (6% vs. 2%), and non-cardiac chest pain (5% vs. 4%).

6.2 Postmarketing Experience

In addition to adverse reactions identified from clinical trials the following adverse reactions have been identified during postapproval 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.

Blood and Lymphatic System Disorders

Agranulocytosis

Immune System Disorders

Angioedema

Hepatobiliary Disorders

Bilirubin increased in combination with increases of ALT and AST

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 CYP1A 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 (12.3)*]. 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 CYP1A Inhibitors

Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET [see *Clinical Pharmacology (12.3)*]. 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 (12.3)*].

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/m² 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/m² 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/m² basis at a maternal dose of 1000 mg/kg/day).

8.3 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.

8.4 Pediatric Use

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

8.5 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.

8.6 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 (12.3)*].

8.7 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 (12.3)*]. 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.

8.8 Smokers

Smoking causes decreased exposure to ESBRIET [see *Clinical Pharmacology (12.3)*], 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.

10 OVERDOSAGE

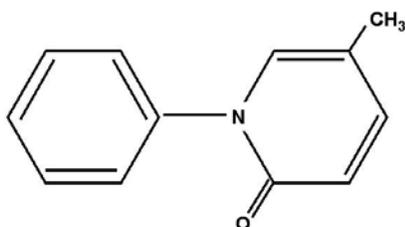
There is limited clinical experience with overdose. Multiple dosages of ESBRIET up to a maximum tolerated dose of 4005 mg per day were administered as five 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation.

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

11 DESCRIPTION

Each ESBRIET capsule contains 267 mg of pirfenidone, which belongs to the chemical class of pyridone. ESBRIET is available as a white hard gelatin capsule for oral administration.

The chemical name of pirfenidone is 5-methyl-1-phenyl-2-1(H)-pyridone. It has a molecular formula of C₁₂H₁₁NO 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 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 dose) 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.

12.3 Pharmacokinetics

Absorption:

After single oral-dose administration of 801 mg ESBRIET, 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 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 Studies (14)*].

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 $\mu\text{g/mL}$). 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

The pharmacokinetics of pirfenidone and the 5-carboxy-pirfenidone metabolite were studied in 18 subjects with mild (CL_{cr} 50 to 80 mL/min), moderate (CL_{cr} 30 to 50 mL/min), and severe (CL_{cr} less than 30 mL/min) renal impairment (n=6/group) and in 6 subjects with normal CL_{cr} (greater than or equal to 80 mL/min) renal function. Results showed that systemic exposure (AUC_{0-inf}) to pirfenidone increased approximately 1.4, 1.5, and 1.2-fold in subjects with mild, moderate and severe renal impairment, respectively. The corresponding AUC_{0-inf} of 5-carboxy-pirfenidone increased 1.7, 3.4, and 5.6-fold, although the change in the patients with mild renal impairment was not statistically significant. The renal clearance of 5-carboxy-pirfenidone decreased significantly in patients with moderate to severe renal impairment.

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

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/m²) 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-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 μ M) was evaluated in the absence and presence of pirfenidone at concentrations ranging from 1 to 1000 μ M in *in vitro* system. Pirfenidone showed weak inhibition (10 to 30%) of Pgp facilitated digoxin B-A efflux at concentrations of 100 μ M 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 μ M (approximately 10-fold the mean human C_{max}). Pirfenidone showed a concentration-dependent inhibition on CYP2C9, 2C19 or 1A2, 2D6, and 3A4. At 1000 μ M, 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.

13 NONCLINICAL TOXICOLOGY

13.1 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/m² basis).

14 CLINICAL STUDIES

The efficacy of ESBRIET was evaluated in patients with IPF in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials (Studies 1, 2, and 3).

Study 1 was a 52-week trial comparing ESBRIET 2403 mg/day (n=278) versus placebo (n=277) in patients with IPF. Study 2 and Study 3 were nearly identical to each other in design, with few exceptions, including an intermediate dose treatment arm in Study 2. Study 2 compared treatment with either ESBRIET 2403 mg/day (n=174) or ESBRIET 1197 mg/day (n=87) to placebo (n=174), while Study 3 compared ESBRIET 2403 mg/day (n=171) to placebo (n=173). Study drug was administered three times daily with food for a minimum of 72 weeks. Patients continued on treatment until the last patient completed 72 weeks of treatment, which included observations to approximately 120 weeks of study treatment. The primary endpoint was the change in percent predicted forced vital capacity (%FVC) from baseline to study end, measured at 52 weeks in Study 1, and at 72 weeks in Studies 2 and 3.

Studies 1, 2 and 3 enrolled adult patients who had a clinical and radiographic diagnosis of IPF (with or without accompanying surgical lung biopsy), without evidence or suspicion of an alternative diagnosis for interstitial lung disease. Eligible patients were to have %FVC greater than or equal to 50% at baseline and a percent predicted diffusing capacity of the lungs for carbon monoxide (%DL_{CO}) greater than or equal to 30% (Study 1) or 35% (Studies 2 and 3) at baseline. In all three trials, over 80% of patients completed study treatment.

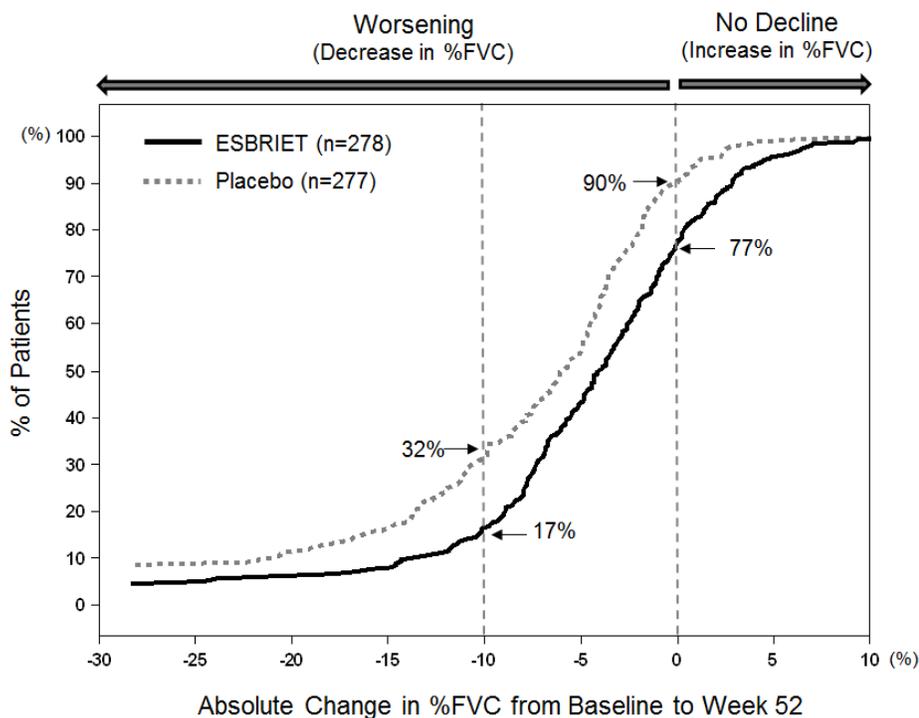
A total of 1247 patients with IPF were randomized to receive ESBRIET 2403 mg/day (n=623) or placebo (n=624) in these three trials. Baseline characteristics were generally balanced across treatment groups. The study population ranged from 40 to 80 years of age (mean age 67 years). Most patients were male (74%), white (95%), and current or former smokers (65%). Approximately 93% of patients met criteria for definite IPF on high resolution computed tomography (HRCT). Baseline mean %FVC and %DL_{CO} were 72% and 46%, respectively. Approximately 15% subjects discontinued from each treatment group.

Change from Baseline in Percent Predicted Forced Vital Capacity

In Study 1, the primary efficacy analysis for the change in %FVC from baseline to Week 52 demonstrated a statistically significant treatment effect of ESBRIET 2403 mg/day (n=278) compared with placebo (n=277) using a rank ANCOVA with the lowest rank imputation for missing data due to death. In Study 2, there was a statistically significant difference at Week 72 for the change in %FVC from baseline. In Study 3, there was no statistically significant difference at Week 72 for the change in %FVC from baseline.

Figure 1 presents the cumulative distribution for all cut-offs for the change from baseline in %FVC at Week 52 for Study 1. For all categorical declines in lung function, the proportion of patients declining was lower on ESBRIET than on placebo. Study 2 showed similar results.

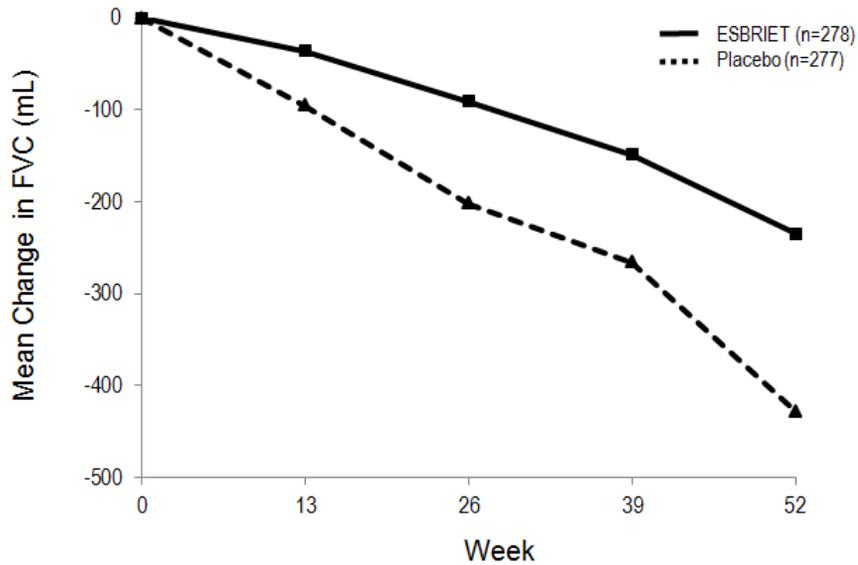
Figure 1. Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 (Study 1). The Dashed Lines Indicate $\geq 10\%$ Decline or $\geq 0\%$ Decline.



Mean Change from Baseline in FVC (mL)

In Study 1, a reduction in the mean decline in FVC (in mL) was observed in patients receiving ESBRIET 2403 mg/day (-235 mL) compared to placebo (-428 mL) (mean treatment difference 193 mL) at Week 52 (see Figure 2). In Study 2, a reduction in the decline in FVC volume was also observed in patients receiving ESBRIET 2403 mg/day compared with placebo (mean treatment difference 157 mL) at Week 72. There was no statistically significant difference in decline in FVC volume seen in Study 3.

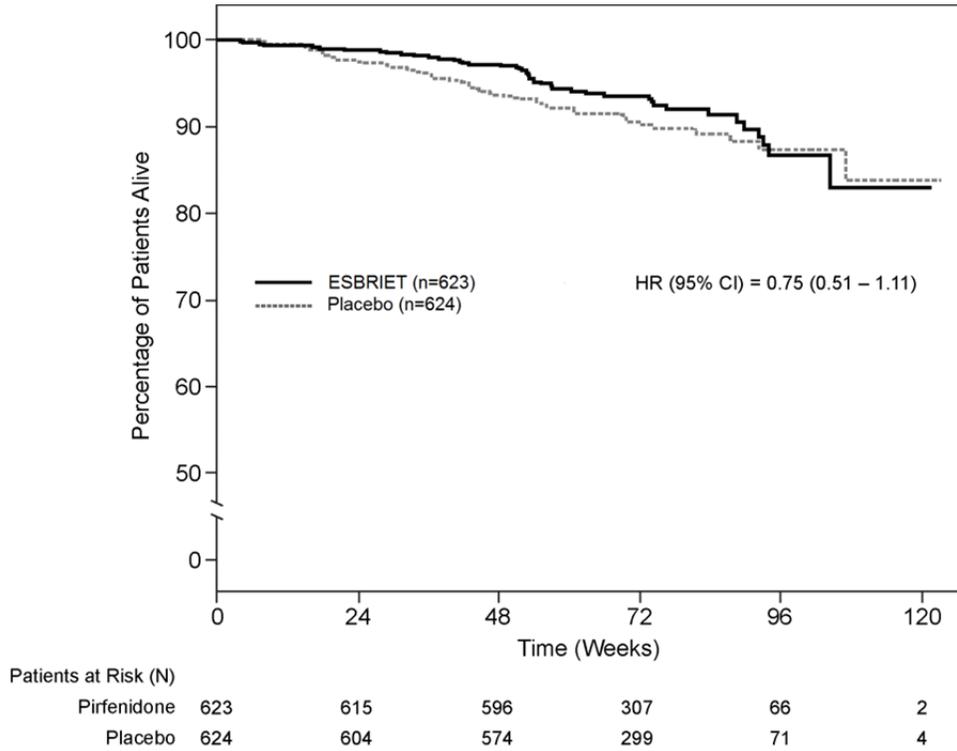
Figure 2. Mean Change from Baseline in Forced Vital Capacity (Study 1)



Survival

Survival was evaluated for ESBRIET compared to placebo in Studies 1, 2, and 3 as an exploratory analysis to support the primary endpoint (FVC). All-cause mortality was assessed over the study duration and available follow-up period, irrespective of cause of death and whether patients continued treatment. All-cause mortality did not show a statistically significant difference (see Figure 3).

Figure 3. Kaplan-Meier Estimates of All-Cause Mortality at Vital Status – End of Study: Studies 1, 2, and 3



16 HOW SUPPLIED/STORAGE AND HANDLING

ESBRIET is a white hard gelatin capsule; each capsule contains 267 mg of pirfenidone. The cap of the capsule is printed with “InterMune[®]” and “267 mg” in brown ink. The capsule is supplied either in a bottle, a 14-day titration blister pack or a 4-week maintenance blister pack.

Bottle for a 30-day supply	Bottle containing 270 capsules and closed with a child-resistant closure	NDC 64116-121-01
14-day Titration Blister Pack	Carton containing a total of 63 capsules in two blister cards – a Week 1 blister card containing 21 capsules (1 capsule per blister well) and a Week 2 blister card containing 42 capsules (2 capsules per blister well)	NDC 64116-121-02
4-Week Maintenance Blister Pack	Carton containing a total of 252 capsules in four blister cards each with 63 capsules (3 capsules per blister well)	NDC 64116-121-03

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Liver Enzyme Elevations

Advise patients that they may be required to undergo liver function testing periodically. Instruct patients to immediately report any symptoms of a liver problem (e.g., skin or the white of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleed or bruise more easily than normal, lethargy) [*see Warnings and Precautions (5.1)*].

Photosensitivity Reaction or Rash

Advise patients to avoid or minimize exposure to sunlight (including sunlamps) during use of ESBRIET because of concern for photosensitivity reactions or rash. Instruct patients to use a sunblock and to wear clothing that protects against sun exposure. Instruct patients to report symptoms of photosensitivity reaction or rash to their physician. Temporary dosage reductions or discontinuations may be required [*see Warnings and Precautions (5.2)*].

Gastrointestinal Events

Instruct patients to report symptoms of persistent gastrointestinal effects including nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain. Temporary dosage reductions or discontinuations may be required [*see Warnings and Precautions (5.3)*].

Smokers

Encourage patients to stop smoking prior to treatment with ESBRIET and to avoid smoking when using with ESBRIET [*see Clinical Pharmacology (12.3)*].

Take with Food

Instruct patients to take ESBRIET with food to help decrease nausea and dizziness.

Manufactured for:
InterMune, Inc.
Brisbane, CA 94005

ESBRIET is a registered U.S. trademark of InterMune, Inc.
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2014XXXX-PFD-US-EN.00

Patient Information
ESBRIET® (es-BREE-et)
(pirfenidone)
capsules

Read this Patient Information before you start taking ESBRIET and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is ESBRIET?

ESBRIET is a prescription medicine used to treat people with a lung disease called idiopathic pulmonary fibrosis (IPF).

What should I tell my doctor before taking ESBRIET?
Before you take ESBRIET, tell your doctor if you:

- have liver problems
 - have kidney problems
 - are a smoker
 - have any other medical conditions
 - are pregnant or plan to become pregnant. It is not known if ESBRIET will harm your unborn baby.
 - are breastfeeding or plan to breastfeed. It is not known if ESBRIET passes into your breast milk. You and your doctor should decide if you will take ESBRIET or breastfeed.
- Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take ESBRIET?

- Take ESBRIET exactly as your doctor tells you to take it.
- Your doctor may change your dosage of ESBRIET as needed.
- Take ESBRIET with food. This may help to decrease nausea and dizziness.
 - Take 1 ESBRIET capsule 3 times each day for days 1 through 7.
 - Take 2 ESBRIET capsules 3 times each day for days 8 through 14.
 - Take 3 ESBRIET capsules 3 times each day on day 15 and each day after.

ESBRIET Dosing Schedule				
Week	Morning (Breakfast)	Afternoon (Lunch)	Evening (Dinner)	Total Pills Each Day
Days 1-7	1	1	1	3
Days 8-14	2	2	2	6
Days 15 onward	3	3	3	9

- If you miss a dose of ESBRIET take your next dose as soon as you remember.
- **Do not** take 2 doses at the same time to make up for your missed dose.
- **Do not** take more than 3 doses each day.
- If you take too much ESBRIET, call your doctor or go to the nearest hospital emergency room right away.
- Your doctor should do certain blood tests before you start taking ESBRIET.

What should I avoid while taking ESBRIET?

- Avoid sunlight. ESBRIET can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You could get a severe sunburn. Use sunscreen (SPF50) and wear a hat and clothes that cover your skin if you have to be in sunlight. Talk to your doctor if you get sunburn.
- Avoid smoking. Smoking may affect how well ESBRIET works.

What are the possible side effects of ESBRIET?**ESBRIET may cause serious side effects, including:**

- **liver problems.** Call your doctor right away if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea colored) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, feeling tired.

Your doctor will do blood tests to check how your liver is working during your treatment with ESBRIET.

- **sensitivity to sunlight (photosensitivity) and rash.** See “What should I avoid while taking ESBRIET?”
- **stomach problems.** ESBRIET may cause stomach problems such as nausea, vomiting, diarrhea, indigestion, heartburn, and stomach pain. Tell your doctor right away if your stomach problems get worse or do not go away. Your doctor may need to change your dose of ESBRIET.

The most common side effects of ESBRIET include feeling tired, headache, dizziness and decreased or loss of appetite.

These are not all the possible side effects of ESBRIET. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ESBRIET?

- Store ESBRIET at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep in a tightly closed container.
- Safely throw away any ESBRIET that is out of date or no longer needed.

Keep ESBRIET and all medicines out of reach of children.

General information about the safe and effective use of ESBRIET.

- Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This Patient Information leaflet summarizes the most important information about ESBRIET. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about ESBRIET that is written for health professionals.
- For more information, go to www.ESBRIET.com or call 1-888-486-6411.

What are the ingredients in ESBRIET?

Active ingredient: pirfenidone

Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, and magnesium stearate

Capsule Shell: gelatin and titanium dioxide

Capsule Brown Printing Ink: shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide

Issued: October 2014

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This Patient Information has been approved by the U.S. Food and Drug Administration



(b) (4)

BAR CODE

Serialization bar code
FPO

Exp:

Lot:

CA05100-01A-00

Esbriet[®]
(pirfenidone)
capsules, 267 mg

NDC 641 16-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

Keep out of reach of children.

Rx ONLY
270 CAPSULES

INTERMUNE[®] **Esbriet**[®]

Each capsule contains:
pirfenidone, 267mg

Dosage: See package insert for
dosage and administration
information.

Store at 25°C (77°F); excursions
permitted to 15°-30°C (59°-86°F) (see
USP Controlled Room Temperature)

Manufactured for:
InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005



NDC 641 16-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

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Room Temperature)

Manufactured for:
InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005

INTERMUNE[®] **Esbriet**[®]

PRO509901A.00

Lot:

Exp:

(b) (4)

NDC 64116-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

Bar Code
Serialization Here?

14-Day Titration Pack

Keep out of reach of children.



Rx ONLY

NDC 64116-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

Titration Pack for your first 2 weeks of therapy only

DOSING INSTRUCTIONS

Week 1: One capsule, three times a day
Week 2: Two capsules three times a day.

14 Day Titration Pack Contents:
Week 1 Dosing contains 21 capsules
Week 2 Dosing contains 42 capsules
Each capsule contains:
pirfenidone, 267 mg

DOSAGE: See package insert for dosage and administration information. Package insert located inside pouch.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) (see USP Controlled Room Temperature)

Keep out of reach of children.



Package insert
inside pouch

Esbriet[®] (pirfenidone)
14-Day Titration Pack



OPENING INSTRUCTIONS
Press & Hold **1**
Pull to slide blister card out **2**



Rx ONLY
14-Day Titration Pack

Esbriet[®] (pirfenidone) capsules, 267 mg



14-Day Titration Pack

Manufactured for:
InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005

BAR CODE

C40510201A.00
Lot:
Exp:

Esbriet[®] (pirfenidone) capsules, 267 mg
14-Day Titration Pack



Lift Here

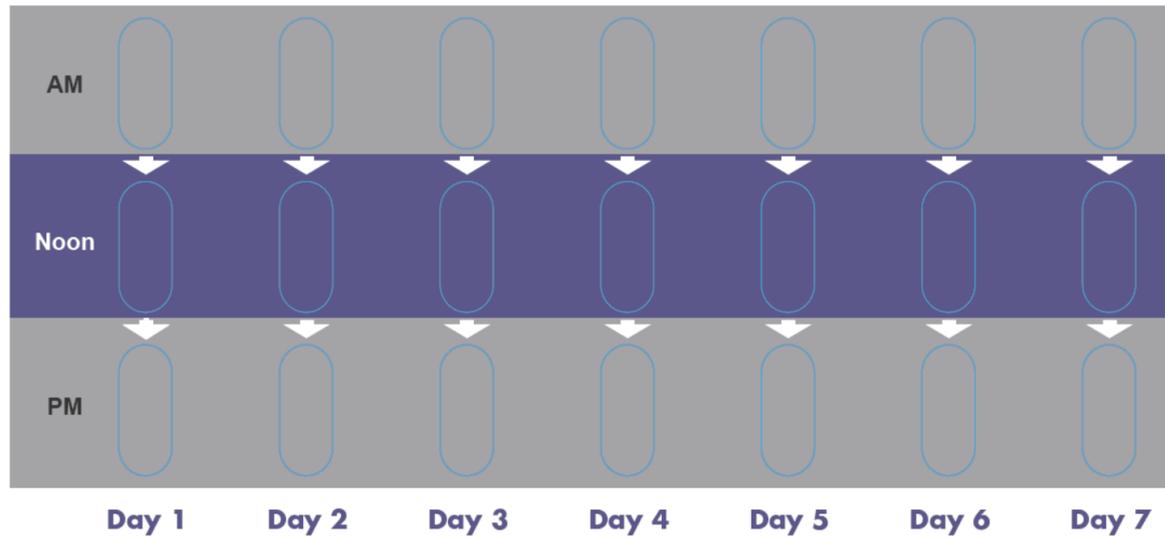
← Pull

Esbriet® (pifenedone)

14 Day Titration Pack

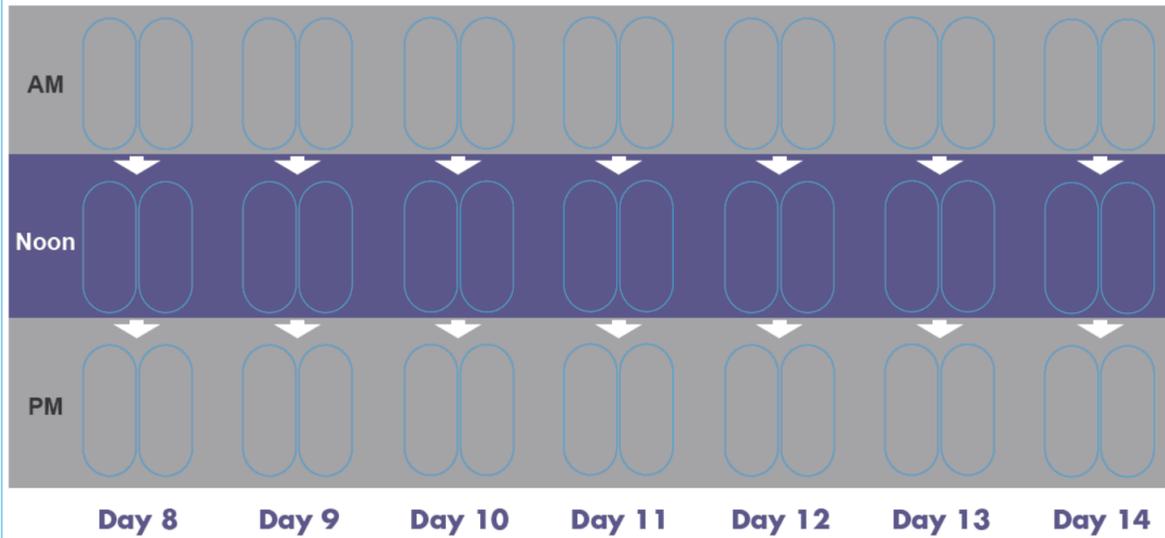
Esbriet® (pifenedone) capsules, 267 mg

W E E K 1 D O S I N G



Esbriet® (pifenedone) capsules, 267 mg

W E E K 2 D O S I N G



Esbriet® (pifenedone) capsules, 267 mg

CA05101-01A.00

PS

(b) (4)

NDC 64116-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

Keep out of reach of children.

INTERMUNE[®] **Esbriet**[®]

Rx ONLY
Weekly Pack

Lift

NDC 64116-XXX-XX

Esbriet[®]
(pirfenidone)
capsules, 267 mg

Maintenance Pack

Each Weekly Pack contains 63 capsules
Each capsule contains: pirfenidone, 267 mg

DOSAGE: See package insert for dosage and administration information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) (see USP Controlled Room Temperature)

INTERMUNE[®] **Esbriet**[®]

Keep out of reach of children.

Esbriet[®] (pirfenidone)

Weekly pack

1
Press Here & Hold Down

OPENING INSTRUCTIONS
Press & Hold **1**
Pull to slide blister card out **2**

Slide blister card out

Rx ONLY
Weekly Pack

Esbriet[®] (pirfenidone) capsules, 267 mg

Here

Weekly Pack

BAR CODE

CA0510401A00

Lot:

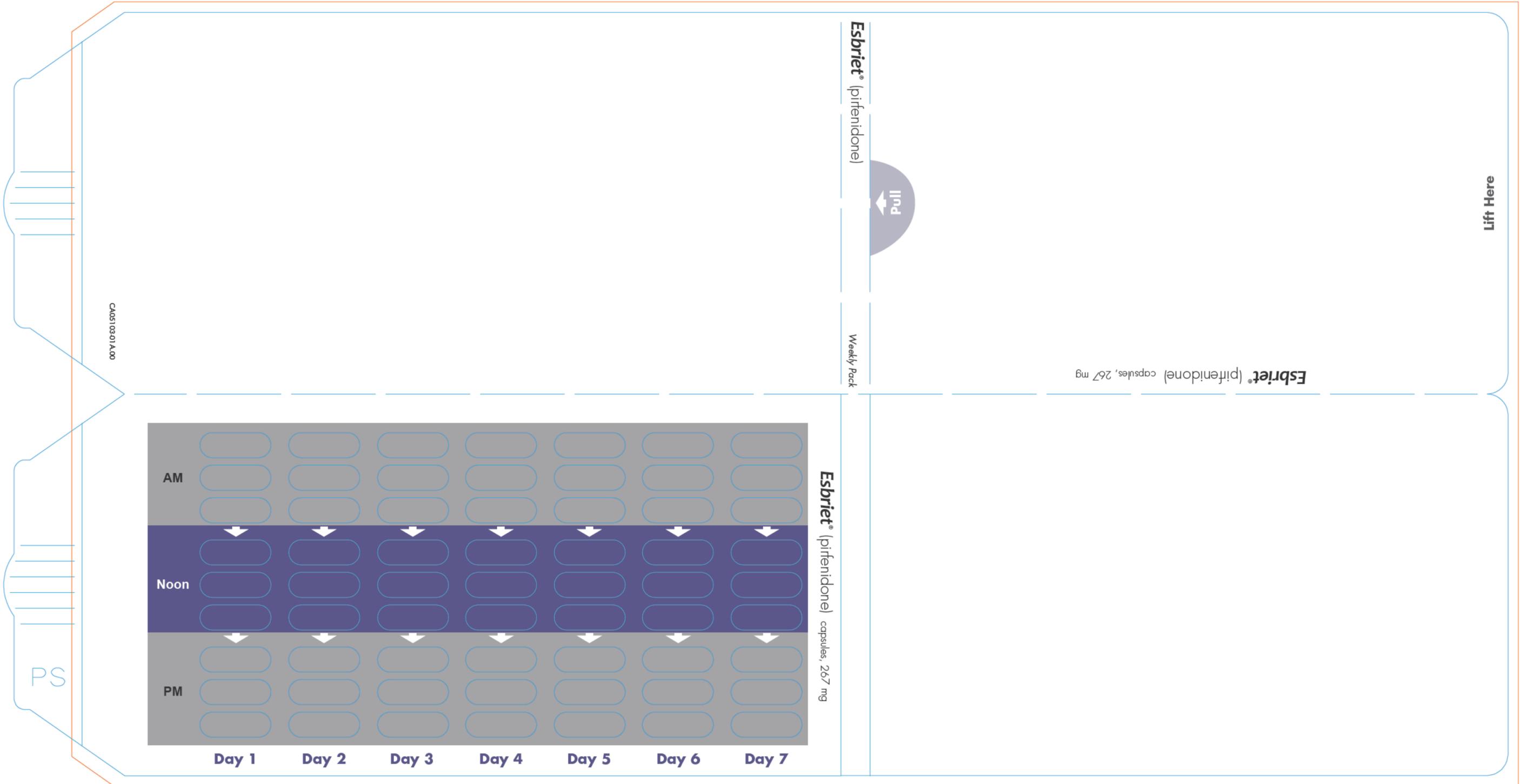
Exp:

Manufactured for:
InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005

Weekly Pack

Esbriet[®] (pirfenidone) capsules, 267 mg

PS



(b) (4)

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/s/

CURTIS J ROSEBRAUGH
10/15/2014