

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA
REVIEW AND EVALUATION**

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Product: ESBRIET[®] (pirfenidone) Film-coated Tablets
Indication: Idiopathic Pulmonary Fibrosis
Applicant: Genentech
Review Division: Pulmonary, Allergy, and Rheumatology Products
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1 Executive Summary

1.1 Introduction

Pirfenidone was approved (under NDA 22535) for the treatment of idiopathic pulmonary fibrosis (IPF) on October 15, 2014. The Sponsor has submitted a New Drug Application for ESBRIET[®] (pirfenidone) film-coated tablets for the treatment of patients with idiopathic pulmonary fibrosis (IPF). ESBRIET[®] film-coated tablets (267 mg, 534 mg, and 801 mg) are being developed to complement the approved 267 mg hard capsule formulation (NDA 22535). The three dosage forms of the film-coated tablets will support the approved dose escalation regimen for ESBRIET[®] in IPF and reduce the pill burden for patients (from nine capsules to three tablets for the daily maintenance dose).

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical pharmacology or toxicology studies were provided in the present application. The Sponsor cross-referenced nonclinical pharmacology and toxicology studies submitted with NDA 22535 dated November 4, 2009. ESBRIET[®] (NDA 22535) was approved for the treatment of IPF on October 15, 2014.

1.3 Recommendations

1.3.1 Approvability

The application is recommended for approval from the nonclinical perspective.

There are no outstanding nonclinical issues.

Recommendations for product labeling are provided below.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The Sponsor submitted revised product labeling for in the present supplement to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The review evaluated nonclinical sections of the proposed product label (i.e., the Established Pharmacological Classification (EPC) in the Indications and Usage Section in the Highlights of Prescribing Information, Sections 8.1 (Pregnancy), 8.2 (Lactation), Section 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology)). There were no changes to labeling for the EPC, Section 12.1, and Section 13. Below is the recommended text for Sections 8.1 (Pregnancy) and 8.2 (Lactation) after revisions to the Sponsor's proposed label. A detailed explanation of labeling changes is described later in this review. Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4) The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risk. In animal reproduction studies, Pirfenidone was not teratogenic in rats and rabbits at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults (b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. (b) (4)

Pirfenidone in these studies at doses up to 3 and 2 times, respectively, the (b) (4) MRDD in adults (on mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, 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, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. 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 oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

Data

Animal Data: A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production (b) (4)

8.4 Pediatric Use

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

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).

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 53179-13-8

Tradename: ESBRIET®

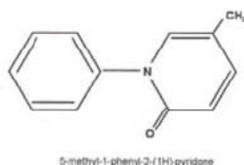
Generic Name: Pirfenidone

Code Name: S-7701 or AMR-69

Chemical Name: 5-methyl-1-phenyl-2-(1H)-pyridone

Molecular Formula/Molecular Weight: C₁₂H₁₁NO / MW = 185.23 g/mole

Structure:



Pharmacologic Class: Pyridone used for the treatment of idiopathic pulmonary fibrosis (claims as an anti-inflammatory and anti-fibrotic agent were not considered substantiated).

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 22535 (Genentech, IPF)

IND 67284 (Genentech, IPF)

2.3 Drug Formulation

Pirfenidone film-coated tablets are available in three strengths: 267 mg (b) (4), 534 mg (b) (4) and 801 mg (b) (4). The unit composition of pirfenidone film-coated tablets, 267 mg, 534 mg, and 801 mg, including reference to the corresponding pharmacopeial standard(s) and the function of each component, is provided below. The three strengths of pirfenidone film-coated tablets are dose proportional, (b) (4).

Table 1 Description of pirfenidone film-coated tablets

Table 2.3.P-1 Description of Pirfenidone Film-Coated Tablets

Strength	Description
267 mg	Yellowish white to pale yellow, oval, biconvex film-coated tablets, debossed with "PFD" (b) (4)
534 mg	[REDACTED]
801 mg	Greyish brown to brownish red, oval, biconvex film-coated tablets, debossed with "PFD"

Table 2 Composition of pirfenidone film-coated tablets, 267 mg, 534 mg, and 801 mg**Table 2.3.P-2 Composition of Pirfenidone Film-Coated Tablets, 267 mg, 534 mg, and 801 mg**

Components ^a	Reference to Standards	Function	Quantity per Unit Dose (mg/tablet)		
			267 mg	534 mg	801 mg
Tablet Core					
Pirfenidone	In-house	Active	267.000	534.000	801.000
Microcrystalline cellulose ^b	NF, Ph. Eur.				(b) (4)
Silica, colloidal anhydrous (b) (4)	NF, Ph. Eur.				
Povidone (b) (4)	USP, Ph. Eur.				
Croscarmellose sodium	NF, Ph. Eur.				
Magnesium stearate	NF, Ph. Eur.				
Tablet Core Weight	—				
Film-Coating Mixture^c					
Polyvinyl alcohol	USP, Ph. Eur.				(b) (4)
Titanium dioxide (b) (4)	USP, Ph. Eur.				
Macrogol (b) (4) (Polyethylene glycol (b) (4))	NF, Ph. Eur.				
Talc	USP, Ph. Eur.				
Iron oxide yellow (b) (4)	NF, EU 231/2012				
Iron oxide red (b) (4)	NF, EU 231/2012				
Iron oxide black (b) (4)	NF, EU 231/2012				
(b) (4)	—				
Total Tablet Weight			329.000	658.000	987.000
^a					(b) (4)
^b Microcrystalline cellulose (b) (4)					
^c					(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients. Levels of excipients are covered by those found in FDA-approved products.

With regard to use of iron oxide yellow, iron oxide red, and iron oxide black, iron oxides and hydrated iron oxides were evaluated for an acceptable daily intake for man (based on use as colors), by the Joint FAO/WHO Expert Committee on Food Additives in 1974, 1978, and 1979. An ADI of 0.5 mg/kg body weight (approximately 30 mg/day) was established. No toxicological monograph was issued. See the FAO JECFA Monographs 5 (2008) – Compendium of Food Additives prepared by the Joint FAO/WHO Expert Committee on Food Additives. The use of iron oxide yellow, iron oxide red, and iron oxide black are within the published ADI.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

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

2.7 Regulatory Background

Pirfenidone was approved (under NDA 22535) for the treatment of idiopathic pulmonary fibrosis (IPF) on October 15, 2014.

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical pharmacology or toxicology studies were submitted in the present application. The Sponsor cross-referenced nonclinical pharmacology and toxicology studies submitted with NDA 22535 dated November 4, 2009. ESBRIET[®] (NDA 22535) was approved for the treatment of IPF on October 15, 2014.

The Sponsor was granted a Pre-NDA meeting and preliminary comments were conveyed on January 28, 2016. The Sponsor subsequently canceled the meeting.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

1. Pharmacology and Toxicology Review of NDA 22535 dated February 24, 2010
2. Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010
3. Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010 (Dr. Grace Lee)
4. Pharmacology and Toxicology Review of NDA 22535 (Appendices) dated April 5, 2010
5. Pharmacology and Toxicology Review of NDA 22535 dated August 13, 14, and 24, 2014

4 Pharmacology

4.1 Primary Pharmacology

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

4.2 Secondary Pharmacology

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

4.3 Safety Pharmacology

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

5.2 Toxicokinetics

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

6 General Toxicology**6.1 Single-Dose Toxicity**

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

6.2 Repeat-Dose Toxicity

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

7 Genetic Toxicology**7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)**

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

7.2 *In Vitro* Assays in Mammalian Cells

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

7.4 Other Genetic Toxicity Studies

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

8 Carcinogenicity

See Pharmacology and Toxicology Review of NDA 22535 dated February 24, 2010

9 Reproductive and Developmental Toxicology**9.1 Fertility and Early Embryonic Development**

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

9.2 Embryonic Fetal Development

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

9.3 Prenatal and Postnatal Development

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

10 Special Toxicology Studies

See Pharmacology and Toxicology Review of NDA 22535 dated April 5, 2010

11 Integrated Summary and Safety Evaluation

Pirfenidone was approved for the treatment of idiopathic pulmonary fibrosis (IPF) on October 15, 2014. Pirfenidone is currently manufactured and commercialized as a

capsule formulation. The recommended daily maintenance dosage is 801 mg (three 267 mg capsules) three times per day, with food, for a total of 2403 mg/day. Pirfenidone 801 mg immediate release (IR) film-coated tablets were developed to simplify the maintenance dosing regimen (3 tablets per day vs. 9 capsules per day). Two lower strength tablets, 267 mg and 534 mg, were additionally developed to allow patients to up-titrate to the maintenance dose or to reduce the dose for the management of adverse events (AEs).

No new nonclinical pharmacology or toxicology studies were submitted with the present application. The Sponsor cross-referenced nonclinical pharmacology and toxicology study reports submitted to NDA 22535 in support of the present application. These studies included pharmacology, safety pharmacology, ADME, toxicology studies with durations up to 6 months in rats and 9 months in dogs, reproductive toxicity, genotoxicity, carcinogenicity in mice and rats, and photosafety.

The mechanism of action of pirfenidone has not been fully established; however, data from in vitro and animal models potentially suggest that pirfenidone has antifibrotic activity. The sponsor contention of anti-inflammatory activity does not appear to be supported.

A full battery of safety pharmacology studies were conducted with pirfenidone that included assessments of neurological, cardiovascular, respiratory, and gastrointestinal effects. Neurological effects of pirfenidone were assessed in mice that received pirfenidone as single oral doses up to 300 mg/kg. A number of clinical signs were observed in a dose-related manner that included sedation, ptosis, abnormal posture, decreased body temperature, disturbance of gait, and lower spontaneous motor activity. All symptoms disappeared by 1-2 hours postdose. Effects of pirfenidone on the respiratory and cardiovascular systems were assessed in rats and dogs that received single oral or intravenous doses up to 300 mg/kg. Dose-related increases of heart rate were observed in both rats and dogs. Reflective of increased heart rate, dose-dependent decreases of the RR interval were observed. Further, sinus tachycardia (heart rate >190 bpm) was evident in dogs that received higher oral or intravenous doses. For dogs that received single oral doses up to 100 mg/kg or an intravenous infusion of 9.2 mg/kg bolus followed by the 88 mg/kg/hour infusion, the QTc interval did not exhibit any evidence of prolongation. With respect to gastrointestinal effects, pirfenidone caused dose-dependent and significant inhibition of the gastric emptying rate at oral doses ≥ 30 mg/kg and small intestinal transport at oral doses ≥ 100 mg/kg in rats. Pirfenidone at 10^{-4} M produced a slight but significant decrease in the muscle tone of the isolated ileum.

In a 6-month oral toxicology study, rats received doses of 20, 100, 500, and 1000 mg/kg/day. Target organs of toxicity included the liver, thyroid gland, adrenal gland, urinary bladder, and kidneys. Hepatocyte necrosis was observed for 17% (2/12) of high dose male rats at the end of the treatment period and 17% (1/6) of high dose female rats at the end of 35-day drug-free recovery period. Centrilobular hypertrophy was observed for 17% (2/12) of high dose males at the end of the treatment period. Liver

weights were increased for males at ≥ 100 mg/kg/day and females at ≥ 500 mg/kg/day, which appeared to be associated with hepatocellular hypertrophy and increases of cytochrome P450 levels and isozyme activities. Follicular cell hyperplasia of the thyroid gland was observed for 8.3% (1/12) high dose males at the end of the treatment period. Of note, findings in the liver and thyroid gland were more pronounced in the 2-year carcinogenicity study in terms of incidence and severity and appeared to correlate with neoplastic findings. An increased incidence of vacuolization of cells in the zona fasciculata of the adrenal gland was observed for high dose males. Inflammatory cell infiltration in the lamina propria of the urinary bladder was observed for 17% (2/12) of high dose males. Transitional cell hyperplasia was observed for 8.3% (1/12) of high dose males. Inflammatory cell infiltration in the renal pelvis of the kidney was observed for 8.3% (1/12) of males in the 1000 mg/kg/day group at the end of the dosing period. Dilatation of the pelvic cavity was observed for 8.3% (1/12) of females in the 1000 mg/kg/day group at the end of the dosing period. Crystals in the urine (attributed to the 5-carboxylic acid metabolite of pirfenidone) were observed for males and females in the 500 and 1000 mg/kg/day groups that might correlate with histopathological findings in the urinary bladder and kidneys. The NOAEL was identified as 500 mg/kg/day based upon histopathological findings in liver, thyroid, adrenal gland, urinary bladder, and kidneys at 1000 mg/kg/day.

In a 9-month oral toxicology study, dogs received pirfenidone at oral doses of 0, 20, 70, and 200 mg/kg/day. Alkaline phosphatase (ALP) activities were increased 1.3- and 2.3-fold for males and females at 70 and 200 mg/kg/day, respectively, during the treatment period although toxicological significance was only achieved for high dose dogs. Target organs of toxicity were the liver and submaxillary glands. Hepatocellular hypertrophy was observed in 3 males and 1 female at 200 mg/kg/day. This finding appeared to be associated with induction of several cytochrome P450 isozymes. The relationship between this histopathological finding and elevation of ALP activity was unclear. Acinar hypertrophy of mucous glands in the submaxillary gland was observed for 1 female at 70 mg/kg/day and 3 males and 3 females at 200 mg/kg/day group. The NOAEL was judged to be 20 mg/kg/day based upon histopathological findings in the submaxillary glands at 70 and 200 mg/kg/day and elevations of ALP activity and histopathological findings in the liver at 200 mg/kg/day. Findings in the submaxillary glands and liver might be judged to be monitorable in a clinical setting. Hepatocellular hypertrophy is generally regarded as an adaptive change and not necessarily adverse. There were relatively comparable findings in a second 9-month toxicology study with dogs that received doses of 10, 35, and 100 mg/kg BID (20, 70, and 200 mg/kg/day, respectively).

Pirfenidone was negative in a standard battery of genotoxicity tests.

Pirfenidone was tumorigenic in mice and rats. In a 2-year mouse carcinogenicity study, pirfenidone produced increased incidences of hepatocellular adenomas and carcinomas and hepatoblastomas. In a 2-year rat carcinogenicity study, pirfenidone produced increased incidences of hepatocellular adenomas and carcinomas and uterine adenocarcinomas. In communication with the medical officer, based upon the morbidity

and short life expectancy associated with IPF, these tumor findings with pirfenidone would not appear to impact approval for the treatment of this disease.

Pirfenidone had no effects on fertility and reproductive performance in rats at oral doses up to 1000 mg/kg/day. In embryofetal development study with rats and rabbits that received oral doses up to 1000 and 300 mg/kg/day, respectively, there was no evidence of teratogenicity. In the presence of maternal toxicity for rats, acyclic/irregular cycles were seen in rats at oral doses ≥ 450 mg/kg. Further, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dose of 1000 mg/kg. Pirfenidone was found to distribute into the milk of lactating female rats at higher exposure levels than found in plasma.

Pirfenidone showed evidence of phototoxicity. In a photoclastogenicity test, pirfenidone produced increased incidences of structural aberrations in irradiated Chinese hamster ovary cells. Results of a photomutagenicity study with bacteria were equivocal. The reliability of these photogenotoxicity tests was judged to be questionable. Studies with guinea pigs and hairless mice that received pirfenidone by the oral route and were irradiated with UV lights for periods up to 1 month were identified with several findings of skin phototoxicity that included erythema, inflammatory cell infiltration, hemorrhage, vascular dilatation, hyperemia within the dermis, extension of the lesion from the dermis to epidermis, and increased thickness of the stratum spinosum (acanthosis). Lengthening the period between drug administration and exposure to sunlight might be beneficial in reducing phototoxic lesions. Use of sunscreens with high SPF and PA values might assist in ameliorating phototoxicity.

Recommendation: The application is recommended for approval from the nonclinical perspective.

There are no outstanding nonclinical issues.

A review of nonclinical sections of the product label is provided below.

Labeling Review:

The Sponsor submitted revised product labeling for in the present supplement to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The review evaluated nonclinical sections of the proposed product label (i.e., the Established Pharmacological Classification (EPC) in the Indications and Usage Section in the Highlights of Prescribing Information, Sections 8.1 (Pregnancy), 8.2 (Lactation), Section 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology)). There were no changes to labeling for the EPC, Section 12.1, and Section 13. Below is the recommended text for Sections 8.1 (Pregnancy) and 8.2 (Lactation) after revisions to the Sponsor's proposed label.

Sections 8.1 and 8.2 were modified to conform to current practices for PLLR labeling.

Additions are shown as underlined text and deletions are shown as strikethrough ~~text~~.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4) The data with ESBRIET use in pregnant women are insufficient to inform on drug associated risk. In animal reproduction studies, Pirfenidone was not teratogenic in rats and rabbits at doses up to 3 and 2 times, respectively, the maximum recommended daily dose (MRDD) in adults [see Animal Data]. (b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

Animal reproductive studies were conducted in rats and rabbits. In a combined fertility and embryofetal development study, female rats received pirfenidone at oral doses of 0, 50, 150, 450, and 1000 mg/kg/day from 2 weeks prior to mating, during the mating phase, and throughout the periods of early embryonic development from gestation days (GD) 0 to 5 and organogenesis from GD 6 to 17. In an embryofetal development study, pregnant rabbits received pirfenidone at oral doses of 0, 30, 100, and 300 mg/kg/day throughout the period of organogenesis from GD 6 to 18. (b) (4)

irfenidone in these studies at doses up to 3 and 2 times, respectively, the (b) (4) MRDD in adults (on mg/m² basis at maternal oral doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits, 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, female rats received pirfenidone at oral doses of 0, 100, 300, and 1000 mg/kg/day from GD 7 to lactation day 20. 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 oral dose of 1000 mg/kg/day).

8.2 Lactation

Risk Summary

No information is available on the presence of pirfenidone in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes clear determination of the risk of ESBRIET to

an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ESBRIET and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

Data

Animal Data: A study with radio-labeled pirfenidone in rats has shown that pirfenidone or its metabolites are excreted in milk. There are no data on the presence of pirfenidone or its metabolites in human milk, the effects of pirfenidone on the breastfed child, or its effects on milk production. (b) (4)

8.4 Pediatric Use

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

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).

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/s/

TIMOTHY W ROBISON
10/17/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 208780

Applicant: Genentech

Stamp Date: March 29, 2016

**Drug Name: Esbriet
(Pirfenidone)**

NDA Type: Original

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable (NA) No new nonclinical pharmacology or toxicology studies were submitted. Module 4 was not included. The nonclinical program was reviewed under the initial submission of NDA 22-535.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			NA. See comment #1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			NA. See comment #1.
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			NA. See comment #1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA. See comment #1.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			NA. See comment #1.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			NA. See comment #1.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			NA. See comment #1.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		The PLLR conversion of Sections 8.1 and 8.2 will be reviewed.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		Will consult with the Review Chemist regarding any impurity issues.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			NA. This is a 505(b)(1) application.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

NONE

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

NONE

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/s/

TIMOTHY W ROBISON
05/13/2016