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Established Name Pirfenidone
(Proposed) Trade Name Esbriet
Therapeutic Class Pyridone
Applicant Genentech, Inc.

Formulation(s) 267 mg, 534 mg and 801 mg
film-coated tablets
Dosing Regimen 801 mg three times a day
Indication(s) Treatment of idiopathic
pulmonary fibrosis to reduce
decline in lung function
Intended Population(s) Adults with idiopathic
pulmonary fibrosis

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1 Recommendations/Risk-benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends Approval of pirfenidone film-coated tablets (Esbriet®) for the treatment of idiopathic pulmonary fibrosis (IPF).

1.2 Risk-benefit Assessment

Pirfenidone capsules are FDA approved for the treatment of IPF (NDA 22,535). In this NDA, the Applicant, Genentech, Inc. in order to support approval of a new pirfenidone tablet formulation, submitted data from a single pharmacokinetic study (GP29830) assessing the bioequivalence (BE) of pirfenidone tablets and the reference listed drug (RLD), pirfenidone capsules. The Applicant cross-referenced the finding of safety and efficacy for the RLD to support the use of pirfenidone tablets in IPF. A biowaiver supports two lower strength tablets through demonstration of similar in vitro dissolution. No separate safety and efficacy studies were performed.

In study GP29830, comparisons of the peak plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) between the proposed drug and RLD were within the prespecified BE limits of 80-125 percent (90 percent confidence intervals). Study GP29830 revealed no new safety signals for pirfenidone; there were no deaths or serious adverse events (SAE), and the pirfenidone label describes the most common adverse events (AE) observed. While the study demonstrated a slightly higher incidence of mild AEs for the tablet formulation in comparison to the RLD, the significance of this finding is limited by the study design. In a chronic, progressive, lethal disease, the small difference in mild AE does not change the risk-benefit assessment for pirfenidone as determined under NDA 22,535.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None beyond standard pharmacovigilance practices.

1.4 Recommendations for Postmarket Requirements and Commitments

None. As an orphan drug product, pirfenidone tablet is exempt from the Pediatric Research Equity Act.

2 Introduction and Regulatory Background

IPF is a chronic progressive, diffuse parenchymal lung disease of unknown etiology that is characterized by scarring of the lungs, non-productive cough, and progressive dyspnea. Median survival time in patients with IPF is estimated to be from 3 to 5 years¹, with respiratory failure being the most frequent cause of death. IPF affects approximately 13.2 to 42.7 out of 100,000 patients in

¹ 2000, American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment, Am J Respir Crit Care Med, 161: 646-664

the USA.^{2,3} Currently, there are two FDA approved drugs for the treatment of IPF: pirfenidone capsule (Esbriet®) and nintedanib esylate (Ofev®). The approval of both drugs in 2014 represented the first FDA approved drug therapies to demonstrate benefit for the treatment of IPF in clinical trials. The current NDA submission is for a new dosage formulation of pirfenidone.

2.1 Product Information

The chemical name for pirfenidone is 5-Methyl-1-phenyl-2-(*H*)-pyridone. Pirfenidone is an orally bioavailable small molecule that has both antifibrotic and anti-inflammatory properties. The exact mechanism of action is uncertain. The FDA approved pirfenidone capsules (Esbriet®) on October 15, 2014, for treatment of IPF at the following dosage (NDA 22,535):

- 2403 mg/day divided into 3 doses (3x267 mg capsules by mouth TID) taken with food
- Upon initiation of treatment, the daily dosage should be titrated to the full dosage of 9 capsules per day over a 14 day period as described in Table 1:

Table 1. Titration Schedule for Pirfenidone Capsule

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

This NDA is for a tablet formulation of pirfenidone in three strengths: 267 mg, 534 mg and 801 mg. The 801 mg pirfenidone tablet is equivalent to three, 267 mg pirfenidone capsules. The proposed maintenance dosage and initial titration for pirfenidone tablets are identical to the RLD on a milligram basis. As the recommended dosage for the capsule formulation requires 9 pills per day, the tablet formulation will reduce the pill burden for IPF patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

While in clinical practice multiple therapies are used off-label to treat IPF, only two drugs are FDA approved for the treatment of IPF (Table 2).

Table 2. FDA Approved Treatments for IPF

Generic name	Brand name	Dosage form and strength
Pirfenidone capsule	Esbriet®	801 mg capsule
Nintedanib esylate	Ofev®	100/150 mg capsules

2.3 Availability of Proposed Active Ingredient in the United States

Pirfenidone is available in the USA in a capsule formulation.

² Coultas DB, Zumwalt RE, Black WC, et al., 1994, The epidemiology of interstitial lung diseases, Am J Respir Crit Care Med, 150: 967–972.

³ Raghu G, Weycker D, Edelsberg J, et al, 2006, Incidence and prevalence of idiopathic pulmonary fibrosis, Am J Respir Crit Care Med, 174:810–816.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no other approved drugs in this class. Pirfenidone carries warnings and precautions for liver function test elevation, photosensitivity and gastrointestinal disorders. Per the label, the most common adverse reactions occurring in (b) (4) subjects included nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue and headache.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Applicant filed IND 67,284 for pirfenidone with the Division on April 18, 2003. Pirfenidone was designated as an orphan drug on March 5, 2004, and breakthrough therapy on July 17, 2014. The FDA approved pirfenidone capsules (Esbriet®) on October 15, 2014, for the treatment of IPF in the United States (NDA 22,535). Prior to the submission of the present NDA, interactions relevant to this application under IND 67,284 included:

May 2015, Type C written response only meeting

- Discussion of chemistry, manufacturing, and controls (CMC) approach for the tablet
- Discussion of the Phase I BE study in humans (Study GPS9830) comparing pirfenidone tablet to marketed capsule formulation as follows:
 - Completion of the PK study in the fasting state and study of the food-effect for the tablet formulation
 - Agreement with equivalence margin: 90 percent confidence interval (CI) for ratio of geometric means of test/reference for the PK parameters between 80 to 125 percent.
 - Discussion of waiver for lower strength tablets (267mg and 534mg)

January 2016: pre-NDA written response only meeting

- Discussion of new NDA submission and cross-reference to NDA 22,535 for modules 2.4, 2.6, 4, 2.7.3, 2.7.4 and 5.3.5.3
- Agreement on submission format and structure

2.6 Other Relevant Background Information

As of February 27, 2016, pirfenidone is approved for the treatment of IPF in 41 countries worldwide including the following:

- Japan, October 2008 (Pirespa®, Shionogi & Co. Ltd.)
- European Union, February 2011 (Esbriet®, InterMune)
- China, September 2011 (Etuary®)
- Canada, October 2012 (Esbriet®)
- Switzerland, September 2015 (Esbriet®)

Section 8 discusses postmarketing safety reporting from the foreign markets. Note that because InterMune and Shinonogi believe their products are sufficiently different, on May 15, 2015 the safety data exchange agreement (SDEA) between InterMune and Shionogi was terminated, and a new SDEA was enacted that limits exchange to significant and emergency safety issues or alerts.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant submitted NDA 208,780 on March 29, 2016. The submission was appropriately indexed and complete to allow for review. There were no issues with the submission quality or data integrity.

3.2 Compliance with Good Clinical Practices

The Applicant conducted the pivotal clinical pharmacology study in accordance with Good Clinical Practices [Module 5, Section 5.3.1.2. GP29830, Clinical Study Report GP29830, page 1]. The Applicant certified that they did not use and would not use, in any capacity, the services of any person debarred under to Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with their application [Module 1, Volume 1.3, Section 1.3.3, page 1].

3.3 Financial Disclosures

The Applicant attested to compliance with the Final Rule on Financial Disclosure by Clinical Investigators. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that no investigator received significant payments as defined in 21 CFR 54.2(f), that none of the investigators disclosed a proprietary interest in the product, or possessed a significant equity interest in the Applicant as defined in 21 CFR 54.2(b) [Module 1, Volume 1.3, Section 1.3.4, page 1].

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review team recommends Approval. See the review written by Dr. Christopher Hough for more details.

Pirfenidone is 5-Methyl-1-phenyl-2-1(*H*)-pyridone. The molecular formula of pirfenidone is C₁₂H₁₁NO, and the molecular weight is 185.23 grams per mole. The pirfenidone drug substance used to produce the tablet was previously described and reviewed under NDA 22,535 (see CMC review by Dr. Xiaobin Shen 9/16/2014).

Pirfenidone film-coated tablets are oval, biconvex tablets debossed with "PFD." Each film-coated tablet contains 267 mg, 534 mg or 801 mg of pirfenidone. Tablets are differentiated by size and color (Table 3).

Table 3. Description of Tablets

Strength	Description	Thickness (mm)	Target weight (mg)
267 mg	Yellowish white to pale yellow	[REDACTED]	(b) (4)
534 mg	[REDACTED] (b) (4)		
801 mg	Greyish brown to brownish red		

Source: Module 2, Volume 2.3, Section 2.3.P, Table 2.3.P-1.

The active ingredients and all excipients of the proposed drug product are listed in Table 4.

Table 4. Active Ingredients and Excipients in Pirfenidone Tablets

Ingredient	Function	mg/tablet (%W/W)		
		267.000	534.00	801.00
Pirfenidone	Active	(b) (4)	(b) (4)	(b) (4)
Microcrystalline cellulose	[REDACTED]	(b) (4)		
Silica, colloidal anhydrous (b) (4)				
Povidone (b) (4)				
Croscarmellose sodium				
Magnesium stearate				
Polyvinyl alcohol				
Titanium dioxide (b) (4)				
Macrogol (b) (4) (Polyethylene glycol (b) (4))				
Talc				
Iron oxide yellow				
Iron oxide red				
Iron oxide black				
Total Weight				

Source: Module 2, Volume 2.3, Section 2.3.P, Table 2.3.P-2. %w/w FDA calculated using Microsoft Excel 2010.

The Applicant uses multiple sites for the manufacturing of pirfenidone tablets. The drug substance is sourced from [REDACTED] (b) (4)

[REDACTED] is an approved drug substance supplier for pirfenidone 267 mg capsules (NDA 22,535, Module 3.2.S), while [REDACTED] (b) (4) is an additional manufacturer for NDA 208,780. Pirfenidone tablets are manufactured by Roche S.p.A. in Segrate, Italy. Genentech Inc. (South San Francisco, CA) completes the batch release.

The Applicant submitted multiple dissolution studies to support the three tablet strengths. The 801 mg commercial trade tablet differs from the 801 mg biobatch tablet used in the BE study with respect to tablet width (9.7 mm vs 9.3 mm, respectively) and trade dress. However, the Applicant demonstrated similar dissolution profiles for the two batches of 801 mg tablets [REDACTED] (b) (4) with more than [REDACTED] (b) (4) percent of drug dissolved within 15 minutes in all media tested. Additional in vitro dissolution studies support the 267 mg and 534 mg tablets in reference to United States Pharmacopeia (USP) <711>, USP <1092> and Ph.Eur 2.9.3. The Applicant demonstrated comparative dissolution profiles of all three strengths in 900 mL of 0.1N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8, and water. The 801 mg, 534 mg, and 267 mg tablets were at or above [REDACTED] (b) (4)

percent average dissolution at 15 minutes in each media, meeting the biowaiver requirement [21 CFR 320.22(d)(2)].

Reviewer comment:

The CMC review team concludes that the Applicant meets the biowaiver requirement for the 267 mg and 534 mg tablets as set forth in the 21 CFR 320.22(d)(2). The Applicant provided sufficient evidence of comparative dissolution for the two, 801 mg batches such that the in vivo characteristics are not likely to differ for the two batches.

4.2 Clinical Microbiology

Pirfenidone tablets are not expected to have a microbiological attribute. The Applicant performed microbiological quality testing consistent with USP <61> and USP <62> with samples from all 12 registration batches. All batches were compliant with the testing requirements [Module 2, Volume 2.3, Section 2.3.P, page 25].

4.3 Nonclinical Pharmacology/Toxicology

The Applicant submitted no new nonclinical data with this NDA. For an in depth review of the nonclinical pharmacology and toxicology data, see the review written by Dr. Timothy Robinson for NDA 22,535.

4.4 Clinical Pharmacology

The clinical pharmacology review team recommends Approval. For a complete review of the clinical pharmacology data, see the review written by Dr. Bhawana Saluja.

4.4.1 Mechanism of Action

As described in the clinical review of pirfenidone capsule under NDA 22,535, the mechanism of action of pirfenidone has not been fully established. In vitro and animal models suggest that pirfenidone exerts both anti-inflammatory and antifibrotic effects. Pirfenidone reduces the production of proinflammatory cytokines including tumor necrosis factor alpha and interleukin-1 beta, and reduces the accumulation of inflammatory cells in response to various stimuli.⁴ The Applicant previously demonstrated that pirfenidone attenuates the production of profibrotic cytokines, including platelet-derived growth factor and transforming growth factor beta, and reduces the accumulation of extracellular matrix components, particularly collagen.⁵

4.4.2 Pharmacodynamics

No new pharmacodynamic studies were performed.

⁴ Hirano A, Kanehiro A, Ono K, Ito W, Yoshida A, et al, 2006, Pirfenidone modulates airway responsiveness, inflammation, and remodeling after repeated challenge. Am J Respir Cell Mol Biol 35(3):366–377.

⁵ InterMune, Inc. 2004. PCLN-PIRF-010. Pirfenidone report. Investigations on the mechanisms of action of pirfenidone. Ono RS1083-T40. On file at InterMune, Inc., Brisbane, CA.

4.4.3 Pharmacokinetics

Clinical pharmacology study GP29830 provides pharmacokinetic data to support the pirfenidone tablet. Section 5.3 summarizes the pharmacokinetic data from study GP29830.

5 Sources of Clinical Data

The Applicant submitted clinical data from study GP29830 to support pirfenidone tablet.

5.1 Tables of Studies/Clinical Trials

Table 5. Summary of Clinical Studies Included in this Submission

Study number (Time)	Study type	Design	Treatment groups	n	Population
GP29830 (Aug 18 – Aug 29, 2015)	Single Dose BE & Food-effect Study	Randomized, open-label, 4 period, 4 treatment, crossover, 4x4 Williams design	A. 3x267 mg cap*, fed B. 1x801 mg tab, fed C. 3x267 mg cap, fasted D. 1x801 mg tab, fasted	44	Healthy men and women, 18-55 years old

*All treatment groups received pirfenidone tablet (tab) or capsule (cap).

Source: Module 5, Section 5.3.1.2. gp29830, Clinical Study Report GP29830, pages 9-10.

5.2 Review Strategy

This Reviewer analyzed clinical data from study GP29830. Study GP29830 was an open-label BE and food-effect study in adult HV. Section 5.3 discusses the protocol and PK results from study GP29830, and Section 7 summarizes the safety data from study GP29830. As study GP29830 did not include nor require efficacy endpoints, no additional efficacy data are reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

Study GP29830

Administrative Information

Study title

A Phase I, Open-Label, Randomized, Four-Treatment Period, Four-Sequence, Single-Dose, Crossover, Pharmacokinetic Bioequivalence Study Comparing Pirfenidone Tablet and Capsule Dosage Forms in Healthy Adult Volunteers

- **Study start date:** August 18, 2015
- **Study completion:** August 29, 2015
- **Study report date:** February 2016
- **Study sites:** United States

Objectives/Rationale

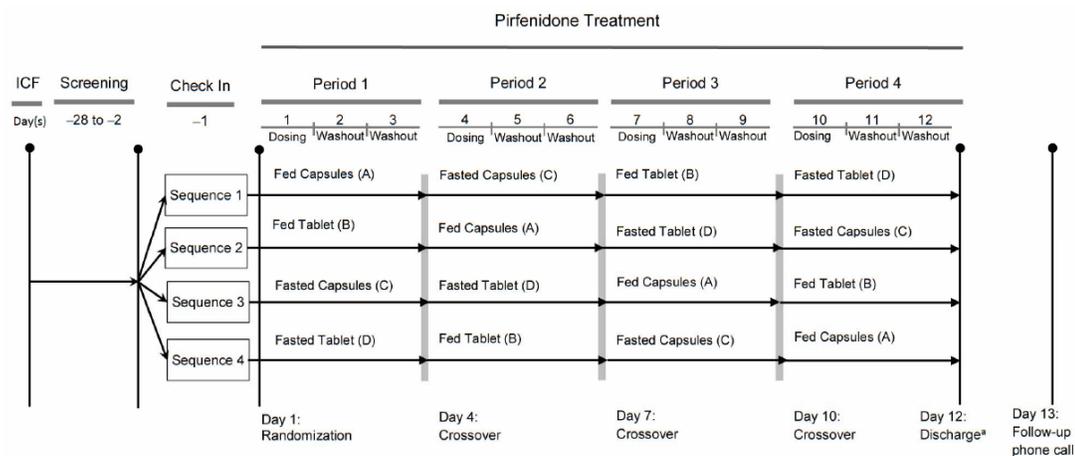
- To assess BE of a single dose of pirfenidone tablet (1x801 mg tablet) relative to a single dose of pirfenidone capsules (3x267 mg capsules) under fed and fasted conditions
- To characterize food-effect on PK of 801 mg pirfenidone tablet after single dose
- To evaluate safety and tolerability of single dose pirfenidone tablet (1x801 mg tablet) and capsule (3x267 mg capsules) under fed and fasted conditions

Study Design and Conduct

Overview

This was a single-dose, 4 treatment, crossover study evaluating relative BE and food-effect of the pirfenidone tablet compared to the RLD. Following a 28 day screening period, 44 adult healthy volunteers (HV) were enrolled in one of four treatment sequences (randomization 1:1:1:1). Each sequence involved four, 3 day treatment periods separated by a 2 day washout period. The four treatment periods included single doses of 801 mg pirfenidone tablet (1x801 mg) under fed and fasting conditions, and single doses of 801 mg pirfenidone capsules (3x267 mg) under fed and fasting conditions. For each treatment period, PK samples were collected predose and postdose at serial intervals up to 24 hours after treatment. The study schema appears in Figure 1.

Figure 1. Study GP29830 Schematic



ICF = informed consent form signed.

^a Discharge after completion of PK blood draws and assessments.

Source: Module 5, Section 5.3.1.2. GP29830, Clinical Study Report GP29830, Figure 1, page 16.

Trial Population

This trial included adult HV.

Treatments

Subjects received two, single oral doses of 801 mg pirfenidone tablet (1x801 mg), and two, single doses of 801 mg pirfenidone capsules (3x267 mg).

Compliance

Compliance was assessed by investigator documentation and comparison of doses received at the site, administered to subjects, not used and sent for destruction.

Ethics

The trial was conducted according to the International Council for Harmonisation guidelines for Good Clinical Practice and Declaration of Helsinki. An institutional review board reviewed and approved this protocol.

Statistical Analysis

Safety analysis

Safety analysis was descriptive with no formal statistical testing. The safety population included all 44 subjects. Safety findings are described in Section 7.

Pharmacokinetic analysis

The primary parameters for BE assessment were C_{max} and total exposure measured as both the AUC from zero to the time of last quantifiable concentration (AUC_{0-t}) and AUC from zero to infinity ($AUC_{0-\infty}$). The Applicant summarized the parameters using descriptive statistics, geometric mean, and geometric coefficient of variation. BE was established using the following pre-specified criteria: two-sided 90 percent CI for geometric mean ratio between the two treatments in the fasted state within the limits of 80.00 to 125.00 percent for the primary PK parameters in the fasted state. The population for pharmacokinetic analysis excluded two fasting subjects and one fed subject due to vomiting that occurred prior to two times the median time to reach peak drug concentration (T_{max}).

Pharmacokinetic Results

The pharmacokinetic parameters from Study GP29830 appear in Table 6.

Table 6. Pharmacokinetic parameters after 801 mg single-dose pirfenidone , Study GP29830

PK parameter	Fed state geometric mean (\pm CV%) N=43 ^a		Fasted state geometric mean (\pm CV%) N=42 ^b	
	Tablet	Capsule	Tablet	Capsule
$AUC_{(0-inf)}$ (ng.h/mL)	40900 (35.5)	39800 (37.0)	49400 (35.5)	49700 (34.9)
$AUC_{(0-t)}$ (ng.h/mL)	40600 (35.0)	39500 (36.6)	49200 (35.1)	49500 (34.5)
C_{max} (ng/mL)	7640 (27.9)	6560 (25.5)	12600 (32.8)	12500 (27.9)

^aOne subject excluded for vomiting. ^bTwo subjects excluded for vomiting. CV = coefficient of variation.

Data Source: Study GP29830 Module 2.7.2. Geometric mean and CV from Clinical Pharmacology Review by Dr. Bhawana Saluja, Tables 4 and 5.

Under fasted conditions, the 90 percent CI for the ratio of geometric means was within the pre-specified BE criteria (80.00 to 125.00 percent) for all three parameters (Table 7).

Table 7. Summary of PK Data for BE in Fasting State, Study GP29830

PK parameter	N ^a	Tablet vs capsules % GLSM ratio ^b	90% CI ^c
AUC _(0-inf) (ng.h/mL)	42	99.61	96.64 – 102.68
AUC _(0-t) (ng.h/mL)	42	99.63	96.66 - 102.69
C _{max} (ng/mL)	42	101.26	94.41 – 108.60

^aN = 42; excludes two subjects due to vomiting.

^bGLSM = geometric least squares mean based on log-transformed parameters

^c90% CI = lower and upper limits of 90% confidence interval on the GMR of pirfenidone

Source: NDA 208780 Module 2.7.1. Data analysis from Clinical Pharmacology Review by Dr. Bhawana Saluja, Table 6.

The pirfenidone tablet C_{max} and integrated exposure [AUC_(0-t) and AUC_(0-inf)] were reduced by 39% and 17% respectively following a high-fat meal.⁶ The observed food effect is consistent with the known food-effect profile for pirfenidone capsule as established under NDA 22,535 (49% reduction in C_{max} and 16% reduction in exposure, respectively).

Reviewer's comments:

Detailed PK data analysis can be found in Clinical Pharmacology review by Dr. Bhawana Saluja, Ph.D. The review team believes that the Applicant has sufficiently demonstrated BE in the fasted state through the prespecified BE margin. In the food-effect study, the food-effect led to a lower C_{max} and exposure for both pirfenidone tablet and capsule, consistent with the known food-effect of pirfenidone capsules. While, the C_{max} for the tablet was higher than the capsule in the fed state, the difference between the two dosage forms is unlikely to be clinically important. The exclusion of the two subjects with vomiting is consistent with FDA guidance.

6 Review of Efficacy

Efficacy Summary

Efficacy for pirfenidone tablet is supported by the demonstration of the BE of pirfenidone tablet and RLD in study GP29830, and the cross-reference to the finding of efficacy for the RLD under NDA 22,535. The FDA did not require additional clinical efficacy studies to support this application.

6.1 Indication

The indication for the proposed drug product is treatment of IPF at a maintenance dose of 801 mg three times daily with food (1x801 mg tablet). Upon initiation of treatment, the daily dosage should be titrated to the full dosage of 2403 mg/day over a 14 day period as follows:

⁶Clinical Pharmacology Review by Dr. Bhawana Saluja, Section 2.4.3

Table 8. Dosage Escalation for Pirfenidone Tablet

Treatment days	Dosage
Days 1 through 7	267 mg three times daily with food
Days 8 through 14	534 mg three times daily with food
Days 15 onward	801 mg three times daily with food

Pirfenidone capsules are currently approved for the treatment of IPF at the same maintenance dosage and initial titration dosage on a milligram basis (NDA 22,535).

6.1.1 Methods

Not Applicable

6.1.2 Demographics

Not Applicable

6.1.3 Subject Disposition

Not Applicable

6.1.4 Analysis of Primary Endpoint(s)

Not Applicable

6.1.5 Analysis of Secondary Endpoints(s)

Not Applicable

6.1.6 Other Endpoints

Not Applicable

6.1.7 Subpopulations

Not Applicable

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not Applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not Applicable

6.1.10 Additional Efficacy Issues/Analyses

Not Applicable

7 Review of Safety

Safety Summary

The Applicant's Clinical Summary consisted of a summary of safety information from study GP29830 and cross-reference to the safety data and postmarketing experience with the RLD under NDA 22,535. Review of the safety data from study GP29830, including AE data, laboratory tests, electrocardiogram (ECG) reports and vital sign (VS) data, identified no additional safety signals for the RLD. Postmarketing experience for pirfenidone capsule is consistent with the known safety profile for pirfenidone (Section 8). The most recent 9th PBRER for NDA 22,535 included a search of medical literature that identified four references addressing the safety of pirfenidone. The submitted literature search and independent FDA literature search revealed no new safety signals for pirfenidone (Section 9.1).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study GP29830 was used to evaluate safety. Additionally, the Applicant cross-references safety from NDA 22,535.

7.1.2 Categorization of Adverse Events

The Applicant recorded all AE that occurred on or after the first dose of study treatment through Day 13 or early withdrawal. AE were assessed daily through safety assessments, observation and subject reporting. Additional phone follow-up occurred 24 hours after discharge from the study. The Applicant classified AE using Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and graded severity as outlined in Table 9.

Table 9. Adverse Event Severity Grading Scale

Demo	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

The study defined a serious adverse event (SAE) as any AE meeting the following outcomes:

- Death
- Life-threatening AE (i.e., one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs)
- Persistent or significant disability/incapacity

- Requires in-patient hospitalization (i.e., admission), or prolongs hospitalization
- Congenital anomaly or birth defect

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data was performed as only a single study was evaluated.

7.2 Adequacy of Safety Assessments

The subject exposure to pirfenidone tablet is limited in study GP29830. However, the cross-referenced clinical development program and postmarketing experience for the RLD under NDA 22,535 provide sufficient safety exposure data.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In study GP29830, a total of 44 adult HV received single 801 mg doses of pirfenidone tablet in both fed and fasted states. Table 10 summarizes the demographics of the study subjects.

Table 10. Demographics of Subjects in Study GP29830

Demographic characteristic	
Overall (n)	44
Gender [n (%)]	
Female	16 (36.36)
Male	28 (63.64)
Race [n (%)]	
White	24 (54.55)
Non-White or unknown	20 (45.45)
Age [years]	
Mean \pm SD	36.09 \pm 10.17
Range	20 to 54

Source: DM.xpt sdtm and [Module 5, Section 5.3.1.2. GP29830, Clinical Study Report GP29830, Table 4, page 34]. Counts and percentages calculated using JMP 12.0. Table includes all subjects receiving study medication.

Reviewer comment:

While the study population tended to be young and male, note that the population pharmacokinetic analysis for pirfenidone under NDA 22,535 showed no significant differences in pharmacokinetics by gender, race and age.

7.2.2 Explorations for Dose Response

The Applicant did not explore the dose response of pirfenidone tablet. Study GP29830 used a dose of pirfenidone tablet that represents the recommended full daily dose of pirfenidone capsule supported by NDA 22,535.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

The Applicant conducted routine clinical tests (hematology, clinical chemistry, urinalysis, and urine drug screen) at screening and study completion in the clinical pharmacology study. Routine VS assessments were conducted before and during the administration of treatment drugs in the clinical pharmacology study. No clinically significant changes from baseline data were noted.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific metabolic, clearance, or interaction studies were performed in this NDA program.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other drugs in the class. However, elevations in liver function tests were noted in the pirfenidone development program. As noted in Section 7.2.4, no clinically significant laboratory changes occurred in study GP29830.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) reported.

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations reported.

7.3.4 Significant Adverse Events

There were no significant AE reported.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All documented AE were mild in severity. Table 11 summarizes common AE observed in study GP29830.

Table 11. Adverse Events Reported in Study GP29830

Adverse event	Total N = 44		Cap, fed N = 44		Tab, fed N = 44		Cap, fasted N = 44		Tab, fasted N = 44	
	n*	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse event	22	(50.0)	1	(2.3)	7	(15.9)	14	(31.8)	16	(36.4)
Gastrointestinal disorders										
Nausea	13	(29.5)	0	(0.0)	3	(6.8)	8	(18.2)	10	(22.7)
Constipation	4	(9.1)	0	(0.0)	3	(6.8)	0	(0)	1	(2.3)
Dyspepsia	2	(4.5)	0	(0.0)	0	(0.0)	1	(2.3)	1	(2.3)
Vomiting	2	(4.5)	0	(0.0)	1	(2.3)	1	(2.3)	1	(2.3)
Paresthesia oral	1	(2.3)	0	(0.0)	0	(0.0)	1	(2.3)	0	(0.0)
Nervous system disorders										
Dizziness	8	(18.2)	0	(0.0)	1	(2.3)	4	(9.1)	6	(13.6)
Headache	4	(9.1)	0	(0.0)	2	(4.6)	2	(4.5)	3	(6.8)
Renal and urinary disorders										
Pollakiuria	1	(2.3)	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders										
Vulvovaginitis	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)
Vascular disorders										
Hot flush	1	(2.3)	1	(2.3)	0	(0.0)	0	(0.0)	0	(0.0)

*Table includes all subjects receiving study medication.

n- number of subjects with AE, each subject counted once; Cap, fed - 3x267mg pirfenidone capsules; Tab, fed- 1x801mg pirfenidone tablets; Cap, fasted - 3x267mg pirfenidone capsules; Tab, fasted - 1x801mg pirfenidone tablet.

Source: XAAE.xpt and [Module 5, Section 5.3.1.2. GP29830, Clinical Study Report GP29830, Table 4, page 41].

Percentages and counts calculated using JMP 12.0.

Reviewer's comment:

Mild AE events occurred more frequently in the tablet periods compared to capsule periods for both fed and fasted states. Most AE are noted in the pirfenidone capsule label. Mild constipation occurred more commonly in the tablet group compared to the capsule group. While constipation is not listed on the current label, constipation was observed in Trials 004 and 006 in the original pirfenidone program (Table 37, Clinical Review of NDA 22,535 by Dr. Banu A Karimi-Shah, MD). The review team notes that the small sample size, open-label design and single dose exposures create difficulty in extrapolating safety findings to chronic

dosing. The primary endpoint of the study was not safety. Further, the label for pirfenidone capsule and proposed label for the tablet recommend a 2 week titration period to reduce AE. Overall, the review team believes the observed AE do not suggest a new safety signal and do not change the risk-benefit ratio for this irreversible, fatal disease.

7.4.2 Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries, and urinalyses at baseline (screening and Day -1) and completion of the treatment phase (Day 12). There were no clinically significant changes in laboratory parameters.

7.4.3 Vital Signs

The Applicant presented mean values for heart rate, blood pressure, respiratory rate and body temperature for all treatment groups. VS were measured predose and 2.5 hr, 24 hr and 48 hr postdose for each treatment period. No clinically relevant changes from baseline were noted.

7.4.4 Electrocardiograms (ECGs)

ECG testing was conducted at baseline. The Applicant provided summary statistics of heart rate, PR interval, RR interval, QRS duration, QT, QTcF and QTcB. There were no clinically significant abnormalities in baseline ECG. A thorough QT study conducted under NDA 22,535 showed no effect on the QT interval (see Clinical Review of NDA 22,535 by Dr. Banu A Karimi-Shah, MD).

Reviewer comment:

The QT study submitted to NDA 22,535 was limited by the absence of an effect with the positive control (moxifloxacin) and the supratherapeutic dose did not cover the maximum pirfenidone exposure. However, these limitations did not preclude approval of pirfenidone capsule. The phase 3 clinical program for pirfenidone capsules included ECG monitoring and showed no evidence of QT prolongation. Additional studies are not necessary for the pirfenidone tablet development program.

7.4.5 Special Safety Studies/Clinical Trials

Not performed.

7.4.6 Immunogenicity

Not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This study included a single dose delivered by two different dosage formulations. As the systemic exposure was similar between the groups, conclusions regarding dose dependent effects cannot be made.

7.5.2 Time Dependency for Adverse Events

No formal analysis was performed.

7.5.3 Drug-Demographic Interactions

Given the small sample size and study population, AEs were not compared by age and sex.

7.5.4 Drug-Disease Interactions

The Application includes no new drug-disease interaction studies. Sections 8 and 12 of the approved pirfenidone label summarize drug-disease interaction data for pirfenidone.

7.5.5 Drug-Drug Interactions

The Application includes no new drug-drug interaction studies. Sections 7 and 12 of the approved pirfenidone label summarize drug-drug interaction data for pirfenidone.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant performed no new human carcinogenicity studies for this application. The Applicant cross-references the nonclinical data submitted to NDA 22,535.

7.6.2 Human Reproduction and Pregnancy Data

No new human reproductive and / or pregnancy data were collected in the single pharmacological study.

7.6.3 Pediatrics and Assessment of Effects on Growth

The submission includes no pediatric subjects. As pirfenidone for IPF is an orphan-designated indication, this Application does not require pediatric assessments.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was no overdose experience reported.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

In support of pirfenidone tablet, the Applicant cross-references postmarketing experience with the currently approved pirfenidone capsule formulation. The most recent Periodic Adverse Experience Report (PADER, 10/21/2015) and 9th Periodic Benefit Risk Evaluation Report (PBRE, 4/28/2016) include pirfenidone postmarketing experience from 41 countries worldwide. Since the pirfenidone international birthdate of February 28, 2011, cumulative total patient exposure is 30,475 patient-years (estimated February 27, 2016). Review of the postmarketing experience identified no safety issues that would alter the risk-benefit profile established for the approved indication.

9 Appendices

9.1 Literature Review/References

The Applicant compiled four literature references relevant to the safety of pirfenidone. The literature survey revealed no new safety signals for pirfenidone. Further, this reviewer searched PubMed with the search terms “idiopathic pulmonary fibrosis” and “pirfenidone” as well as “pirfenidone” and “safety.” No new safety signals were identified from this literature search.

9.2 Labeling Recommendations

Proposed labeling, submitted in physician’s labeling rule (PLR) format, references the labeling of pirfenidone capsule (NDA 22,535, approved on 10/15/14). As the Applicant does not plan to market the 534 mg tablet at this time, the label does not include the 534 mg tablet. The negotiations of the final labeling are ongoing at the time of this review.

9.3 Advisory Committee Meeting

An advisory committee meeting is not necessary for this NDA.

9.4 Assessment Schedule, Study GP29830

Table 12. Study Assessment Schedule

Activities / Assessments	Screening (day)	Check-in (day)	Treatment Phase (inpatient)												Early WD	Phone F/U (day)	
			Period 1 (day)			Period 2 (day)			Period 3 (day)			Period 4 (day)					
			-28 to -2	-1	1	2	3	4	5	6	7	8	9	10			11
Informed Consent	X																
Medical hx, I/E criteria	X	X															
PE	X													X	X		
Weight	X	X												X	X		
VS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine alcohol / drug screen	X	X															
Hematology, chemistry, HCG	X	X												X	X		
ECG, UA, HIV, hep B/C panel	X																
Study drug			X			X			X			X					
Medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: Adapted from [Module 5, Section 5.3.1.2. GP29830, Clinical Study Report GP29830, Appendix 1, page 545].

Clinical Investigator Financial Disclosure Review Template

Application Number: 208,780

Submission Date(s): 3/29/2016

Applicant: Genentech, Inc.

Product: Esbriet, pirfenidone film-coated tablets

Reviewer: Courtney McGuire, MD

Date of Review: 11/21/2016

Covered Clinical Study (Name and/or Number): Study GP29830

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>9</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)

Clinical Review
Courtney McGuire, MD
NDA 208,780
Esbriet, pirfenidone film-coated tablets

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0

Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
--------------------------------------------	------------------------------	------------------------------------------------------------------

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COURTNEY S MCGUIRE
11/22/2016

ANTHONY G DURMOWICZ
11/22/2016
I concur

MEDICAL OFFICER REVIEW			
Division of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)			
Application:	208,780	Application Type:	NDA
Sponsor:	Genentech	Proprietary Name:	Esbriet
Investigator:		USAN Name:	Pirfenidone
Category:		Route of Administration:	Oral
Reviewer:	Courtney McGuire, MD	Review Date:	5/12/16
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Stamp Date:	PDUFA Date:	Submission Type:	Comments:
3/29/2016	1/29/2017	NDA 208,780	NDA, 505(b)(1)
RELATED APPLICATIONS :			
Document Date	Application Type	Comments	
11/4/2009	NDA 22,535	Pirfenidone capsule	
REVIEW SUMMARY:			
<p>Genentech submitted a new Type 3 NDA (208,780) for pirfenidone film-coated tablet. The FDA approved the capsule dosage form of pirfenidone (NDA 22,535) on October 15, 2014 for the chronic treatment of idiopathic pulmonary fibrosis (IPF). The proposed indication for the tablet dosage form is also chronic treatment of IPF. The drug development program for tablet dosage form under NDA 208,780 is a clinical pharmacology program. As a basis for the 505(b)(1) application, the Applicant cites the reference listed drug (RLD), pirfenidone capsules (NDA 22,535), and cross-references the FDA finding of safety and efficacy for the RLD.</p> <p>The clinical pharmacology program includes a single bioequivalence (BE) study (GP29830). Study GP29830 was a single center, 4-treatment, 4-period crossover study evaluating the bioequivalence (BE) of 1x801 mg pirfenidone tablet to 3x267 mg pirfenidone capsules, and the food effect. A total of 44 healthy volunteers (HV) enrolled in study GP29830. The Applicant calculated the following PK parameters during the study: AUC_{0-∞}, AUC_{0-t}, AUCR, t_{1/2}, C_{max}, T_{max} and λ_z. No deaths or serious adverse events (SAE) occurred in the study. The most common adverse events (AE) were nausea, dizziness, headache and constipation, with more AE reported in the tablet group compared to the reference product. While previous review cycles for the RLD noted concerns with LFT elevations, the Applicant reports no clinically significant laboratory abnormalities in study GP29830.</p> <p>The Applicant bridges the 801 mg tablet to two lower dose tablets by comparative dissolution and seeks a biowaiver for 267 mg and 534 mg pirfenidone tablets under 21 CFR 320.22(d)(2). The proposed product labeling incorporates the approved product labeling for the RLD and revisions under the Pregnancy and Lactation Labeling Rule (PLLR). This submission is adequately indexed, organized, and complete to allow for review. The filing checklist is attached.</p>			
OUTSTANDING ISSUES: None			
RECOMMENDED REGULATORY ACTION:			
New clinical studies:	<input type="checkbox"/> Clinical Hold	<input type="checkbox"/> Study May Proceed	
NDA/Supplements:	<input checked="" type="checkbox"/> Fileable	<input type="checkbox"/> Not Fileable	
	<input type="checkbox"/> Approvable	<input type="checkbox"/> Not Approvable	
Other Action			
Medical Reviewer: Courtney McGuire, MD			
Medical Team Leader: Anthony Durmowicz, MD			

1. GENERAL INFORMATION

This is a 505(b)(1) application for pirfenidone film-coated tablet. The proposed indication is “chronic treatment of IPF.” The application is submitted electronically by Genentech. As a basis for the 505(b)(1) submission, the Applicant cross-references the Agency's finding of safety and effectiveness for pirfenidone capsules (NDA 22,535).

2. CLINICAL DEVELOPMENT PROGRAM

The clinical pharmacology program for this product includes a single BE study (GP29830) addressing the BE and food effect for pirfenidone tablet in reference to pirfenidone capsules (Table 1).

Table 1. Summary of BE Study GP29830

Study Number (Dates)	Study Type	Design	Treatment Groups*	n	Population
GP29830 8/18/2015 to 8/29/2015	Single Dose BE & Food Effect Study	Randomized, open label, 4-period, 4-treatment, crossover, 4x4 Williams design	A. 3x267 mg capsule, fed B. 1x801 mg tablet, fed C. 3x267 mg capsule, fasted D. 1x801 mg tablet, fasted	44	Healthy men and women, 18-55 years old

* Pirfenidone tablet or capsules.

3. FOREIGN MARKETING AND REGULATORY HISTORY

The Applicant filed IND 67,284 for the proposed drug with the Division on April 18, 2003. The FDA approved pirfenidone capsules on October 15, 2014 for the treatment of IPF in the United States.

As of February 27, 2016, pirfenidone is approved for the treatment of IPF in 41 countries worldwide including the following:

- Japan, October 2008 (Pirespa® by Shionogi & Co. Ltd.)
- European Union, February 2011 (Esbriet)
- China, September 2011 (Etuary)
- Canada, October 2012 (Esbriet)
- Switzerland, September 2015 (Esbriet).

Prior to the submission of this NDA, interactions relevant to this application under IND 67,284 included:

May 2015, Type C Written Response Only Meeting

- Discussion of CMC approach for the tablet
- Discussion of Phase I BE study in humans (GPS9830) comparing pirfenidone tablet to marketed capsule formulation.
 - FDA recommended completion of the BE study in the fasting state

- FDA recommended providing food effect information on the tablet formulation
- FDA agreed with equivalence margin of 0.8 -1.25 and 90% CI for ratio of geometric means of test/reference for the PK parameters
- Discussion of requirements for dissolution studies to support a biowaiver for lower strength tablets (267 mg and 534 mg)

January 2016: Type B Pre-NDA Written Response Only Meeting

- Discussion of new NDA submission and cross-reference to NDA 22,535 for modules 2.4, 2.6, 4, 2.7.3, 2.7.4 and 5.3.5.3
- Agreement on submission format and structure

4. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The submission includes the following pertinent items for the clinical review:

- Application form (FDA 356h) [m1\1.1-forms\1.1.2-fda-form-356h]
- Summary [m2\2.7-clinical summary]
- Clinical technical section
 - Clinical study reports and good clinical practice certification
 - Study GP29830 [m5\5.3-clin-stud-rep\5.3.1-rep-biopharm-stud\5.3.1.2-compar- BA-BE-stud-rep]
 - Debarment certification [m1\1.3-administrative-information\1.3.3-debarmentcertification]
 - Pediatric use [m1\1.9-pediatric-administrative-information\1.9.6-other-correspondence-pediatric-exclusivity-study-plans\pediatric-administrative-information]
- Labeling [m1\1.14-labeling\1.14.1-draft-labeling]
- Financial disclosure [m1\1.3-administrative-information\1.3.4-financial-certificationdisclosure]

The Applicant cross-references the NDA 22,535 for modules 2.4, 2.6, 4, 2.7.3, 2.7.4 and 5.3.5.3.

5. CLINICAL STUDIES

Study GP29830 was a randomized, open label, 4-period, 4-treatment, crossover study involving 44 adult HV. The applicant randomized each subject to one of four treatment sequences. Each three-day treatment period included a single dose of pirfenidone tablet (1x801 mg tablet) under fed and fasting conditions and a single dose of pirfenidone capsules (3x271 mg capsules) under fed and fasting conditions. A 2-day washout period separated the four treatment periods. The Applicant collected PK samples predose and at serial intervals up to 24 hours postdose. Collected PK variables included $AUC_{0-\infty}$, AUC_{0-t} , $AUCR$, $t_{1/2}$, C_{max} , T_{max} and λ_z .

The most common AE reported were nausea, dizziness, headache and constipation. More AE occurred in subjects receiving the proposed drug product compared to the RLD. The Applicant reports no deaths or SAEs.

6. BRIEF REVIEW OF PROPOSED LABELING

The proposed product labeling incorporates the approved product labeling for pirfenidone capsule, NDA 22,535. The label includes revisions to section 8.1 and 8.2 maintain consistency with the PLLR. Section 8.3 is omitted. No major label issues were identified.

7. DSI REVIEW AND AUDIT

The clinical pharmacology review team has requested DSI audit for the single study center used in this NDA application.

8. SUMMARY

Genentech submitted a new NDA (208,780) for pirfenidone film-coated tablets. The proposed indication is chronic treatment of IPF. As a basis for the 505(b)(1) application, the Applicant cites the RLD pirfenidone capsules (NDA 22,535). The drug development program for pirfenidone tablet is a clinical pharmacology program depending on the BE of the proposed drug and RLD. The Applicant cross-references the safety and efficacy of the RLD (NDA 22,535).

The clinical pharmacology program includes a single bioequivalence (BE) study (GP29830) evaluating the bioequivalence (BE) of 1x801 mg pirfenidone tablet to 3x267 mg pirfenidone capsules, and the food effect. A total of 44 healthy volunteers enrolled in study GP29830. The Applicant calculated the following PK parameters during the study: $AUC_{0-\infty}$, AUC_{0-t} , AUCR, $t_{1/2}$, C_{max} , T_{max} and λ_z . No deaths or serious adverse events (SAE) occurred in the study. The most common adverse events (AE) were nausea, dizziness, headache and constipation, with more AE reported in the tablet group compared to the reference product. While previous review cycles for the RLD noted concerns with LFT elevations, the Applicant reports no clinically significant laboratory abnormalities in study GP29830.

The Applicant seeks approval for three strengths of the pirfenidone tablet: 267 mg, 534 mg and 801 mg. The Applicant bridges the 801 mg tablet to both lower dose tablets by comparative dissolution and seeks a biowaiver for 267 mg and 234 mg pirfenidone tablets under 21 CFR 320.22(d)(2).

The proposed product labeling incorporates the approved product labeling for pirfenidone capsule. This submission is adequately indexed, organized, and complete to allow for review. The filing checklist is attached.

9. REVIEW TIMELINE

The PDUFA goal date is January 27, 2017. The schedule for review is provided in Table 2. Write-up will be concomitant with the review process. The review will

culminate with the proposed label, which will include comparison to the referenced listed product.

Table 2: Review timeline for NDA 208,780

Milestone	Target date for completion
Filing and planning meeting	May 12, 2016
MCR Meeting	August 30, 2016
Label Meeting	TBD
Wrap-up meeting	December 19, 2016
Final draft review complete	December 25, 2016
PDUFA Goal date (10 months)	January 27, 2017

Clinical Filing Checklist

NDA/BLA Number: 208,780

Applicant: Genentech

Stamp Date: 3/29/16

Drug Name: Pirfenidone film-coated tablets

NDA/BLA Type: 505(b)(1)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	x			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			Cross-referenced NDA 22,535 for 2.4, 2.6, 2.7.3, 2.7.4
8.	Has the applicant submitted the integrated summary of safety (ISS)?			x	Cross-referenced NDA 22,535
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			x	Cross-referenced NDA 22,535
10.	Has the applicant submitted a benefit-risk analysis for the product?			x	Cross-referenced NDA 22,535
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	x			505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			x	
14.	Describe the scientific bridge (e.g., BA/BE studies)			x	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms:			x	Applicant proposes already approved dosage regimen for NDA 22,535

	Content Parameter	Yes	No	NA	Comment
	Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			x	Cross-referenced NDA 22,535 for efficacy
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	Cross-referenced NDA 22,535 for efficacy
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	Cross-referenced NDA 22,535 for efficacy
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Cross-referenced NDA 22,535 for efficacy
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	Cross-referenced NDA 22,535 for safety.
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	Cross-referenced NDA 22,535 for safety findings.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?			x	Cross-referenced NDA 22,535
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary ²	x			MedDRA Version

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	used for mapping investigator verbatim terms to preferred terms?				18.0
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Obtained safety labs on subjects pre and post dose
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	No deaths or AE dropouts
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			BE study with food effect
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self-selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Exempt due to Orphan Drug Status
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm) ?		x		Revises the label from NDA 22,535 per PLLR format. Cross-references NDA 22,535 including PADER, PSUR submissions.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	No new foreign data
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	Cross-referenced NDA 22,535 for efficacy
37.	Are all datasets to support the critical safety analyses available and complete?			x	Cross-referenced NDA 22,535 for safety
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints			x	Cross-referenced NDA 22,535 for

	Content Parameter	Yes	No	NA	Comment
	included?				efficacy
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	No deaths, SAE or adverse dropouts
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	No additional CRF requested
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

 Reviewing Medical Officer Date

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COURTNEY S MCGUIRE
05/13/2016

ANTHONY G DURMOWICZ
05/13/2016