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*APPLICATION NUMBER:*

**208780Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 15, 2016
<b>From</b>	Anshu Marathe, Ph.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 208,780
<b>Supplement#</b>	
<b>Applicant</b>	Genentech Inc.
<b>Date of Submission</b>	March 29, 2016
<b>PDUFA Goal Date</b>	January 29, 2016
<b>Proprietary Name / Established (USAN) names</b>	ESBRIET® / Pirfenidone
<b>Dosage forms / Strength</b>	Film-coated tablets/ 267 mg, 534 mg and 801 mg
<b>Proposed Indication(s)</b>	Treatment of idiopathic pulmonary fibrosis (IPF)
<b>Recommended:</b>	Approval

### 1. Introduction

Genentech, Inc., submitted this 505(b)(1) application for use of pirfenidone film-coated tablets for the treatment of idiopathic pulmonary fibrosis (IPF) on March 29, 2016. Pirfenidone as capsules was approved for the same indication under NDA 22,535 on October 15, 2014. This application is based on a clinical pharmacology program designed to show bioequivalence between the tablet formulation and the capsule formulation. The Applicant cross-referenced the finding of safety and efficacy for the capsule formulation to support the use of pirfenidone tablets in IPF. No separate safety and efficacy studies were performed. The bioequivalence study is conducted comparing the rate and extent of absorption of the 801 mg pirfenidone tablet dose strength with 3 x 267 mg pirfenidone capsules in study GP29830. A biowaiver supports two lower strength tablets (267 mg and 534 mg) through demonstration of similar in vitro dissolution. At this time, the Applicant does not plan to market the 534 mg tablet and is seeking approval only for the 267 mg and 801 mg dose strengths. The previously approved formulation is available only as 267 mg capsules and the rationale to develop tablets at higher dose strength is to reduce the daily pill burden.

### 2. Background

The active ingredient of ESBRIET® is pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone or 5-methyl-1-phenyl-2-(1H)-pyridone) which belongs to the chemical class of pyridine. The FDA approved pirfenidone capsules 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

In the current application, the Applicant is seeking approval for pirfenidone film-coated tablets (267 mg and 801 mg) to complement the approved pirfenidone capsule formulation. The two strengths of the film-coated tablets will support the approved dose escalation regimen for pirfenidone in IPF, and is likely to improve subject experience by reducing the pill burden for patients (from nine capsules per day to three tablets per day for daily maintenance dose). The dose escalation steps for pirfenidone film-coated tablets are presented in Table 2.

**Table 2 Dose escalation steps for pirfenidone film-coated tablet**

Treatment days	Dosage
Days 1 through 7	a dose of 267 mg (one 267 mg tablet) administered three times a day with meals (801 mg/day)
Days 8 through 14	a dose of 534 mg (two 267 mg tablets) administered three times a day with meals (1602 mg/day)
Days 15 onward	a dose of 801 mg (one 801 mg tablet) administered three times a day with meals (2403 mg/day)

### 3. CMC/Device

The drug substance, pirfenidone is an achiral molecule that exists in solid state under ambient conditions. The drug is sparingly soluble in water and has no ionizable groups. There are two separate suppliers of pirfenidone. (b) (4)

(b) (4) The process controls are adequate and characterization studies support the proposed chemical structure. Drug substance-related impurities are adequately characterized and controlled. The specification includes tests and acceptance criteria for identity, water content, residue on ignition, melting range, heavy metals, assay, related impurities, and particle size, and it is also supported by batch data. The drug substance has a high level of purity and is extremely stable with no degradation observed on stability or during stress testing. The retest period for the drug substance is (b) (4) when stored at (b) (4) (b) (4).

The drug load of the tablets (all three strengths), is relatively high at (b) (4)% (w/w) and compendial-grade and common excipients are used. Tablets are distinguished by size and color (all have same shape and imprint). A single HDPE bottle container closure system is proposed

for the drug product. The applicant has provided only 9 months of stability data and apparently makes no argument to leverage previously submitted stability data for their approved capsule version of this drug. The limited 9 months of stability data support an expiry period of 18 months for all three strengths.

From the biopharmaceutics perspective, the Applicant's overall approach for bridging between the currently approved 267 mg hard capsule and the proposed new film-coated tablet formulations/strengths involved a determination of bioequivalence to compare 1 × 801 mg film-coated tablet with 3 × 267 mg hard capsules of pirfenidone. The lower strength film-coated tablets 267 and 534 mg were compared with the film-coated tablet 801 mg bio-batch by means of comparative *in vitro* dissolution profiles. The difference in the to-be-marketed formulation and the formulation used in the pivotal bioequivalence study GP29830 is the tablet width (length × widths: 20 × 9.7 mm with bioequivalence batch vs. 20 × 9.3 mm with commercial batch). This minor change in dimensions was bridged by multi-media dissolution profiles in the same way as for the bio-waiver of the lower strength film-coated tablets.

The applicant has developed the proposed (b) (4) manufacturing process based on the process of their approved capsule product (NDA 22,535), (b) (4)

(b) (4)

(b) (4) The process is controlled adequately for (b) (4)

The process produces drug product meeting the regulatory specification. The selected manufacturing process has been studied and validated adequately and registration batches are the same scale as those proposed for commercial production.

The application and associated inspectional documents for the facilities responsible for manufacturing pirfenidone tablets have been evaluated and there are no significant outstanding risks for these facilities, i.e., all facilities were found to be acceptable with no inspections required.

The application is recommended for approval from a CMC perspective. A shelf-life or expiration dating period of 18 months is granted for all strengths of the drug product.

## 4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology studies were provided in the present application. The Applicant cross-referenced nonclinical pharmacology and toxicology studies submitted with NDA 22,535 dated November 4, 2009. The Applicant submitted revised

product labeling in the present supplement to comply with the Pregnancy and Lactation Labeling Rule (PLLR) which was reviewed.

The application is recommended for approval from a Nonclinical perspective.

## 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology package submitted for this NDA consisted of a single pivotal bioequivalence (BE) study (GP29830) conducted in 44 healthy adult volunteers. The objective of the clinical study was to determine and compare the rate and extent of absorption of pirfenidone from film-coated tablet to that from capsule under both fasted and fed conditions. This was an open-label, single-dose, randomized, four-period, four-sequence crossover study under fasted and fed conditions. The treatment arms and the statistical summary are presented below.

Treatment arms –

- Treatment A = pirfenidone 3 × 267-mg pirfenidone capsules administered as a single oral dose in fed state
- Treatment B = pirfenidone 1 × 801-mg pirfenidone film-coated tablet administered as a single oral dose in fed state
- Treatment C = pirfenidone 3 × 267-mg pirfenidone capsules administered as a single oral dose in fasted state
- Treatment D = pirfenidone 1 × 801-mg pirfenidone film-coated tablet administered as a single oral dose in fasted state

Bioequivalence summary statistics of PK parameters for pirfenidone following single dose (801 mg) administration of pirfenidone film-coated tablet and pirfenidone capsule under fasted conditions:

**Table 3 Results of Bioequivalence Analysis**

PK Parameter	Tablet/Capsule ratio (%)	90% CI
AUC <sub>(0-inf)</sub>	99.61	96.64, 102.68
AUC <sub>(0-t)</sub>	99.63	96.66, 102.69
C <sub>max</sub>	101.26	94.41, 108.60

Source: NDA 208780 Module 2.7.1

Overall, the test product, pirfenidone film-coated tablet (801 mg), is bioequivalent to the corresponding reference product, pirfenidone capsule (3 X 267 mg), under fasted conditions.

Administration of high fat meal decreased the exposure (AUC<sub>(0-inf)</sub>) of the pirfenidone film-coated tablet (801 mg) by 17% and C<sub>max</sub> by 39% after. This effect of food on pirfenidone exposure was consistent between the pirfenidone film-coated tablet and pirfenidone capsule. In the same study, food led to approximately 48% and 20% reduction in C<sub>max</sub> and AUC<sub>(0-inf)</sub> for pirfenidone capsule, respectively. The effect of food on pirfenidone exposure was also

consistent with the known effect from pirfenidone capsule drug product label (NDA 22,535); food led to a 49% reduction in  $C_{max}$  and 16% reduction in AUC of pirfenidone. Although the  $C_{max}$  was slightly higher for the pirfenidone tablet as compared to the pirfenidone capsules in the fed state, the difference in  $C_{max}$  between the two dosage forms is not expected to have any clinically meaningful impact on the safety and efficacy of pirfenidone. In addition, there was no corresponding increase in exposure [ $AUC_{(0-t)}$  and  $AUC_{(0-inf)}$ ] of pirfenidone between the tablet and the capsule in the fed state.

The application is recommended for approval from a Clinical Pharmacology perspective.

## 6. 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.

## 7. Clinical/Statistical- Efficacy

No clinical studies were required or conducted to support this application. The program was based on demonstration of bioequivalence in the clinical pharmacology program as discussed above. The efficacy findings from the capsule formulation of pirfenidone are applicable to this product.

## 8. Safety

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 capsule formulation 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. Postmarketing experience for pirfenidone capsule is consistent with the known safety profile for pirfenidone. The most recent 9<sup>th</sup> 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.

The application is recommended for approval from a Clinical perspective.

## 9. Advisory Committee Meeting

An advisory committee was not convened for this application. Pirfenidone as capsule formulation is currently approved for treatment of IPF and there are no issues that warrant discussion at an advisory committee meeting.

## 10. Pediatrics

Idiopathic pulmonary fibrosis is a disease of older adults. Pediatric studies were waived for pirfenidone as IPF does not occur in the pediatric patient population. In addition, as a drug with orphan designation, a pediatric development plan is not required.

## 11. Other Relevant Regulatory Issues

OSIS inspection was requested for the clinical and analytical sites for pivotal BE study GP28930. The analytical site was not inspected based on past inspection history. Based on the inspection of the clinical site, OSIS recommended accepting the clinical portion of the study GP29830 for further Agency review. The inspectional outcomes from the inspections were classified as No Action Indicated.

## 12. Labeling

The Applicant submitted labeling which incorporated information on the film-coated tablet formulation. In addition, product labeling was revised to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The label has been reviewed by specific disciplines and consultants (OPDP, DMPP, DMEPA etc.). Minor edits are being discussed. Final labeling is pending at the time of this review.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for the proposed pirfenidone film-coated tablet formulation is approval. Genentech Inc. has submitted adequate data to support approval of pirfenidone film-coated tablet for treatment of IPF. The pivotal study, GP29830 demonstrated that pirfenidone film-coated tablet (801 mg) is bioequivalent to the pirfenidone capsule (3 X 267 mg). Therefore, the company is able to rely on the Agency's previous determinations of safety and efficacy for pirfenidone capsules. In addition, no new safety findings were observed in study, GP29830 and postmarketing experience for pirfenidone capsule.

- Risk Benefit Assessment

Based on the Agency's previous determination of safety and efficacy for pirfenidone capsules for treatment of IPF, the overall risk and benefit assessment of pirfenidone film-coated tablet is considered acceptable.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

None.

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12/15/2016