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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: January 11, 2017

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Subject: Division Director Summary Review

NDA Number: 208,780

Applicant Name: Genentech Inc.

Date of Submission: March 29, 2016

PDUFA Goal Date: January 29, 2017

Proprietary Name: Esbriet

Established Name: Pirfenidone

Dosage form: Film-coated tablets

Strength: 267 mg, 534 mg, and 801 mg

Proposed Indications: Treatment of patients with idiopathic pulmonary fibrosis (IPF)

Action: Approval

1. Introduction

Genentech submitted this 505(b)(1) application to provide a film-coated tablets dosage form of pirfenidone for the treatment of IPF. Pirfenidone as capsules at a strength of 267 mg was approved for IPF on October 15, 2014 (NDA 22,535). The rationale to develop tablets is to provide an alternate to capsules, and the rationale to develop higher dose strengths is to reduce the daily pill burden to patients. This application is based on a clinical pharmacology program comparing the pirfenidone 801 mg tablets to pirfenidone 3x267 mg capsule to show equivalent exposure, and in vitro studies showing similar dissolution to support the lower strengths of 267 and 534 tablets. This summary review will provide an overview of the application, with a focus on clinical pharmacology studies.

2. Background

IPF is a diffuse progressive parenchymal lung disease of unknown etiology, characterized by fibrotic interstitial infiltrates that are consistent with the histopathologic pattern of usual interstitial pneumonia.¹ It is the most common type of interstitial lung disease, estimated to affect 132,000 to 200,000 people in the United States. Approximately 50,000 new cases are diagnosed each year, and as many as 40,000 patients in America die from IPF each year. IPF is typically seen in older adults, more commonly in men than women, usually occurring between the ages of 50-70 years, and is characterized by

¹ ATS/ERS. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med.* 2000;161:(2 Pt 1):646-64.

progressive dyspnea, non-productive cough, and progressive pulmonary insufficiency. The natural course of IPF is variable. As the interstitial fibrosis and architectural distortion advance, the lung becomes increasingly non-compliant, and the work of breathing and dyspnea increase. Patients with IPF typically experience slowly progressive worsening of lung function over time, but some experience rapid declines and frequent hospitalizations in the late stage of the disease.² While the course of the disease is variable, the prognosis is uniformly poor, with a median survival of about 3-5 years after diagnosis. Currently, there are two FDA approved drugs for the treatment of IPF, these are pirfenidone (Esbriet) and nintedanib (Ofev), both approved in 2014. Other treatments often used in IPF are corticosteroids and immunosuppressive agents, such as azathioprine and cyclophosphamide. Lung transplantation is also an option for some patients with IPF.

Pirfenidone has been studied for various diseases including IPF for a long time. The development of pirfenidone was initiated in the US by Marnac, Inc. InterMune acquired the rights to pirfenidone in the US from Marnac in 2002. Another company called Shionogi, licensed the rights to pirfenidone in Japan. Shionogi received marketing approval for pirfenidone for IPF in Japan in October 2008, under the tradename Pirespa as a 200 mg tablet. InterMune was granted marketing authorization for pirfenidone for IPF in various countries in Europe starting in 2011 and in Canada in 2012. As noted above, pirfenidone as capsules was approved for IPF in the United States in 2014.

3. Chemistry, Manufacturing, and Controls

Esbriet is an approved marketed product as capsules. This NDA provides a new oral film-coated tablet dosage form in three strengths differentiated by size and color. The three dosage strengths contain 267 mg, 534 mg, and 801 mg of the active moiety pirfenidone and standard compendial excipients. The active pharmaceutical ingredient will be manufactured at ^{(b) (4)}

 The drug product will be manufactured by Roche in Segrate, Italy. Batch release testing will be done at Genentech, San Francisco, California. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 18 months is proposed and supported by submitted data.

As noted above, the highest dose strength of 801 mg pirfenidone tablets was used in the clinical pharmacology program, and the two lower dosage strengths were supported by in vitro dissolution data. The submitted in vitro data are adequate to support all strengths.

² Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005;142 (12 Pt 1):963-7.

4. Nonclinical Pharmacology and Toxicology

No new nonclinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

Genentech conducted a single clinical pharmacology study (Study GP29830) to support the pirfenidone tablet dosage form by linking to the capsule dosage form. The study was an open-label, single-dose, randomized, four-period, four-sequence crossover study under fasted and fed conditions conducted in 44 health adults. The pirfenidone 801 mg tablet and the pirfenidone 3x267 mg capsule under fasted condition resulted in similar exposure (Table 1). Administration of high fat meal decreased the exposure ($AUC_{(0-\infty)}$) of pirfenidone tablet (801 mg) by 17% and C_{max} by 39%. This effect of food on pirfenidone exposure was consistent between the pirfenidone tablet and pirfenidone capsule dosage forms. These data are adequate to support the efficacy and safety of the pirfenidone tablet dosage form.

Table 1. Study GP29830, Summary Analysis of relative bioavailability

	Parameter	Mean Ratio	90% CI
Pirfenidone Tablet vs Capsule, Fasted State	C_{max}	101.26	94.41, 108.60
	$AUC_{0-\infty}$	99.61	96.64, 102.68
	$AUC_{0-tlast}$	99.63	96.66, 102.69

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

No clinical study with efficacy measures were required or conducted for this application.

b. Design and conduct of studies

Not applicable

c. Efficacy findings and conclusions

Efficacy for the pirfenidone tablets can be concluded from PK data as discussed in Section 5 above.

8. Safety

a. Safety database

The safety assessment of pirfenidone tablets is based on safety information from the PK Study GP29830 and previous safety data and post marketing experience with the pirfenidone capsules.

b. Safety findings and conclusion

The safety data submitted and reviewed with this submission do not raise any new safety concerns for the pirfenidone tablet dosage form.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. The data submitted in this NDA are straightforward and did not warrant discussion at an Advisory Committee meeting.

10. Pediatric

Specific pediatric studies are not necessary because IPF is a disease of adults and does not occur in the pediatric population. Furthermore, as an orphan drug program, pediatric studies are not required.

11. Other Relevant Regulatory Issues

a. DSI Audits

An inspection by the Office of Study Integrity and Surveillance (OSIS) was requested for the clinical and analytical sites of the clinical pharmacology study. The inspection of the clinical study site did not identify any irregularities that would impact data integrity; the recommendation regarding the analytical site was to accept the data without an on-site inspection based on previous inspection results.

During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No investigators with significant equity interest in Genentech were involved in the study used to support this NDA.

c. Other

There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Esbriet was previously reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Genentech submitted a label that contained information on the tablet dosage form. In addition, the labeling was revised to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The label has been reviewed by various disciplines in this Division and by consultants. The Division and Genentech have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Patient labeling is not impacted substantially by the introduction of the tablet dosage form of pirfenidone. There is no Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Genentech has submitted adequate data to support approval of the oral tablet dosage form of pirfenidone for the treatment of patients with IPF. The action on this NDA will be Approval.

b. Risk Benefit Assessment

Pirfenidone is a marketed product as capsules. The systemic exposure from the pirfenidone tablets is similar to that from the capsules. Therefore, the previously concluded favorable risk benefit assessment of pirfenidone capsules applies to pirfenidone tablets.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

No PMR or PMC studies are recommended.

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