CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 6, 2014
Reviewer:	Bob Pratt, Pharm.D. Division of Risk Management
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Risk Management
Acting Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
Subject:	Evaluation to determine if a REMS is necessary
Drug Name(s):	Esbriet (Pirfenidone)
Therapeutic Class:	Anti-fibrotic and anti-inflammatory agent
Dosage and Route:	801 mg (three 267 mg capsules) by mouth three times daily
Application Type/Number:	NDA 22-535
Applicant/sponsor:	InterMune, Inc.
OSE RCM #:	2014-1160

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity pirfenidone, an anti-fibrotic and anti-inflammatory agent. Pirfenidone is proposed for the treatment of idiopathic pulmonary fibrosis (IPF), a relentlessly progressive and fatal disease that is at present without an approved medical therapy. In clinical studies, pirfenidone demonstrated substantial efficacy in significantly improving the decline of lung function in patients with IPF when compared with placebo. The most important safety concerns associated with pirfenidone are possible liver injury and photosensitivity/rash, though elevated liver enzymes have been reversible with dose reduction or discontinuation, and there have been no hepatic adverse events that resulted in liver failure or death. Few photosensitivity reactions and rash adverse events were severe or serious in the clinical studies. Based on the currently available data, the benefit-risk profile for pirfenidone is acceptable and a REMS is not necessary to ensure the benefits outweigh the risks.

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) pirfenidone. On May 23, 2014, the Agency received a resubmission to New Drug Application (NDA) 22-535 from InterMune, Inc., for Esbriet (pirfenidone) for the treatment of idiopathic pulmonary fibrosis (IPF). The applicant submitted a risk management strategy that did not include a REMS or risk management tools that go beyond labeling or routine pharmacovigilance.

1.1 DISEASE BACKGROUND[1-3]

IPF is a specific form of chronic, progressive, fibrosing interstitial lung disease of unknown cause. The disease effects are limited to the lungs. IPF is an orphan disease with an estimated prevalence of 14 to 43 per 100,000 persons. Using the upper limit of the prevalence estimate and a U.S. population estimate of 315 million, the current U.S. prevalence is approximately 135,000 persons. The majority of patients are older than 55 years of age and more men than women are affected. Most cases present with slowly progressive dyspnea and nonproductive cough, though patients also experience exacerbations and acute worsening. IPF usually follows a relentlessly progressive and lethal course, with most patients dying of respiratory failure within five to 10 years of diagnosis. Although the pathogenic factors in the development of IPF are unknown, inflammation and disordered epithelial-fibroblast remodeling of the lung interstitium may be responsible for the scarring and distorted lung architecture seen with the disease.

There are currently no FDA-approved therapies for the treatment of IPF. (Nintedanib is a tyrosine kinase inhibitor currently under FDA review for the treatment of IPF.) Medical therapy has historically included corticosteroids, cyclophosphamide, azathioprine, N-acetylcysteine, and other agents, but efficacy has not been established for these treatments and

[1] King TE. Treatment of idiopathic pulmonary fibrosis. In: UpToDate, Flaherty KR and Hollingsworth H (Eds), UpToDate, Waltham, MA, 2014.
[2] Cool CD. Idiopathic interstitial pneumonias: Clinical manifestations and pathology. In: UpToDate, King TE, Nicholson A, and Hollingsworth H (Eds), UpToDate, Waltham, MA 2014.
[3] Schwarz MI and King TE (2011). Idiopathic Pulmonary Fibrosis. In: Interstitial Lung Disease (5th ed.), Shelton, CT: People's Medical Publishing House - USA.

each carry risks of complications. Lung transplantation may be an option for patients who have early disease and minimal comorbid conditions.

1.2 PRODUCT BACKGROUND

Pirfenidone has anti-inflammatory and antifibrotic properties. Although the exact mechanism of action is unknown, the antifibrotic effects may result from inhibition of growth factors such as transforming growth factor beta (TGF-β), which stimulates collagen synthesis and accumulation in the lung. Pirfenidone has also been shown to suppress fibroblast proliferation in vitro and inhibit production of other pro-fibrotic cytokines. The recommended dosage is 801 mg (three 267 mg capsules) by mouth three times daily. Because of gastrointestinal intolerance (e.g., nausea, vomiting, diarrhea) a two week upward titration to the maintenance dose is used to initiate therapy. Dosage reductions or treatment interruptions may be necessary for patients who experience significant adverse reactions.

1.3 REGULATORY HISTORY

March 5, 2004: Pirfenidone is designated by the Agency as an Orphan Product for the treatment of IPF.

November 4, 2009: The Agency received an original NDA 22-535 from InterMune for pirfenidone for the treatment of IPF. The Applicant voluntarily proposed a REMS that set goals to encourage informed benefit-risk decisions; to minimize the potential risks of hepatotoxicity; and to minimize the potential risks of photosensitivity and rash. The elements for the proposed REMS included a Medication Guide, and a communication plan with educational materials for healthcare professionals, patients, and pharmacies. The Applicant also proposed the use of a closed distribution system using specialty pharmacies, but this was not to be required as an element under the REMS.

April 26, 2010: DRISK defers comment on the REMS proposal because of the Agency's plan to issue a Complete Response (CR) letter for the review cycle.

May 4, 2010: The Agency issues a Complete Response to NDA 22-535 because the Applicant did not provide substantial evidence of efficacy of pirfenidone for the proposed indication. (Nonclinical and microbiology deficiencies were also found during review of the application.) Only one of two randomized placebo-controlled pirfenidone pivotal trials met the primary efficacy endpoint of change from baseline in percent predicted Forced Vital Capacity (FVC). In the analysis of other efficacy endpoints, neither trial demonstrated a mortality benefit or a significant benefit in the time to worsening of IPF, though one of the trials demonstrated a significant result for progression free survival.

May 23, 2014: The Agency received a Class 2 resubmission to NDA 22-535 in which the Applicant provided the results of a third placebo-controlled study. The resubmission includes a "risk management strategy" that briefly summarizes the combined clinical trial and postmarketing safety experience (pirfenidone was approved in Europe in 2011 and Canada in 2012, among other countries) and concludes that the risks can be adequately managed by the proposed labeling and pharmacovigilance without the need for a REMS.

July 17, 2014: The Agency grants Breakthrough Therapy designation for pirfenidone for the treatment of IPF.

2 MATERIALS REVIEWED

- November 4, 2009, Applicant Original Submission NDA 22-535
    - Section 1.16, Proposed REMS
- April 23, 2010, Cross-Discipline Team Leader Review, Sally Seymour, M.D.
- April 26, 2010, DRISK REMS Review, Kendra Worthy, Pharm.D.
- May 4, 2010, Complete Response Letter NDA 22-535
- May 23, 2014, Applicant Resubmission NDA 22-535
    - Section 1.14, Draft Labeling
    - Section 1.16, Risk Management Strategy
    - Section 1.16, Overview of Benefit-Risk Framework
    - Section 2.5, Clinical Overview
    - Section 5.3.5.3, Resubmission Safety Update
- July 11, 2014, CDER Medical Policy Council Brief, Breakthrough Therapy Designation Review
- September 24, 2014, Cross-Discipline Team Leader (CDTL) Draft Review, Banu Karimi-Shah, M.D.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

For the original NDA submission in 2009, the Applicant completed and presented two randomized, double-blind, placebo controlled, Phase 3 studies (PIPF-004 and PIPF-006) of pirfenidone in patients with IPF. The primary efficacy endpoint for both trials was the change in percent predicted FVC, a measure of the decline in lung function, from baseline to Week 72. Secondary efficacy endpoints included the time to worsening of IPF, progression free survival, and other endpoints. The Agency also analyzed overall survival as an exploratory endpoint. It was determined that substantial evidence of pirfenidone efficacy in the treatment of IPF had not been demonstrated (as only Study 004 demonstrated efficacy) and a CR action was taken. Therefore, the Applicant conducted an additional Phase 3 study (PIPF-016) of nearly identical design (except for treatment duration) to PIPF-004 and PIPF-006 to support approval of the NDA. Upon completion, Study 016 demonstrated a statistically significant improvement in the change from baseline in percent predicted FVC. Furthermore, when a pre-specified, integrated analysis was conducted for all three studies (PIPF-004, PIPF-006, and PIPF-016), pirfenidone showed an improvement in survival over placebo. The details of each trial are explained below.

In PIPF-004, 435 patients were randomized to 2403 mg/day or 1197 mg/day of pirfenidone, or placebo. The mean change in FVC (percent of predicted value) was -8.0% in the 2403 mg/day group compared with -12.4% in the placebo group, for an absolute difference of 4.4% ($p<0.001$). In PIPF-006, 344 patients were randomized to pirfenidone 2403 mg/day or placebo. In contrast to the results of PIPF-004, the mean change in predicted FVC was -9.0% for the pirfenidone group and -9.6% for the placebo group, a difference of 0.6% that was not significant ($p=0.501$). In terms of secondary endpoints, neither study demonstrated a significant benefit with regard to worsening of IPF, and progression free survival was significantly better only in PIPF-004 (Hazard Ratio=0.64 [95% C.I. 0.44–0.95]). There was a numerical trend in favor of an overall survival benefit when the data from PIPF-004 and PIPF-006 were pooled, however, this did not reach statistical significance.

The Applicant completed an additional Phase 3 study (PIPF-016) of nearly identical design (except for treatment duration) to PIPF-004 and PIPF-006 to support approval of the NDA. The primary efficacy endpoint for PIPF-016 was examined at Week 52 (instead of Week 72). In addition, a mortality analysis at Month 12 was conducted with data pooled from the three studies. A total of 555 patients were randomized in PIPF-016 to pirfenidone 2403 mg/day or placebo. The mean change in FVC (percent of predicted value) was -3.7% in the 2403 mg/day group compared with -6.6% in the placebo group, for an absolute difference of 2.9% ($p<0.001$). In the pooled mortality analysis of PIPF-004, 006, and 016 at Month 12, the risk of all-cause mortality was significantly lower in the pirfenidone 2403 mg/day group (3.5%, 22 of 623 patients) compared with the placebo group (6.7%, 42 of 624 patients), with a Hazard Ratio of 0.52 [95% CI, 0.31–0.87]. However, analysis of survival at the end of study showed only a numeric trend towards improved survival (mortality in pirfenidone group 6.9% vs. placebo group 9.1%) that was not statistically significant.

3.2 SAFETY CONCERNS

For the purpose of this review, severe adverse events associated with pirfenidone are defined as Grade 3-4 using the Modified NCI Common Terminology Criteria for Adverse Events. Safety data from the three Phase 3 clinical studies were pooled, which included data from 623 patients who received 2403 mg/day of pirfenidone and 624 patients who received placebo.

3.2.1 Serious Adverse Events

Nonfatal serious adverse events (SAEs) of any nature were reported in 168 (27%) of 623 patients who received pirfenidone and in 178 (29%) of 624 patients who received placebo. The most commonly reported SAEs were IPF (progression of disease), which was reported in 5.3% of the pirfenidone group and 9.3% of the placebo group; and pneumonia, which was reported in 3.5% of the pirfenidone group and 4.3% of the placebo group.

Fewer patients in the pirfenidone group than in the placebo group died within 28 days of the last dose of treatment [27 (4.3%) vs. 44 (7.1%)]. IPF was the most common cause of death in both groups; 10 patients (1.6%) died from IPF in the pirfenidone group compared with 21 patients (3.4%) who received placebo. Other causes of death in more than two patients were respiratory failure (5 patients [0.8%] in each group) and pneumonia (3 patients [0.5%] in each group).

3.2.2 Severe adverse events

Approximately equal proportions of patients in the pirfenidone group (33%) and placebo group (32%) experienced severe adverse events. Among common adverse events, the system organ classes with the highest frequency of severe adverse events were the respiratory disorders (pirfenidone 7.5%; placebo 13.3%), infections (pirfenidone 5.1%; placebo 6.4%), and gastrointestinal disorders (pirfenidone 4.0%; placebo 1.6%). Severe gastrointestinal adverse events that occurred at a higher frequency in the pirfenidone group included nausea, vomiting, and diarrhea; three pirfenidone-treated patients required hospitalization for these events.

3.2.3 Hepatic adverse events

Serious adverse hepatic events were reported in six pirfenidone patients (1.0%) and one placebo patient (0.2%). The SAEs associated with pirfenidone were reported as hepatitis (n=2), liver function test abnormal (n=2), ALT and AST increased (n=1), and hepatic neoplasm (n=1). Three of the six events (two hepatitis and one liver function test abnormal) met criteria for a severe adverse event. Liver enzyme abnormalities resolved or approached the normal range

after pirfenidone therapy was interrupted or discontinued (with the exception of one patient with hepatic malignancy). No hepatic adverse event resulted in liver failure or death.

Transaminase elevations of any nature occurred in more patients treated with pirfenidone than placebo. In the pirfenidone group, 23 (3.7%) patients experienced AST or ALT elevations from > 3 – 20 times the upper limit of normal (x ULN), compared with 4 (0.6%) patients in the placebo group. In the pirfenidone cases, most patients experienced Grade 2 elevations of > 3 – 5 x ULN. Eight patients treated with pirfenidone experienced Grade 3 elevations (5 - 20 x ULN) compared with one patient in the placebo group. No patient who received pirfenidone experienced a Grade 4 elevation (> 20 x ULN). Liver enzymes became elevated within the first six months of treatment in most pirfenidone-treated patients, and in all cases followed over time the transaminase elevations were reversible following dose reduction or discontinuation.

Four cases have met the criteria for Hy's law in the global safety experience. One case from PIPF-016 was reported as a potential case, though the patient was also receiving concomitant medications and underwent genetic testing that confirmed a diagnosis of Gilbert's disease. Pirfenidone was discontinued and the hepatitis resolved, though the patient subsequently died from his underlying IPF. The CDTL draft review noted that confounding medications, underlying liver disease and the presence of cholestasis preclude a definitive determination of this as being a Hy's law case. Of the three additional Hy's law cases, one case occurred in a Phase 2 foreign clinical study whereas the other two cases involved patients enrolled in a European early access program. All four Hy's law cases occurred within two months of treatment initiation and the associated hepatic lab abnormalities returned to or approached the normal range after pirfenidone was discontinued.

3.2.4 Photosensitivity and rash

More patients treated with pirfenidone compared with placebo reported rashes (n=189 [30.3%]) vs. n=64 [10.3%]) or photosensitivity reactions (n=58 [9.3%] vs. n=7 [1.1%]). These adverse events occurred within the first six months of treatment in the majority of patients. Severe rash was experienced by 4 (0.6%) patients in the pirfenidone group and 1 (0.2%) patient in the placebo group. Similarly, severe photosensitivity reactions were experienced by more patients treated with pirfenidone than with placebo (5 [0.8%] vs. 1 [0.2%]). There were no rash or photosensitivity events that were Grade 4 or that resulted in fatal outcomes, and only two cases (one rash and one photosensitivity reaction) were reported as SAEs. No cases of Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis have been reported in clinical studies.

4 DISCUSSION

Substantial evidence of the efficacy of pirfenidone for the treatment of IPF has been demonstrated based on the significant improvement in the change from baseline in percent predicted FVC in studies PIPF-004 and PIPF-016, and a numeric improvement in survival at the end of study observed from the pooled analysis of the three Phase 3 studies (PIPF-004, PIPF-006, and PIPF-016) compared with placebo.

In terms of serious or severe adverse events, the safety profile of pirfenidone was similar to placebo. Although there was a high rate of SAEs in patients treated with pirfenidone, this rate was lower than that observed in the placebo group; the rate of severe adverse events was also high but similar to placebo. The CDTL review noted the overall high proportion of patients

with an SAE is not surprising given the long duration of the trials and an older patient population with a severe disease and multiple co-morbid conditions. The most important safety concerns associated with pirfenidone are possible liver injury and photosensitivity/rash. Pirfenidone appears to cause liver injury in some patients, though elevated liver enzymes were reversible with dose reduction or discontinuation, and there have been no hepatic adverse events that resulted in liver failure or death. Photosensitivity reactions and rash occurred at a higher rate in patients treated with pirfenidone than placebo, but few of these events were severe or serious. Patients will be advised to use sunscreen and avoid sun exposure. Gastrointestinal intolerance is an additional safety concern that will require dose titration to initiate treatment and possible dosage reduction or interruption.

The Applicant's currently proposed risk management strategy does not include a REMS. A communication plan REMS for pirfenidone was proposed in the original NDA submission in 2009. However, the Applicant now believes a REMS is no longer warranted because of the additional safety data and experience acquired in both the clinical and international postmarketing settings, and that the risks of hepatic adverse events, photosensitivity and rash, and gastrointestinal intolerance can be managed with the labeling and pharmacovigilance. (The Applicant also plans to make pirfenidone available in the U.S. through a voluntary managed distribution system of specialty pharmacies.)

Across a variety of therapeutic areas, there are a number of approved drugs associated with hepatotoxicity that rely on labeling alone to communicate this risk. Correspondingly, there are relatively few drugs with a REMS to address liver abnormalities or hepatotoxicity. Of five drugs approved with a REMS to address hepatic risks, three drugs (bosentan, lomitapide, mipomersen) include a Boxed Warning for hepatotoxicity in the labeling and elements to assure safe use (ETASU) that require, at minimum, prescriber certification and pharmacy certification. The Boxed Warning for bosentan includes reports of serious clinical outcomes (i.e., liver failure and cirrhosis) in the treatment of pulmonary arterial hypertension. Additionally, lomitapide and mipomersen were approved for the treatment of homozygous familial hypercholesterolemia based on extremely small clinical development programs that were unlikely to detect adverse outcomes given their size and duration, with serious hepatic safety concerns and substantial concern for much broader use beyond the indicated population; these factors collectively affected the decision to require a REMS. The other two REMS programs for hepatic adverse events (dronedarone, tocilizumab) consist of communication plans that address multiple other risks in addition to liver injury/dysfunction, for the treatment of atrial fibrillation and rheumatoid arthritis, respectively.

Finally, IPF is a progressive and fatal disease with no other approved treatments at this time. The Agency has designated pirfenidone as a breakthrough therapy, and the drug has demonstrated substantial efficacy in significantly improving the decline of lung function as well as evidence that survival is numerically trending in favor of pirfenidone compared with placebo. There are no Boxed Warnings under consideration for the main safety concerns associated with pirfenidone, which include elevated liver enzymes, photosensitivy/rash, and gastrointestinal intolerance. The most likely prescribers of pirfenidone are pulmonologists who are familiar with the management of IPF; treatment efforts for IPF have included cytotoxic agents, immunosuppressants, and other agents that have important and significant safety profiles. Therefore, practitioners who treat IPF should have experience with monitoring and treating patients with drugs that have serious risks similar to those seen with pirfenidone (e.g.,

photosensitivity with certain antibiotics and elevated liver enzymes with cytotoxic agents). A monitoring schedule for the testing of liver function will be provided in the pirfenidone prescribing information. Therefore, it is DRISK's assessment that the risks associated with pirfenidone will be adequately communicated by the labeling.

5 CONCLUSION

In conclusion, risk mitigation measures beyond the labeling are not warranted for pirfenidone. The efficacy of pirfenidone for the treatment of IPF has been demonstrated, which includes survival data that supports the primary efficacy endpoint. The risks associated with the drug are elevations in liver enzymes, photosensitivity/rash, and gastrointestinal intolerance. The benefit-risk profile for pirfenidone is acceptable and the risks can be communicated through the labeling.

Should the Division of Pulmonary, Allergy, and Rheumatology Products have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

ROBERT G PRATT
10/06/2014

REEMA J MEHTA
10/06/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 26, 2010
To:	Badrul Chowdhury, M.D., Director Division of Pulmonary Allergy and Rheumatology Products
Thru:	LaShawn Griffiths, MSHS-PH, BSN, RN, Patient Product Information Reviewer Team Leader Division of Risk Management (DRISK)
From:	**OSE Esbriet REMS Review Team** **Scientific Lead:** LCDR Kendra Worthy, Pharm.D., Drug Risk Management Analyst (DRISK) **Team Members:** Mary Dempsey, Risk Management Program Coordinator (DRISK)) Kate Heinrich, M.A., Health Education Reviewer (DRISK) Shawna Hutchins, MPH, BSN, RN, Patient Product Information Reviewer (DRISK) Suzanne Robottom, Pharm.D., Team Leader (DRISK) Carolyn Volpe, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Esbriet® (pirfenidone) Capsules
Application Type/Number:	NDA 22-535
Applicant/sponsor:	Intermune, Inc.
OSE RCM #:	2009-2306

We acknowledge the Sponsor's November 4, 2009 voluntary proposed REMS for Esbriet® (pirfenidone) capsules. Due to nonclinical deficiencies and lack of substantial evidence of efficacy, the Division of Pulmonary Allergy and Rheumatology Products (DPARP) plans to issue a Complete Response (CR) letter for this review cycle.

DRISK will defer comment on the Medication Guide and REMS proposal at this time. A final review on the appropriate risk management strategy for pirfenidone will be provided once a clearer understanding of the risk benefit profile can be elucidated.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

KENDRA C WORTHY
04/26/2010

LASHAWN M GRIFFITHS
04/26/2010