CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022535Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022535

COMPLETE RESPONSE

InterMune, Inc.
3280 Bayshore Blvd.
Brisbane, CA 94005

Attention: Marianne Armstrong, Ph.D.
Senior Vice President, Chief Regulatory and Safety Officer

Dear Dr. Armstrong:

Please refer to your November 4, 2009, New Drug Application (NDA), received November 4, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Esbriet (pirfenidone) 267 mg capsules.

We acknowledge receipt of your amendments dated November 13 and 19, and December 3 and 30, 2009, and January 7, 12, 13, 14, 21, 26, 27, 28 and 29, February 5, 9, 12, 15, 17, 18, and 19, and March 5, 12, 18, 22, and 25, 2010.

We note that your November 4, 2009 submission included a proposed risk evaluation and mitigation strategy (REMS) for Esbriet (pirfenidone).

We further acknowledge receipt of your submissions dated November 4, 2009, and April 5, 6, 13, and 15, 2010, which were not reviewed in their entirety for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. The submitted data do not provide substantial evidence of efficacy of pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. The positive finding of forced vital capacity (FVC) in trial PIPF-004 was not replicated in trial PIPF-006. The clinical program also does not provide substantial replicate evidence of efficacy on other clinically meaningful efficacy measures. Mortality is the ideal primary endpoint in clinical trials in patients with IPF. The submitted data did not demonstrate a statistically significant benefit in all-cause mortality.

To support approval of pirfenidone for patients with idiopathic pulmonary fibrosis, conduct a placebo-controlled clinical trial that demonstrates a statistically significant benefit in all-cause mortality with pirfenidone. Alternatively, to support approval of pirfenidone for patients with idiopathic pulmonary fibrosis to reduce decline in lung function, conduct a clinical trial with FVC as the primary endpoint that replicates the efficacy of pirfenidone compared to placebo. The findings must be robust and provide evidence of a clinically meaningful response, including a responder analysis that favors pirfenidone. All-cause mortality data from the to-be-conducted clinical trial pooled with the all-cause mortality data from trials PIPF-004 and PIPF-006 should also provide supportive evidence of benefit.

NONCLINICAL

2. The impurity (b) (4) possesses an (b) (4). The specification for this impurity in the drug substance is (b) (4)%, in the drug product at release is (b) (4)%, and at the end of shelf life is (b) (4)%. For specifications at (b) (4) and (b) (4)%, the potential daily doses are (b) (4) mcg/day, respectively. These levels (b) (4) the limit of 1.5 mcg/day specified by the *Draft Guidance for Industry - Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*. Based upon the CDER Computational Toxicology Analysis of (b) (4), it was predicted to be either equivocal or positive in bacterial mutagenicity assay dependent upon whether specificity or sensitivity, respectively, was emphasized in the analysis. Qualify (b) (4) by conducting a bacterial mutagenicity assay. Submit a GLP compliant, final audited report for this study. We remind you that if this impurity is positive in the bacterial mutagenicity assay, you will need to ensure levels (b) (4) 1.5 mcg/day.

MICROBIOLOGY

3. It is not clear from the methods provided that an adequately representative sample is actually subjected to a test for total aerobic microbial count (TAMC) or for yeasts and mold (TY&M). You have demonstrated that a (b) (4) dilution of sample is needed to avoid interference. These methods appear to reduce the amount of sample tested to (b) (4) or (b) (4) gram. Provide methods that test 10 grams as indicated in USP <61>.

4. The dilution of samples to a (b) (4) level when the acceptance criterion is (b) (4) cfu/mL for yeasts and mold is not adequately sensitive. It is not acceptable to assume that the distribution of microorganisms in a suspension would allow reliable detection at the (b) (4) cfu/mL level. Provide a method that can detect a reliable and reproducible level of yeasts and mold (and bacteria) if present in the product at the specified limits. It appears that a filtration or Most Probable Number (MPN) method may be more appropriate for this product.

LABELING

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Eunice Chung, Pharm.D., Regulatory Project Manager, at (301) 796-4006.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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

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

/s/

CURTIS J ROSEBRAUGH
05/04/2010