

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-081

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Sciences, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado
7575 West 103rd Ave., Suite #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

Please refer to your new drug application (NDA) dated December 13, 2006 submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We acknowledge receipt of your submission(s) dated January 11 and 26, February 28, March 2, 13, 16, and 26, April 6, 17, and 24, May 1, 11, 14, 15, and 30, and June 1, 6, and 11, 2007.

This new drug application provides for the use of Letairis (ambrisentan) 5 and 10 mg Tablets for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

We have completed our review of this application. It is approved with restrictions to assure safe use under the provisions of the Subpart H regulations (21 CFR 314.520), effective on the date of this letter, for use as recommended in the enclosed labeling text, Medication Guide, RiskMAP, and carton and container labels. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced restricted distribution approval regulations.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide, RiskMAP, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-081.**" Approval of this submission by FDA is not required before the labeling is used.

The Pediatric Research Equity Act is not applicable to drugs granted orphan drug designation.

The postmarketing study commitments that have been agreed upon based on your written correspondence dated 6/15/07 are listed below:

1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at peak and trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.

Protocol Submission: by 10/1/2007
Study Start: by 06/2008
Final Report Submission: by 12/2009

2. Gilead agrees to submit the results of the Phase 1 ketoconazole drug interaction study that has already been completed.

Final Report Submission: by 10/2007

3. Gilead agrees to a post-approval commitment to explore the interaction potential of strong inhibitors of CYP2C19 (e.g. omeprazole) on ambrisentan pharmacokinetics in humans. Gilead further agrees to explore the interaction potential of cyclosporine A (strong inhibitor of OATP and P-gp) and rifampin (inhibitor of OATP and inducer of P-gp, CYPs 3A and 2C19) on ambrisentan pharmacokinetics in humans.

Protocol Submission: by 10/1/2007
Study Start: by 04/2008
Final Report Submission: by 12/2008

This commitment might also be addressed by analysis of existing data.

4. With regard to the RiskMAP, Gilead agrees to submit to the FDA by July 15, 2007, the following documents:

- i. The pregnancy exposure root cause analysis plan including the questionnaire that will be used in the analysis plan;
- ii. The patient and prescriber knowledge, attitude, and behavior survey tools for the RiskMAP evaluation plan;
- iii. The Pharmacy Standard Operating Procedures (SOPs); and
- iv. The Pharmacy Audit Plan.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have determined that Letairis poses a serious and significant public health concern relating to women of child-bearing potential and patients with liver impairment. This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of

information concerning risks that could affect their decision to use or continue to use the drug, and/or assure effective use of the drug.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Letairis. Therefore, format the proposed Medication Guide in a manner that will assure its appropriate distribution to patients and include a plan to ensure distribution. In addition, submit proposed container and/or carton labels for Letairis that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Dan Brum, PharmD, MBA, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**Appears This Way
On Original**