DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081/S-008

Gilead Sciences, Inc.
Attention: Ms. Hansa Isokoski
3333 Walnut St.
Boulder, CO 80301-2515

SUPPLEMENT APPROVAL

Dear Ms. Isokoski:

Please refer to your supplemental new drug application (sNDA) dated September 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg Tablets. This amendment contained a proposed Risk Evaluation and Mitigation Strategy (REMS) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified Letairis (ambrisentan) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We also refer to your submissions dated March 3, and May 28, 2009.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Letairis to ensure the benefits of the drug outweigh the risks of hepatotoxicity and teratogenicity. Your proposed REMS, submitted on September 19, 2008, as amended, and appended to this letter, is approved. The REMS consists of the Medication Guide, elements to assure safe use, and the timetable for submission of assessments of the REMS and related documents appended to the REMS.

We acknowledge that you will continue to submit RiskMAP assessments for the period ending on May 29, 2009 until July 14, 2009.

You will collect and report all data required for assessments of the approved REMS. The REMS Assessment Plan should include but is not limited to the following data:

1. Reports of operational audits, including results of distribution data reconciliation
2. Results of prescriber and patient surveys, including information on patient reported compliance with contraceptive use
3. The total number of patients and female patients of childbearing potential receiving the product
4. Drug use patterns (reasons for use, patient demographics, prescribing medical specialties)
5. The number (percent) patient reported compliance with:
    - Monthly pregnancy testing for female patients of childbearing potential by quarter and overall
    - Liver function testing by quarter and overall

6. Cases of liver injury and reports of pregnancy exposures
7. In the case of pregnancy, the root-cause analysis to determine the reason the REMS failed to prevent the pregnancy exposure
8. The number of pregnancy exposures (pregnancy exposures will be recorded within the REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the REMS database to cases in the global safety database)
9. An analysis of the numbers and reasons for pharmacist calls to prescribers
10. The results of surveys of certified dispensers on the number and type of interactions that occur between pharmacists and prescribers as part of your REMS
11. The frequency of interruptions in therapy, why such interruptions occurred, and, how long any shipment was delayed (e.g., the number of times a shipment was held because the patient had not had their monthly laboratory tests)
12. The number and reasons for discontinuation therapy with Letairis (ambrisentan)
13. The frequency and reasons for dispensing >30 day supply
14. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified
15. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24
16. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the amendment containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-081 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22-081
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-081
REMS ASSESSMENT

If you do not submit electronically, please send 5 copies of REMS-related submissions.

DEAR HEALTHCARE PROFESSIONAL LETTER

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the 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 to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-081/S-008**".

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: REMS

Medication Guide

Final product labeling

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

/s/

Norman Stockbridge

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