DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022081/S-039

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: April Given
Manger, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Givens:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 5, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 mg and 10 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Letairis risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Letairis was originally approved on October 29, 2009, and the most recent REMS modification was approved on November 30, 2018. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS establishes a Single Shared System (SSS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Letairis and ANDAs referencing Letairis, called the Ambrisentan REMS Program.

Your proposed modified REMS, submitted on December 5, 2017, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised. Submit REMS Assessments annually from the date of the initial REMS approval (03/28/2019). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Submit each assessment so that it will be received by the FDA on or before the due date.

The revised REMS assessment plan must include, but is not limited to, the following:

1. **REMS Program Utilization (for each reporting period and cumulatively)**
    a. Prescribers
        i. Number of certified prescribers, and the number and percentage of enrolled health

care providers who have prescribed Ambrisentan stratified by medical specialty

b. Pharmacies
   i. Number of certified pharmacies by pharmacy type (inpatient and outpatient)
c. Patients
   i. Number and percentage of enrolled patients by patient type:
      1) Females of reproductive potential (FRP)
      2) Pre-pubertal females (as classified on the Ambrisentan REMS Program Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form)
      3) Females of non-reproductive potential (FNRP)
   ii. Number of patients, new and total, by patient type grouped by the following age ranges
      1) < 6
      2) 6 - < 18
      3) 18 - < 65
      4) 65+
d. Number of prescriptions dispensed for FRPs and FNRPs.

2. **Reproductive Potential Status Changes (for each reporting period and cumulatively)**
   Both in a flowchart and in the report narrative, report the following regarding the ***Change in Reproductive Potential Status and Prepubertal Annual Verification Forms*** including:
   a. Number of ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms*** received, including the number of forms noted as a misclassification, error in classification, or correction to classification.
   b. Number of status changes to an FRP status, including the rationale for the change as indicated on the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***. Also, report:
      i. Time between receipt of ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
      ii. Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following a change in status to an FRP
      iii. Number of times Ambrisentan was dispensed prior to the patient getting their first pregnancy test following the status change to FRP, any resulting adverse events, and corrective actions
   c. Number of status changes to an FNRP, including rationale for the change as indicated on the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***
   d. The number of ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms*** returned reporting annual verification that a patient remains a Pre-Pubertal Female
   e. The number of ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms*** returned reporting annual verification that a patient remains a Pre-Pubertal Female that are expected
   f. Number of shipments suspended as a result of the prescriber's failure to return the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** for pre-pubertal females
   g. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any female patient within 10 business days after the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** is signed.

h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis.

3. **Pharmacy and Distributer Audit Summary (for each reporting period and cumulatively)**
Provide a report of audit activities for certified inpatient pharmacies; certified outpatient pharmacies, certified specialty pharmacies; the REMS Coordinating Center; and distributors performed during the reporting period to include:
    a. The number of audited sites in each category listed directly above.
    b. A summary of critical and major (define both categories) observations identified during audits and corrective actions taken to address any non-compliance including whether any required corrective and preventive action (CAPA) plans were initiated and satisfactorily completed.
    c. A comparison of the findings to findings of previous audits and an assessment whether any trends are observed.
    d. An overview of the site-audit plan

4. **Ambrisentan REMS Program Compliance (for each reporting period and cumulatively)**
    a. Number of Ambrisentan prescriptions dispensed that were written by non-certified or deactivated prescribers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions
    b. Number of prescriptions dispensed by non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
    c. Number of prescriptions dispensed:
        i. with an expired REMS dispensing authorization
        ii. without a REMS dispensing authorization
    d. Number of shipments sent to non-certified pharmacies, source of report(s), actions taken to remove Ambrisentan from these pharmacies, actions taken to prevent future occurrences and outcome of such actions
    e. The number of certified prescribers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action
    f. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of ten or more days), focusing especially on delays in pregnancy testing with a root cause analysis to identify why pregnancy testing wasn't completed. Further, include:
        i. The mean and median duration (including the standard deviation) of the observed treatment interruptions; and
        ii. Any adverse events resulting from the treatment interruption.
    g. Number of prescriptions dispensed of greater than 30-day supply for an FRP and reasons for such dispensations
    h. Noncompliance with the Ambrisentan REMS Program requirements, source of report(s), and any corrective action(s) or resolution(s).

5. **Pregnancy Cases (for each reporting period and cumulatively)**
    a. The number of pregnancy exposures reported and stratified by source of exposure report (spontaneous report, reported via the REMS Program, etc.). A cumulative summary of both U.S. and worldwide pregnancy cases should be provided and at a minimum, include the following information:
        i. Event identification number
        ii. Indication for Ambrisentan
        iii. Contraceptive methods used

iv. Weeks gestation at termination if pregnancy terminated
v. Outcome for each pregnancy
vi. Age of patient

b. Follow-up of outstanding pregnancy reports from the previous assessment reporting period

c. Root cause analysis of each reported pregnancy to determine the reason the REMS program failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis

6. **Evaluation of Knowledge of the Ambrisentan REMS Program and Risks of Ambrisentan Surveys (starting with the 12-month assessment then annually)**
   a. An evaluation of certified prescribers' knowledge of:
      i. the risks of embryo-fetal toxicity associated with ambrisentan
      ii. the need to monitor patients at baseline and monthly
      iii. the need to counsel patients about: these risks; the need to use highly reliable contraception; and the need for monthly monitoring
      iv. the need to enroll patients in the REMS
   b. An evaluation of certified inpatient, outpatient and specialty pharmacy authorized representatives' and trained pharmacists' knowledge of:
      i. the risks of embryo-fetal toxicity
      ii. the need to confirm that appropriate patient monitoring and counseling occur before dispensing Ambrisentan.
   c. An evaluation of enrolled patients' knowledge of:
      i. the risks of embryo-fetal toxicity
      ii. appropriate baseline and monthly monitoring
      iii. appropriate contraception.

7. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its

goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022081 REMS ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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

NDA 022081 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022081/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022081/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 022081

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
301 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
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