



NDA 022081/S-038

**SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION**

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

Dear Ms. Given:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 28, 2017G, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 mg, And 10 mg Tablets.

We also acknowledge receipt of your amendments dated September 1 and 8, 2017.

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Letairis (ambrisentan) was originally approved on October 29, 2009, and the most recent modification was approved on July 21, 2017. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of the addition of an online enrollment option for patient and prescriber enrollment.

Your proposed modified REMS, submitted on July 28, 2017, amended on September 8, 2017, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 7, 2013.

We have determined that your REMS assessment plan requires revision because approval of this modification allows for enrollment online and via fax.

The REMS assessment plan must include but is not limited to the following items. Additions are noted by underline and deletions are noted by ~~striketrough~~.

1. Assessment of the dispensing of the Medication Guide in accordance with 21 CFR 208.24
2. Enrollment into the Letairis REMS Program
 - a) Patients: new and total across previous assessment reporting periods who received at least one shipment of Letairis, age, gender, diagnosis, number and percentage of females of reproductive potential, number and percentage of pre-pubertal females
 - b) Dispensers: new and total
 - c) Prescribers: new and total, stratified by medical specialty
 - d) Number of prescribers enrolled online or via fax
 - e) Number of patients enrolled online or via fax
3. Report on Letairis REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification forms including:
 - a. Number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification* forms received
 - i. 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
 - ii. 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 expected
 - iii. Whether any shipments were suspended as a result of the prescriber's failure to return the form for pre-pubertal females
 - b. Number of status changes to a female of reproductive potential, including:
 - i. Rationale for the change as indicated on the form and time between receipt of form and start of routine monthly pregnancy testing
 - ii. Number of times Letairis was dispensed prior to the patient getting their first pregnancy test following the status change, any resulting adverse events, and corrective actions
 - c. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the form
4. Compliance with the Letairis REMS
 - a) Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
 - b) The number of patients who experience a shipment delay due to reporting a missed pregnancy test, the reasons for the missed pregnancy test, and any adverse event occurring as a result of treatment interruptions.
 - c) A summary of audit activities for the REMS Coordinating Center and certified pharmacies, reports of critical observations identified and the associated corrective and preventive action (CAPA) plans, and whether the CAPA plans were satisfactorily completed.

5. An analysis of the post-marketing cases of pregnancy reported in association with Letairis (during the reporting period and cumulative) with attention to but not limited to:
 - a. The number of pregnancy exposures* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via the Letairis REMS Coordinating Center, enrolled in the pregnancy registry), age, and other demographics.
 - b. The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).
 - c. Follow-up of outstanding pregnancy reports from previous assessment reporting period
 - d. Root cause analysis of each reported pregnancy to determine the reason the Letairis REMS program failed to prevent the pregnancy exposure; and
 - e. Discussion of any new information provided in the most recent Periodic Safety Update Report (PSUR) or Periodic Benefit Evaluation Report (PBRER) regarding pregnancy. In the electronic REMS assessment submission, include a hyperlink to the most recent PSUR/PBRER that provides information on worldwide pregnancies.

*All pregnancy exposures reported to the sponsors from any source should be reported and analyzed as part of the REMS assessment. Pregnancy exposures will be recorded within the Letairis REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the Letairis REMS database to cases in the global safety database.
6. 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. Provide information to address each requirement for the current reporting period and for previous reporting periods. When possible, a tabular format is recommended.

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 1 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 of 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 the 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 022081REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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

**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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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(S):
REMS

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

/s/

MARY R SOUTHWORTH
09/27/2017