NDA 022081/S-042

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: April Given
Senior Manager, Regulatory Affairs
33 Lakeside Drive
Foster City, CA 94404

Dear Ms. Given:

Please refer to your supplemental new drug application (sNDA) dated and received November 10, 2020, 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 Ambrisentan 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 shared system REMS for ambrisentan products (which includes Letairis) was approved on March 28, 2019. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of updates to the following:

- In the Prescriber and Pharmacy Guide and on the REMS website changes were made to:
    - Clarify inpatient pharmacy requirements for when an enrolled patient is continuing ambrisentan in the inpatient setting and is already under the supervision and care of a certified prescriber to align with the existing inpatient pharmacy requirements in the approved REMS document.
    - include a provision for prescribers to authorize a greater than 30-day supply for females of reproductive potential due to travel or personal extenuating circumstances at the prescriber's medical discretion.
- Addition of certified outpatient pharmacy listings and links to Spanish language REMS materials on the REMS website.
- A new office contact portal.

Your proposed modified REMS, submitted to Drug Master File (DMF) 34591 on June 26, 2020, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 28, 2019.

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

REMS Implementation and Operations

1. **REMS Certification and Enrollment Statistics (for each reporting period and cumulatively)**

    a. Healthcare Providers
        i. Number and percentage of newly certified healthcare providers, and the number and percentage of active health care providers (i.e. who have prescribed ambrisentan) stratified by medical specialty and geographic region (as defined by US Census)
    b. Pharmacies
        i. Number and percentage of newly certified pharmacies and the number and percentage of active certified pharmacies (i.e. have dispensed ambrisentan) stratified by pharmacy type (i.e. inpatient and outpatient) and geographic region (as defined by US Census)
    c. Patients
        i. Number and percentage of newly enrolled patients and the number and percentage of active patients (i.e., have received ambrisentan) stratified by geographic region (defined by US Census) 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)
    d. Wholesaler/Distributors
            a. Number and percentage of newly enrolled wholesaler/distributors and the number and percentage of active wholesaler / distributors (i.e., have shipped ambrisentan)

2. **REMS Utilization Data (for each reporting period and cumulatively)**

a. Number and percentage of unique patients who received ambrisentan, new and total, by patient type grouped by the following age ranges:
    i. < 10
    ii. 10 - < 18
    iii. 18 - < 25
    iv. 25 - < 45
    v. 45 - < 53
    vi. 53+
b. Number and percentage of prescriptions (first-fills and refills) dispensed for FRPs and FNRPs stratified by:
    i. Healthcare Provider Specialty
    ii. Reproductive Status (FRP or FNRP)
    iii. Patient age as outlined in 2a above

3. **REMS Infrastructure and Performance (for each reporting period and cumulatively)**
    a. REMS Coordinating Center
        i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler(s)/distributor(s), other)
        ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by reporter (authorized representative, pharmacy, healthcare provider, patient, other)
        iii. Summary of frequently asked questions (FAQ) by stakeholder type
        iv. Summary report of REMS-related problems identified and resulting corrective actions
    b. REMS Website
        i. Number of visits and unique visits to the REMS website
        ii. Number of REMS materials downloaded and printed for each material

4. **Pharmacy and Distributor Audit Summary (for each reporting period and cumulatively)**
    a. Provide a report of audit findings for each stakeholder (e.g. certified inpatient pharmacies; certified outpatient pharmacies; certified specialty pharmacies; the REMS Coordinating Center; wholesalers/distributors) including but not limited to:
        i. A copy of the audit plan for each stakeholder
        ii. The number of audits expected, and the number of audits conducted

iii. The number of type of deficiencies noted for group of audited stakeholders
iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describer actions taken
vi. Use a unique ID for stakeholders that had deviations to track deviations by stakeholders over time
vii. Confirm documentation of completion of training for relevant staff
viii. Verify the existence of documented processes and procedures for complying with the REMS
ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

5. **Ambrisentan REMS Program Compliance (for each reporting period and cumulatively)**
    a. Provide a summary of the non-compliance identified, including but not limited to:
        i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
        ii. The number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of non-compliance, report the following information:
            1. The unique ID(s) of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
            2. The source of the non-compliance data
            3. The results of the root cause analysis
            4. What action(s) were taken in response and whether any follow up is planned
    b. 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

c. Number of prescriptions dispensed by non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
d. Number of prescriptions dispensed:
    i. with an expired REMS dispensing authorization
    ii. without a REMS dispensing authorization
e. 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
f. The number of certified prescribers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action
g. An evaluation of dispensing delays (defined as a delay in dispensing/shipment of ten or more days) which resulted in an actual treatment interruption, due to missing pregnancy testing. Include a root cause analysis to identify why pregnancy testing was not completed along with the protocol used to conduct the root cause analysis. For each treatment interruption, 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.
h. Number of prescriptions dispensed of greater than 30-day supply for an FRP and a breakdown of reasons for the dispenses (i.e. Prescriber Authorization, Pharmacy Non-Compliance, Patient Travel, Insurance Needs, or Other). Include any corrective actions as appropriate
i. Noncompliance with the Ambrisentan REMS Program requirements, source of report(s), and any corrective action(s) or resolution(s)

Safe Use Behaviors

6. **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. Include the reasons these were classified as misclassifications or errors.

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 the *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 expected 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
        i. For any forms expected for a Pre-Pubertal female, but not received, conduct follow up in order to determine the cause, outcome, and any corrective actions taken
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 by completing and submitting the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* within ten (10) days of becoming aware of the change
h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis

Health Outcomes and Surrogate of Health Outcomes

7. Pregnancy Cases (for each reporting period and cumulatively)

Each manufacturer will provide in their submission an analysis of all cases of pregnancy reported in association with ambrisentan from any source including but not limited to the following:

a. The number of pregnancy exposures reported and stratified by source of exposure report (i.e. spontaneous report, reported via the REMS Program, etc.).
b. Pregnancy rate
c. 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
d. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
e. 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

Knowledge

8. 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 appropriate contraception; and the need for monthly monitoring
    iv. the need to enroll patients in the REMS
    v. Identification of any burdens to the healthcare system as a result of 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

iii. identification of any burden of the healthcare system as a result of the REMS

c. An evaluation of enrolled patients' knowledge of:
   i. the risks of embryo-fetal toxicity
   ii. appropriate baseline and monthly monitoring
   iii. appropriate contraception
   iv. Identification of any burden or difficulties in accessing care as a result of the REMS

9. 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
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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 LABELING 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.

[Note to division: Confirm with DRISK reviewer that the REMS Document and REMS materials (e.g., forms, educational materials) are in their final format before appending to the letter. Append both the REMS Document and all REMS materials in their final format (with color and graphics). Do *not* attach the REMS Supporting Document to the letter.]

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, call Lori Anne Wachter, RN, BSN, RAC (US), Regulatory Project Manager for Safety , at 301 796-3975.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
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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