NDA 204410/S-020

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals, Ltd.
Attention: Kevin Holman
Senior Director, Global Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Mr. Holman:

Please refer to your supplemental new drug application (sNDA) dated and received May 24, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opsumit (macitentan) 10 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Opsumit 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 Opsumit was originally approved on October 18, 2013, and the most recent REMS modification was approved on June 10, 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 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) Opsumit and ANDAs referencing Opsumit, called the Macitentan REMS Program, which will become applicable on the date of full approval of the first ANDA joining a shared system with Opsumit. The modification being approved results in a two-part REMS consisting of: (1) the requirements of the previously approved Opsumit REMS, and (2) the new SSS REMS for macitentan products. The requirements of the previously approved Opsumit REMS will remain applicable until full approval of the first ANDA joining a shared system with Opsumit, at which time, they will automatically be replaced by the requirements of the single, shared system.

Your proposed modified REMS, submitted on April 8, 2020, amended and appended to this letter, is approved.

The timetable for submission of assessments of the modified REMS is the same as that approved in the Opsumit REMS on October 18, 2013, until full approval of the first ANDA joining a shared system with Opsumit. Upon full approval of the ANDA joining a shared system with Opsumit, you must submit REMS assessments to the FDA 12 months from the effective date of the SSS REMS, and annually thereafter.

1. There are no changes to the Opsumit REMS assessment plan described in our July 11, 2019 letter.

2. The SSS REMS assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1. Communication Plan (6-month and 1-year assessments only)
   a. Sources of the distribution lists for healthcare providers
   b. Number of healthcare providers targeted
   c. The date(s), number and medical specialty of healthcare providers who were sent the letter for prescribing healthcare providers by the methods of distribution.
   d. The date(s) and number of pharmacists, and distributors/wholesalers who were sent the introductory letter to the REMS by the methods of distribution
   e. The date(s), number and names of Professional Societies that were sent the Letter for Professional Societies by the methods of distribution
   f. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients

Program Implementation and Operations

2. REMS Program Implementation (6-month and 1-year assessments only)
   a. Date when the Macitentan REMS website became live and fully operational
   b. Date(s) when previously enrolled healthcare professionals, patients, and inpatient pharmacies that were in the Opsumit REMS were migrated into the Macitentan REMS
   c. Date(s) when new healthcare professionals, patients, and pharmacies (inpatient and outpatient) could become certified/enrolled into the Macitentan REMS
   d. Date(s) when wholesalers/distributors could register with the Macitentan REMS
   e. Date when the REMS call center was established and fully operational

3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)
   a. Healthcare Providers

i. Number of newly certified, migrated, and active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by professional designation, (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (e.g., Pulmonology, Cardiology Rheumatology, Other) and geographic region
ii. Method of healthcare provider certification (online, fax or email)

b. Pharmacies
   i. Number of newly certified, migrated, and active (i.e., have dispensed macitentan at least once during the reporting period) pharmacies stratified by geographic region and pharmacy type (e.g., inpatient, outpatient) and geographic region
   ii. Method of pharmacy certification (online, fax or email)
   iii. Number of pharmacies that were unable to become certified and reason why

c. Patients
   i. Number of newly enrolled, migrated, and active (received at least one dispensation of macitentan during the reporting period) patients stratified by age, gender, race, geographic region, and diagnosis necessitating macitentan treatment
   ii. Number and percentage of newly enrolled and active certified patients by reproductive potential status:
      1. Females of reproductive potential (FRP)
      2. Pre-pubertal females (as classified on the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form) (PPF)
      3. Females of non-reproductive potential (FNRP)
   iii. Number of patients who have discontinued therapy and the reason for discontinuation
   iv. Method of patient enrollment (online, fax or email)

d. Wholesalers/Distributors
   i. Number of newly enrolled and active (i.e., have shipped macitentan) wholesalers/distributors

4. Macitentan Utilization Data (provide previous, current, and cumulative reporting periods)
   a. Number of prescriptions (new and refills) dispensed stratified by
      i. Prescriber specialty, degree/, professional designation, and geographic region
      ii. Patient demographics (age, gender~~,~~ reproductive potential status, and geographic region)
   b. Number of unique patients receiving macitentan, stratified by age, gender, race, reproductive potential status, and geographic region

5. REMS Infrastructure and Performance (provide previous, current, and cumulative reporting periods)
   a. REMS Website
      i. Number of visits and unique visits to the REMS website
      ii. Number of REMS materials downloaded or printed for each material
   b. Coordinating Center Report
      i. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, wholesalers/distributors, etc.)
      ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type (e.g., patient/caregiver, healthcare provider, pharmacy, wholesalers/ distributors, etc.).
      iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
      iv. A summary report of corrective actions resulting from issues identified
   c. Report on Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form Data (provide previous, current, and cumulative reporting periods)
      Both in a flowchart and in the report narrative, report the following regarding the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Forms including:
      i. Methods of submission of the forms to the REMS (e.g., online, fax, etc.)
      ii. Number of forms received, including the number of forms received in error and the reasons these were classified as errors
         1. Time between when the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form indicating a change to FRP status is submitted to the REMS and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
            a) Number of instances where a prescriber did not perform a pregnancy test within 10 business days after the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form is submitted to the REMS.
         2. Number of times macitentan was dispensed prior to the patient getting her first pregnancy test following the status change to FRP, any resulting pregnancies, and corrective actions
      iii. Number of changes in reproductive potential status to an FNRP, including rationale for the change as indicated on the form

iv. 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
v. 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
vi. 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 Forms for pre-pubertal females
vii. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis with every assessment report.

6. REMS Compliance (provide previous, current, and cumulative reporting periods)
   a. Provide a summary of non-compliance identified, including but not limited to:
      i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which events lead to suspension or decertification from the REMS.
      ii. Provide a copy of the audit plan for each stakeholder.
      iii. Report audit findings for certified outpatient pharmacies; certified inpatient pharmacies; the REMS Coordinating Center; and wholesalers/distributors to include:
         1. Number of audited sites in each category listed directly above.
         2. Number of audits expected, and the number of audits performed
         3. Number and types of deficiencies noted for each group of audited stakeholders
         4. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
         5. For any that did not complete the CAPA within one month of the audit, describe actions taken.
         6. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
         7. Documentation of completion of training for relevant staff
         8. The existence of documented processes and procedures for complying with the REMS
         9. Verification that each audited stakeholder's site that the designated authorized representative remains the same.

If different, include the number of new authorized representatives and verification of the site's recertification.

b. Healthcare Providers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
    i. Number of prescribing healthcare providers who were non-compliant with conducting monthly pregnancy tests for FRPs or other Macitentan REMS program requirements.
    ii. Number of prescriptions written by non-certified healthcare providers and the outcome (number dispensed, number rejected, number of healthcare providers who became certified)
    iii. Number of healthcare providers that were suspended or de-certified and reasons for decertification. Include if any healthcare providers were re-certified.
c. Number of patients not enrolled in the REMS program or registry who were dispensed macitentan
d. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken).
    i. Number and type of pharmacy for which non-compliance with the REMS is detected
    ii. Number and type of non-certified pharmacies that dispensed macitentan and the number of incidents for each
    iii. Number of macitentan prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences
    iv. Number of macitentan prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences
    v. Number of macitentan prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences
    vi. Number of times a macitentan prescription was dispensed either because a certified pharmacy bypassed REMS authorization processes, or did not receive a REMS Dispense Authorization (RDA), to include a description of how the events were identified and any corrective actions taken
    vii. Number of macitentan prescriptions dispensed for more than a 30 days' supply and reasons for such dispensing, including any corrective actions as appropriate
    viii. Number of pharmacies suspended or decertified, the reasons for such actions, and actions to address non-compliance
    ix. Number of first patient shipments sent prior to receipt of a Patient Enrollment Form.

e. Wholesalers/distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
    i. The number of authorized wholesalers/distributors for which noncompliance with the REMS is detected
    ii. Number of wholesalers suspended or de-enrolled, reasons for such action, and actions to address non-compliance
    iii. Number of times macitentan was distributed to a non-certified pharmacy or directly to patients, and actions taken to recover the macitentan.

f. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of five or more days) focusing especially on delays on pregnancy testing with a root cause analysis to identify why pregnancy testing was not completed and the source of the prescriber and/or pharmacy error. Include:
    i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
    ii. Any adverse events resulting from the treatment interruption.
    iii. With every assessment report submission, include the protocol used to conduct this root cause analysis

Safe Use Behaviors

1. Report on Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form Data (provide previous, current, and cumulative reporting periods)

    Both in a flowchart and in the report narrative, report the following regarding the Change in Reproductive Potential Status and Pre-pubertal Annual Verification Forms including:

    a. Methods of submission of the forms to the REMS (e.g., online, fax, etc.)

    b. Number of forms received, including the number of forms received in error and the reasons these were classified as errors

        i. Time between when the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form indicating a change to FRP status is submitted to the REMS and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)

            1. Number of instances where a prescriber did not perform a pregnancy test within 10 business days after the Change in Reproductive Potential Status

and Pre-Pubertal Annual Verification Form is submitted to the REMS.

2. Number of times macitentan was dispensed prior to the patient getting her first pregnancy test following the status change to FRP, any resulting pregnancies, and corrective actions

c. Number of changes in reproductive potential status to an FNRP, including rationale for the change as indicated on the form

d. 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. 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

ii. 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 Forms for pre-pubertal females

iii. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis with every assessment report.

2. **Health Outcomes and/or Surrogates of Health Outcomes**

3. Pregnancy Events (provide previous, current, and cumulative reporting periods)

a. An analysis of all cases of pregnancy reported in association with macitentan from any source including but not limited to:

i. The number of pregnancy exposures reported and stratified by source of exposure report (spontaneous report, for example).

1. Provide a cumulative summary of both U.S. and worldwide pregnancy cases from the original Opsumit

approval date should be provided and at a minimum, include the following information:

a) Event identification number

b) Indication for Macitentan

c) Contraceptive methods used

d) Weeks' gestation at termination if pregnancy terminated

e) Outcome for each pregnancy

f) Age of patient

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

iii. 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

4. Stakeholder Surveys

a. An evaluation of certified prescribing healthcare providers' knowledge of:

i. The risks of embryo-fetal toxicity associated with macitentan

ii. The need for appropriate baseline and monthly monitoring

iii. The need to counsel patients about these risks; the need to use reliable contraception; and the need for appropriate monitoring; and

iv. The need to enroll patients in the macitentan REMS Program

b. An evaluation of certified inpatient and outpatient pharmacy authorized representatives' and staff pharmacists' knowledge of:

i. The risks of embryo-fetal toxicity associated with macitentan; and

ii. The need to confirm that appropriate patient monitoring and counseling occur before dispensing macitentan

c. An evaluation of patients' knowledge of

i. The risks of embryo-fetal toxicity associated with macitentan

ii. The need for appropriate baseline and monthly monitoring

iii. The need for appropriate contraception

5. 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 204410 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 204410 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 204410/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204410
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204410
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204410
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 204410

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
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):
- 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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