DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204410/S-002

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals
Director, Global Drug Regulatory Affairs
1820 Chapel Avenue West
Suite 300
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opsumit (macitentan) 10 mg Tablets.

We acknowledge receipt of your amendments dated December 1, 3, 2014, and July 1, 2015.

This supplemental new drug application provides for proposed modifications to the approved Opsumit risk evaluation and mitigation strategy (REMS), and the Opsumit Medication Guide. This supplement is in response to our September 18, 2014, REMS Modification Notification letter.

APPROVAL& LABELING

We have completed our review of this supplemental application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this

supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).
We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Opsumit was originally approved on October 18, 2013. 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. In order to ensure the benefits of Opsumit outweigh its risks, we determined that you were required to make the following REMS modifications:

1. REMS Document
   - o Modify a statement in the REMS document to ensure that all certified outpatient pharmacies will be audited within 180 days after they are certified in the Opsumit REMS program.
   - o Make changes to clarify the roles and responsibilities of the inpatient and outpatient pharmacy authorized representatives.
2. Reproductive Potential Status Form
   - o Change the title to "Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form."
   - o Add a field (Reason for change in classification) to capture reasons for previous misclassification of reproductive status.
3. Add a new female of non-reproductive potential subcategory ("Other medical reasons for permanent, irreversible infertility") and update all relevant sections of the REMS document and related forms and Medication Guide to reflect this change.

Your proposed modified REMS, submitted on November 12, 2015, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 18, 2013.

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

1. Assessment of the dispensing of the Medication Guide in accordance with 21 CFR 208.24.
2. Report on enrollment into the Opsumit REMS Program: Provide the following data for the current reporting period, the previous reporting period, and cumulatively
   a. Female Patients:
      i. Number of all females who have received at least one shipment of Opsumit; include age, diagnosis, number and percentage of females of reproductive potential
   b. Certified Dispensers
   c. Certified Healthcare Providers stratified by medical specialty; the number and percentage of enrolled health care providers who have prescribed Opsumit

3. Report on Opsumit REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification forms including:

   a. Number of forms received

   b. Number of status changes to a female of reproductive potential, including rationale for the change as indicated on the form and time between receipt of form and confirmation by the certified pharmacy that monthly pregnancy testing occurred

   c. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the form

4. Evaluation of the compliance with the Opsumit REMS:

   a. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

   b. An evaluation of shipment holds due exclusively to the absence of pregnancy test results, which resulted in an actual treatment interruption, root cause analysis to identify why pregnancy testing wasn't completed, and a summary of root cause analysis and any adverse events resulting from the treatment interruption

   c. A summary of operational monitoring activities performed during the reporting period including but not limited to a summary report of critical observations identified during monitoring, results of distribution data reconciliation, and corrective actions taken to address any non-compliance.

   d. A summary of audit activities for Actelion Pathways, certified pharmacies, and distributors performed during the reporting period including but not limited to:

      i. An overview of the site-audit plan;

      ii. The number of audited sites in each category (i.e. REMS Coordinating Center, certified outpatient pharmacies, certified inpatient pharmacies, and certified distributors). The facility type should be included for all inpatient pharmacies.

      iii. Summarize critical observations identified during audits and corrective actions taken to address any non-compliance including but not limited to whether required corrective and preventive action plans were initiated or completed during the reporting period.

5. An analysis of all cases of pregnancy reported in association with Opsumit from any source (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 of exposure report. A cumulative summary of pregnancy cases world-wide should be provided and at a minimum, include the following information:

      i. Event identification number

      ii. Indication for Opsumit

      iii. Birth control methods

      iv. Root cause of contraception failure

      v. Weeks gestation at termination if pregnancy terminated

      vi. Age of patient

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

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

6. With respect to each goal included in the Opsumit REMS, an assessment of the extent to which the approved REMS, including each element of the REMS, is meeting the goal or whether 1 or more such goals or such elements should be modified.

For the 24-month and all subsequent REMS assessments submitted annually thereafter, the following assessment will also be included:

1. An evaluation of patients' awareness and understanding of the risk of teratogenicity associated with Opsumit, including an evaluation of patient-reported compliance with contraceptive use and monthly pregnancy testing for females of reproductive potential.
2. An evaluation of pharmacists' awareness and understanding of the risk of teratogenicity associated with Opsumit and the need to exclude a pregnancy before dispensing Opsumit

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 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 204410 REMS ASSESSMENT

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

or

NEW SUPPLEMENT FOR NDA 204410/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204410/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 204410/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 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

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 Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
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
11/17/2015