DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204410

NDA APPROVAL

Actelion Pharmaceuticals, LTD.
c/o Actelion Clinical Research, Inc.
Attention: Cheryl Czachorowski
Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Please refer to your New Drug Application (NDA) dated October 19, 2012, received October 19, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opsumit (macitentan) 10 mg Tablets.

We acknowledge receipt of your amendments dated January 11, 18, 22, and 24, February 7, 15, and 26, March 6, 26, and 29, April 16, May 5, 10, and 15, June 6 and 21, July 11, and October 15 and 17, 2013.

This new drug application provides for the use of Opsumit (macitentan) Tablets for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

We have completed our review of this 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, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your July 11, 2013, submission containing final printed carton and container labels.

ADVISORY COMMITTEE

Your application for Opsumit (macitentan) tablets was not referred to an FDA advisory committee because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical study designs are similar to that of previously approved products in the class, and the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of hepatotoxicity for Opsumit (macitentan).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2093-1 A long-term prospective observational study (product exposure registry) to evaluate potential serious hepatic risks related to the use of Opsumit (macitentan). The registry will include a sample of patients prescribed Opsumit (macitentan) and enroll at least 5000 patients. Patients should be followed for at least 1 year.
A target sample size, supported by a sample size calculation, with an explanation of the underlying assumptions for the PAH patient population (e.g. incidence of AST/ALT elevations, study/registry dropout rates) should be included in the protocol. Even if the proposed sample size targeting approach seems reasonable at this time, if the underlying assumptions are not met or there are other concerns, an extension of the registry enrollment may be deemed warranted at a later point by the Agency.

The timetable you submitted on October 11, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2014
Interim Report #1 (# study sites and patients enrolled):	June 2014
Interim Report #2 (results):	December 2014
Interim Report #3 (# study sites and patients enrolled):	June 2015
Interim Report #4 (results):	December 2015
Interim Report #5 (# study sites and patients enrolled):	June 2016
Interim Report #6 (results):	December 2016
Interim Report #7 (# study sites and patients enrolled):	June 2017
Interim Report #8 (results):	December 2017
Interim Report #9 (# study sites and patients enrolled):	June 2018
Final Study Report:	December 2018

2093-2 An assessment and analysis of reports of serious hepatic adverse events (to be defined in the protocol) in patients treated with Opsumit (macitentan) submitted according to the schedule outlined below. Specialized follow up should be obtained on these cases to collect additional information on the reports. Summary information should include the total number of cases, a summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series. Hepatic adverse events of special interest will require expedited reporting to the Agency.

The timetable you submitted on October 11, 2013, states that you will provide these assessment reports according to the following schedule:

Final Protocol Submission:	January 2014
Interim Report #1:	June 2014
Interim Report #2:	December 2014
Interim Report #3:	June 2015
Interim Report #4:	December 2015
Interim Report #5	June 2016

Interim Report #6:	December 2016
Interim Report #7:	June 2017
Interim Report #8:	December 2017
Interim Report #9:	June 2018
Final Study Report:	December 2018

Submit the protocol(s) to your IND 77258, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Opsumit (macitentan) to ensure the benefits of the drug outweigh the risk of teratogenicity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Opsumit (macitentan) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Opsumit (macitentan). FDA has determined that Opsumit (macitentan) is a product for which patient labeling could help prevent serious adverse effects, and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients'

decisions to use, or continue to use, Opsumit (macitentan), and that the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Opsumit (macitentan).

Pursuant to 505-1(f)(1), we have also determined that Opsumit (macitentan) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of teratogenicity that is listed in the labeling. The elements to assure safe use will minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Opsumit (macitentan) by certifying healthcare providers and pharmacies, and by documenting safe use conditions.

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.

Your proposed REMS, submitted on October 17, 2013, and appended to this letter, is approved. 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 REMS must be fully operational before you introduce Opsumit (macitentan) into interstate commerce.

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

For the 6-month assessment and all subsequent REMS assessments submitted thereafter:

1. Assessment of the dispensing of the *Medication Guide* in accordance with 21 CFR 208.24
2. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
3. Number of dispensers and prescribers (stratified by medical specialty) certified, and patients enrolled during the current REMS assessment reporting period and during each previous REMS assessment reporting period
4. Patient demographics for the current REMS assessment reporting period and for previous REMS assessment reporting periods to include age, diagnosis, and the percentage number (%) of females of reproductive potential
5. An evaluation of any shipment holds due exclusively to the absence of pregnancy test results, which resulted in an actual treatment interruption and a summary of root cause analysis and any adverse events resulting from the treatment interruption
6. The frequency and reasons for dispensing >30 day supply to females of reproductive potential
7. Report on *Opsumit REMS Reproductive Potential Status Forms* including:
    a. Number of *Opsumit REMS Reproductive Potential Status 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 start of routine monthly pregnancy testing

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

8. Reports of critical observations identified during operational monitoring, including results of distribution data reconciliation
9. Critical observations identified during Regulatory Compliance Audits and corrective actions taken to address any non-compliance
10. An evaluation of inpatient pharmacies' compliance with REMS requirements for dispensing Opsumit (macitentan)
11. An analysis of all cases of pregnancy reported in association with Opsumit (macitentan) 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.

    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

12. With respect to the Opsumit 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

For the 12-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 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 healthcare providers' awareness and understanding of:

    a. The risk of teratogenicity associated with Opsumit (macitentan)

    b. The need to exclude a pregnancy before initiating Opsumit (macitentan) therapy

    c. The need for patients to consistently use reliable birth control and what the reliable methods of contraception are

Under section 505-1(g)(2)(C), FDA may require the submission of a REMS assessment if FDA determines that that an assessment is needed to evaluate whether the approved strategy should be modified to ensure the benefits of the drug outweigh the risks of the drug or minimize the burden on the health care delivery system of complying with the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

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

NDA 204410 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 204410
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204410
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for

NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

You will be contacted by ERG to schedule the interview following this action on your application; ERG will provide specifics about the interview process at that time. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call:

Edward Fromm, R.Ph., RAC
Regulatory Project Manager
(301) 796-1072

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS
Carton and Container Labeling

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/s/

ROBERT TEMPLE
10/18/2013