NDA 218490

NDA APPROVAL

Actelion Pharmaceuticals US, Inc.
Attention: Paula Clark
Director, Global Drug Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Paula Clark:

Please refer to your new drug application (NDA) dated May 24, 2023, received May 24, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opsynvi (macitentan and tadalafil) tablets.

This NDA provides for the use of Opsynvi (macitentan and tadalafil) tablets for the chronic treatment of adults with pulmonary arterial hypertension (WHO Group I and WHO Functional Class (FC) II-III).

APPROVAL & LABELING

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

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) 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 *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling or carton and container labeling submitted on December 28, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218490**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Opsynvi (macitentan and tadalafil) tablets shall be 24 months from the date of manufacture when stored at 25 °C.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 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.

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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Opsynvi to ensure the benefits of the drug outweigh the risk of embryo-fetal toxicity.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Opsynvi can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of embryo-fetal toxicity listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

You propose to use a shared system for the elements to assure safe use and the REMS assessments. This shared system, known as the Macitentan-Containing Products REMS, includes the products listed on the FDA REMS website available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

Your proposed REMS, submitted on May 24, 2023, amended and appended to this letter, is approved.

The REMS consists of 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 Opsynvi into interstate commerce.

Opsynvi will be a member of the Macitentan-Containing Products REMS, and the assessment plan will be the same assessment plan required for the other products covered by the shared system REMS. Data on the Macitentan-Containing Products REMS should be submitted with the REMS assessment report due on April 06, 2025.

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

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable), unless otherwise noted.

REMS Outreach and Communication

1. Communication Plan (For REMS Assessment Report #2 due on April 6, 2024)
   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 **Dear Healthcare Provider Letter** by the methods of distribution.
   d. The date(s) and number of pharmacists, and wholesalers-distributors who were sent the **Dear Pharmacy Letter** and the **Dear Wholesaler-Distributor Letter** by the methods of distribution.
   e. The date(s), number and names of Professional Societies that were sent the stakeholder letters 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.

REMS Implementation and Operations

2. REMS Implementation (For REMS Assessment Report #2 due on April 6, 2024).
   a. Date when the Macitentan REMS website became live and fully operational.
   b. Date when the Macitentan-Containing Products REMS website became live and fully operational.
   c. Date(s) when previously certified/enrolled healthcare professionals, patients, and inpatient pharmacies that were in the Opsumit REMS were migrated into the Macitentan REMS.
   d. Date(s) when new healthcare professionals, patients, and pharmacies (inpatient and outpatient) could become certified/enrolled into the Macitentan REMS.
   e. Date(s) when wholesalers-distributors could register with the Macitentan REMS.
   f. Date when the REMS Coordinating Center was established and fully operational.

3. REMS Certification and Enrollment Statistics
   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. Office contacts

i. Number of newly authorized office contacts.
ii. Number of active office contacts (i.e., associated with an active prescriber).

c. Pharmacies
i. Number of newly certified, migrated, and active (i.e., have dispensed macitentan-containing products 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.

d. Patients
i. Number of newly enrolled, migrated, and active (received at least one dispensation of macitentan-containing products during the reporting period) patients stratified by age, reproductive potential status, and geographic region.
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 been disenrolled and the reason for disenrollment.
iv. Method of patient enrollment (online, fax, or email).

e. Wholesalers-Distributors
i. Number of newly enrolled and active (i.e., have shipped macitentan- containing products) wholesalers-distributors.

4. Macitentan-Containing Products Utilization Data
a. Number of prescriptions (new and refills) dispensed stratified by
i. Prescriber specialty, degree/professional designation, and geographic region.
ii. Patient demographics (age, reproductive potential status, and geographic region).
b. Number of unique patients receiving macitentan-containing products, stratified by age, reproductive potential status, and geographic region.

5. REMS Infrastructure and Performance
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).
    ii. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type (e.g., patient/caregiver, healthcare provider, pharmacy, wholesalers-distributors).
    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.

6. REMS Compliance
a. Provide a summary of noncompliance identified, including but not limited to:
    i. Provide a copy of the Noncompliance Plan, including the criteria for noncompliance for each stakeholder, actions taken to address noncompliance 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 submitted a corrective and preventive action (CAPA) plan within one month of Audit Report receipt.
        5. For any that did not submit the CAPA within one month of the Audit Report receipt, 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 noncompliance event, provide the source of the report, a description of the event, the root cause of the event, and corrective actions taken)
    i. Number of prescribing healthcare providers who were noncompliant with conducting monthly pregnancy tests for FRPs or other Macitentan-Containing Products REMS 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 who were dispensed macitentan-containing products.
d. Pharmacies (For each noncompliance 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 noncompliance with the REMS is detected.
    ii. Number and type of non-certified pharmacies that dispensed macitentan-containing products and the number of incidents for each.
    iii. Number of macitentan-containing products prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.
    iv. Number of macitentan-containing products prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
    v. Number of macitentan-containing products prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences.
    vi. Number of times a macitentan-containing products prescription was dispensed either because a certified pharmacy bypassed REMS authorization processes, or did not obtain an RDA, to include a description of how the events were identified and any corrective actions taken.
    vii. Number of macitentan-containing products 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 noncompliance.
    ix. Number of first patient shipments sent prior to receipt of a Patient Enrollment Form.

e. Wholesalers-distributors (For each noncompliance 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 non-compliance with the REMS is detected.
    ii. Number of wholesalers-distributors suspended or de-registered, reasons for such action, and actions to address noncompliance.
    iii. Number of times macitentan-containing products was distributed to a non-certified pharmacy or directly to patients, and actions taken to recover the macitentan-containing products.

f. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of five or more days) due to 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 and/or provide an explanation.

Safe Use Behaviors

7. Report on **Change in Reproductive Potential Status** and **Pre-pubertal Annual Verification Form** data, 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)
    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-containing products 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.

Health Outcomes and/or Surrogates of Health Outcomes

8. Pregnancy Events
    a. An analysis of all cases of pregnancy reported in association with macitentan- containing products 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 REMS approval date should be provided and at a minimum, include the following information:
                a) Event identification number
                b) Indication for Macitentan-containing products.
                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 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

9. Stakeholder Surveys (For REMS Assessment Report #2 due on April 6, 2024 and annually thereafter)
    a. An evaluation of certified prescribing healthcare providers' knowledge of:

i. The risks of embryo-fetal toxicity associated with macitentan containing-products.
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-Containing Products REMS.

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

c. An evaluation of patients' knowledge of
   i. The risks of embryo-fetal toxicity associated with macitentan-containing products.
   ii. The need for appropriate baseline and monthly monitoring.
   iii. The need for appropriate contraception.

Overall Assessment of REMS Effectiveness

10. 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success.

Prominently identify any submission containing assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 218490 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

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). 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, proposed 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 218490 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 218490/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218490/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 218490/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 218490/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 REVISION FOR NDA 218490

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.

SUBMISSION OF 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 Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Bridget Kane, Regulatory Project Manager, at (240) 402-2170 or bridget.kane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, & Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

[7] https://www.uspnf.com/

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/

NORMAN L STOCKBRIDGE
03/22/2024 03:46:40 PM