NDA 204410/S-023

SUPPLEMENT APPROVAL

Janssen Research & Development, LLC
Attention: Paula Clark
Director, Drug Regulatory Affairs
1820 Chapel Avenue
Suite 300
Cherry Hill, NJ 08002

Dear Ms. Clark:

Please refer to your supplemental new drug application (sNDA) dated and received August 4, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Opsumit (macitentan) tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Macitentan Shared System (SS) 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 SS REMS for macitentan products, of which Opsumit is a member, was originally approved on April 6, 2021. The SS 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 consist of:

1. Streamlining the REMS by removing redundancies and unnecessary features including the Patient Enrollment Form – For VA Use Only, Patient Pre-Enrollment functionality, Patient Portal, and patient's ability to initiate Prescriber Transfer.
2. Changes to the outpatient pharmacy certification and REMS Dispensing Authorization (RDA) processes to ensure REMS requirements are met prior to dispensing.
3. Updates to the Prescriber and Pharmacy Guide to include additional instructions for pharmacies to provide reasons for dispensing a greater than 30 days' for a female of reproductive potential and to provide reasons for treatment interruption.
4. Updates to the REMS assessment timetable.
5. Updates to the REMS website URL and website functionality to remove duplicate screens and to align with updated processes.

Your proposed modified REMS, submitted to Drug Master File (DMF) (b) (4) on July 29, 2022, amended and appended to this letter, is approved.

The modifications to the approved REMS must be fully implemented within 188 calendar days of the date of this letter.

This shared system REMS, known as the Macitentan SS REMS, currently includes products listed on the FDA REMS website[1].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to submit REMS assessments beginning on April 6, 2023, and annually thereafter. The first submission must include data from August 20, 2021 (the last Opsumit 8-year REMS Assessment report data cutoff) to the established Macitentan SS REMS Assessment Report data cutoff of February 5, 2023.

The revised 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 04/06/2024)
    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 04/06/2024)
    a. Date when the Macitentan REMS website became live and fully operational

[1] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

b. Date(s) when previously certified/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 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. 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, 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)

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

4. Macitentan 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, 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 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 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 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.
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 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 an 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 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 noncompliance 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 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) 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 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 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
            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 04/06/2024 and annually thereafter)
    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
    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

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 5051(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
(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 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/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 LABELING 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, 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

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 more 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.*[2]

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

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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 – Drugs (US), Regulatory Project Manager for Safety, at 301 796-3975.

[2] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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
02/01/2023 03:19:59 PM