NDA 204441/S-010

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Company, Ltd.
Attention: Aditi Shah, MSc.
Associate Director, Global Regulatory Affairs
508 Carnegie Center Drive
Princeton, NJ 08540

Dear Aditi Shah:

Please refer to your supplemental new drug application (sNDA) dated and received July 14, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jynarque (tolvaptan) tablets.

This Prior Approval supplemental new drug application provides for a proposed modification to the approved Jynarque risk evaluation and mitigation strategy (REMS).

This supplement is in response to our June 15, 2023, REMS Modification Notification letter.

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 Jynarque was originally approved on April 23, 2018, and the most recent REMS modification was approved on November 25, 2020. The REMS consists of a communication plan, 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 Jynarque outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated June 15, 2023. In addition, the following modifications were communicated during the course of the review: revision of the REMS Document audit language to reflect the audit requirement for wholesaler-distributors and that pharmacy audits include all pharmacies, and to include annual audits of a representative sample based on the audit plan after the initial audit.

Your proposed modified REMS, submitted on July 14, 2023, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on April 23, 2018.

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.

Program Implementation and Operations

1) Post -Training Knowledge Assessments (KA)
    a. Number of completed post-training knowledge assessment for healthcare providers including method of completion and number of attempts to complete
2) REMS Certification and Enrollment Statistics
    a. Patients
        i. Number and percentage of newly enrolled patients with demographics
        ii. Number and percentage of active patients who have received at least one outpatient dispense during the reporting period with demographics (age, sex)
        iii. Number and percentage of patients who have discontinued therapy
    b. Healthcare providers
        i. Number and percentage of newly certified healthcare providers, stratified by profession (e.g., physician, advanced practice nurse, physician assistant), and specialty
        ii. Number and percentage of active (i.e., who have prescribed at least once during the reporting period) healthcare providers stratified by profession (e.g., physician, advanced practice nurse, physician assistant), and specialty
    c. Pharmacies
        i. Number and percentage of newly certified pharmacies, stratified by pharmacy type (i.e., outpatient, inpatient)
        ii. Number and percentage of active (i.e., have dispensed tolvaptan within reporting period) pharmacies, stratified by pharmacy type (i.e., outpatient, inpatient)
    d. Wholesalers-Distributors
        i. Number of authorized wholesalers-distributors
        ii. Number and percentage of newly authorized wholesalers-distributors
        iii. Number and percentage of active authorized wholesalers-distributors (i.e., have shipped drug)
3) Utilization Data
    a. Number of Jynarque prescriptions (new and refills) dispensed stratified by:
        i. Pharmacy type

ii. Method of dispensing authorization (on-line versus phone)
iii. Prescriber specialty
iv. Patient demographics (ex. age, sex, race)

4) REMS Infrastructure and Performance
   a. Call Center Report
      i. Number of contacts by stakeholder type (patient/caregiver, prescriber, pharmacy, other)
      ii. Summary of frequently asked questions (FAQ) by stakeholder type
      iii. Summary report of REMS-related problems identified and resulting corrective actions
      iv. A summary and analysis of calls that may indicate an issue with patient access or burden on the healthcare delivery system. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, healthcare availability, or other issues.
      v. A summary report of corrective actions resulting from issues identified

5) REMS Compliance
   a. Audits
      i. Provide a report of audit findings for each stakeholder including but not limited to:
         1. A copy of the audit plan for each stakeholder
         2. Number of audits expected and performed
         3. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for audited stakeholders
         4. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
         5. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken
         6. Use a unique ID for stakeholders that had deviations to track deviations by stakeholders over time
         7. Confirm documentation of completion of training for relevant staff
         8. Verify the existence of documented processes and procedures for complying with the REMS
         9. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed
   b. Non-Compliance
      i. Provide a summary of the non-compliance identified, including but not limited to:
         1. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under

what circumstances a stakeholder would be suspended or de-certified from the REMS

2. Number of Jynarque prescriptions dispensed that were written by non- certified prescribers and the actions taken to prevent future occurrences.
3. Number of Jynarque prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
4. Number of Jynarque prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences.
5. Number of times a Jynarque prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.
6. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.
7. Number of prescribers, pharmacies and distributors de-certified, reasons for decertification, and actions to address non-compliance.
8. Failures of Rx dispensing authorization due to calls to the REMS Program for authorization when the REMS Coordinating Center was closed or when the prescriber/patient verification portion of the website was down.

Safe Use Behaviors

6) Report on Patient Status Forms including:
   a. Number of ***Patient Status Forms*** expected, received, outstanding, and not due as of the cut-off date by the number of active patients.
   b. Number of ***Patient Status Forms*** not received within 115 calendar days for the first 18 months of treatment and the prescription disposition (discontinued, continued)
   c. Number of ***Patient Status Forms*** not received within 205 calendar days after 18 months of treatment and the resulting prescription disposition (discontinued, continued)
   d. Number of ***Patient Status Forms*** outstanding at the end of the reporting period (include the number of unique patients and possible reasons such as lost to follow up or deaths) and outreach strategies to obtain outstanding forms
   e. Number and percent of prescriber responses attesting to patient compliance with required monitoring based on the patient status form

f. Number and percent of patients whose physician attested as being compliant with the required monitoring based on the patient status form

Health Outcomes and/or Surrogates of Health Outcomes

7) Safety surveillance
   a. Number of ***Patient Status Forms*** that reported a patient experiencing a serious and potentially fatal liver injury event
   b. Number of ***Liver Adverse Events Reporting Forms*** submitted and resulting prescription disposition (discontinued, continued)
   c. Number of calls made to REMS Coordinating Center reporting serious and potentially fatal liver injury event and resulting prescription disposition (discontinued, continued)
   a. Provide a summary of all adverse event assessments of severe and potentially fatal hepatic injury; include the search strategy used to identify cases (via a REMS gateway or a safety database) and specific MedDRA terms used to identify cases of interest. Describe which actions were taken (e.g., discontinuation of Jynarque) and outcome for each unique patient. Provide a root cause analysis and whether the data warrants further detailed assessment, labeling changes, and/or communication.
   d. A study to evaluate prescribers' adherence to baseline and periodic liver function monitoring as described in the PI, for those adverse event cases which are confirmed suggestive of severe and potentially fatal hepatic injury, provide results for each unique case, by case number, in addition to aggregate results. Provide an overall summary, including a root cause analysis, and whether the data warrants further detailed assessment.

Knowledge

8) Evaluation of Knowledge of Jynarque REMS and Risks of Jynarque
   a. An assessment of patient understanding of:
      i. The risk of serious and potentially fatal liver injury associated with the use of Jynarque
      ii. The importance of regular liver testing as described in the ***Patient Guide***
   b. An assessment of prescriber understanding of:
      i. The risk of serious and potentially fatal liver injury associated with the use of Jynarque
      ii. The requirement for monitoring at baseline and periodic monitoring as described in the PI
      iii. The need to counsel patients about the risk of serious and potentially fatal liver injury associated with the use of Jynarque and the need for monitoring at baseline and periodic monitoring as described in the PI

9) 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 204441 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 204441 REMS ASSESSMENT**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 204441/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 204441/S-000**
> **PRIOR APPROVAL SUPPLEMENT**

PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 204441/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 204441/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 204441

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.

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.

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
09/29/2023 12:04:55 PM