

NDA 204441/S-014

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Company, Ltd.
Attention: Bhavana Chalupadi
Senior Manager, Global Regulatory Affairs
508 Carnegie Center Drive
Princeton, New Jersey 08540

Dear Bhavana Chalupadi:

Please refer to your supplemental new drug application (sNDA) dated and received November 6, 2024, and your amendments dated March 14, 2025 and April 10, 2025, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jynarque (tolvaptan) oral tablets.

This Prior Approval sNDA provides for proposed modifications to the approved Jynarque 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 REMS for Jynarque was originally approved on April 23, 2018, and the most recent REMS modification was approved on September 29, 2023. The 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 establishes a shared system (SS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Jynarque and ANDAs referencing Jynarque, called the Tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) SS REMS Program.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

Removal of the patient registry and the associated requirements, including the Liver Adverse Events Reporting Form and update the goal to remove the objectives of:

- Ensuring that Healthcare Providers (HCPs) are educated on the following:
 - the risk of serious and potentially fatal liver injury associated with the use of JYNARQUE
 - the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

- the need to counsel patients about the risk of serious and potentially fatal liver injury and the need for monitoring at baseline and periodic monitoring as described in the Prescribing Information
- Ensuring that patients are informed about:
 - the risk of serious and potentially fatal liver injury associated with use of JYNARQUE
 - the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information
- Enrollment of all patients in a registry to further support long term safety and safe use of JYNARQUE

Elements to Assure Safe Use: In addition, we have determined that an element to assure safe use is no longer necessary because the requirement for each patient using the drug to be enrolled in a registry is no longer necessary to assess the known serious risk of hepatotoxicity associated with the use of Jynarque (tolvaptan).

Your proposed modified REMS, submitted on November 6, 2024, amended and appended to this letter, is approved.

The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

This shared system REMS, known as the Tolvaptan for ADPKD SS REMS Program will be posted on the FDA REMS website¹.

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 annually from the date of initial approval of the REMS.

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) REMS Implementation (first assessment only)
 - a. Date of first commercial distribution of generic tolvaptan for ADPKD
 - b. Date when the Tolvaptan for ADPKD Shared System **REMS Website** became live and fully operational
 - c. Date when healthcare providers could become certified
 - d. Date when pharmacies could become certified
 - e. Date when patients could become enrolled

¹ <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>

- f. Date when the REMS Coordinating Center was established and fully operational
- 2) Post-Training Knowledge Assessments (KA)
- a. Number of completed post-training knowledge assessments for healthcare providers including method of completion and number of attempts to complete
 - b. Descriptive statistics regarding the number of completed knowledge assessments, the number of attempts needed to successfully complete, and the mean/median/range for number of attempts required
 - c. Summary analysis of the most frequently missed KA questions (first assessment only)
 - d. A summary of potential comprehension or perception issues identified with the KA (first assessment only)
- 3) 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)
- 4) Utilization Data
- a. Number of tolvaptan for ADPKD 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)
- 5) REMS Infrastructure and Performance
- a. Call Center Report
 - i. Number of contacts by participant type (patient/caregiver, prescriber, pharmacy, other)
 - ii. Summary of frequently asked questions (FAQ) by participant 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
- 6) REMS Compliance
- a. Audits
 - i. Provide a report of audit findings for each participant including but not limited to:
 - 1. A copy of the audit plan for each participant
 - 2. Number of audits expected and performed
 - 3. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for audited participants
 - 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 participants that had deviations to track deviations by participants 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 participant, actions taken to address non-compliance for each event, and

- under what circumstances a participant would be suspended or de-certified from the REMS
2. Number of tolvaptan for ADPKD prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences, stratified by inpatient and outpatient pharmacies
 3. Number of tolvaptan for ADPKD prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences, stratified by inpatient and outpatient pharmacies
 4. Number of tolvaptan for ADPKD prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences, stratified by inpatient and outpatient pharmacies
 5. Number of times a tolvaptan for ADPKD 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, stratified by inpatient and outpatient pharmacies
 7. Number of prescribers, pharmacies (stratified by inpatient and outpatient pharmacies), and distributors de-certified, reasons for de-certification, and actions to address non-compliance
 8. Failures of Rx dispensing authorization due to calls to the REMS for authorization when the REMS Coordinating Center was closed or when the prescriber/patient verification portion of the website was down
 9. Number of inpatient pharmacies that did not have processes and procedures in place to
 - a. Verify the prescriber is certified,
 - b. Verify the patient is enrolled, and
 - c. Dispense no more than a 15-day supply of tolvaptan for ADPKD upon discharge of patient

Safe Use Behaviors

- 7) 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**
- g. Number of **Patient Status Forms** received within the REMS required timeframes (every 3 months for the first 18 months of treatment and every 6 months thereafter) (numerator)
- h. Number of **Patient Status Forms** expected within the REMS required timeframes (every 3 months for the first 18 months of treatment and every 6 months thereafter) (denominator)
- i. Number of **Patient Status Forms** received within the REMS required timeframes (every 3 months for the first 18 months of treatment and every 6 months thereafter) (numerator) divided by the number of **Patient Status Forms** expected within the REMS required timeframes (every 3 months for the first 18 months of treatment and every 6 months thereafter) (denominator), calculated as a percentage

8) REMS authorization

- a. Number of requested REMS authorizations that were rejected and reasons for rejection
- b. Number of prescriptions dispensed where requirements to fulfill the REMS authorization were not met, but a REMS authorization was provided

Health Outcomes and/or Surrogates of Health Outcomes

9) Safety surveillance

- a. Number of **Patient Status Forms** that reported a patient experiencing a serious and potentially fatal liver injury event
- b. Number of calls made to REMS Coordinating Center reporting serious and potentially fatal liver injury event and resulting prescription disposition (discontinued, continued)

- c. 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 tolvaptan for ADPKD) 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. An evaluation of 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.
- 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 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.

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, contact Lori Anne Wachter, RN, BSN, RAC – Drugs (US), Regulatory Project Manager for Safety, at 301 796-3975 or lori.wachter@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology
and Nephrology
Office of New Drugs
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/

ALIZA M THOMPSON
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