DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204441

NDA APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Mariana Tran, PhD, RAC
Associate Director, Global Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Tran:

Please refer to your New Drug Application (NDA) dated March 01, 2013, received March 1, 2013, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jynarque (tolvaptan) 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg oral immediate release tablets.

We acknowledge receipt of your amendment dated October 24, 2017, which constituted a complete response to our August 28, 2013, action letter.

This new drug application provides for the use of Jynarque (tolvaptan) to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

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 text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your April 20, 2018, submission containing final printed carton and container labels.

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of hepatotoxicity associated with the use of Jynarque.

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

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

3384-1 Conduct a prospective cohort study of patients enrolled in the Jynarque (tolvaptan) Risk Evaluation and Mitigation Strategies (REMS) registry, with the primary objective of determining the incidence rate of severe (fatal and potentially fatal) drug induced liver injury (DILI). The incidence rate should be compared to that observed in the development program (in TEMPO and REPRISE trials). Incidence rates should be stratified by important risk factors for

DILI which at a minimum should include: age, gender, race, alcohol use, cumulative dose of tolvaptan and duration of tolvaptan use.

The timetable you submitted on April 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	August 31, 2018
Final Protocol Submission:	November 30, 2018
Interim Report #1	April 30, 2019
Interim Report #2	April 30, 2020
Interim Report #3	April 30, 2021
Interim Report #4	April 30, 2022
Interim Report #5	April 30, 2023
Study Completion:	April 30, 2024
Final Report Submission:	April 30, 2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of excessive drug toxicity from drug-drug interactions of tolvaptan or its metabolite with substrates of BCRP, OATP1B1/3, and OAT3.

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

3384-2 Conduct a clinical drug interaction study to evaluate the potential interaction between tolvaptan and a relevant BCRP substrate.

The timetable you submitted on April 23, 2018 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	01/2019
Final Protocol Submission:	03/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3384-3 Conduct a clinical drug interaction study to evaluate the potential interaction between DM-4103 and a relevant OATP1B1/3 substrate.

The timetable you submitted on April 23, 2018 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	06/2019
Trial Completion:	11/2020
Final Report Submission:	03/2021

3384-4 Conduct a clinical drug interaction study to evaluate the potential interaction between DM-4103 and a relevant OAT3 substrate.

The timetable you submitted on April 23, 2018 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	06/2019
Trial Completion:	11/2020
Final Report Submission:	03/2021

Submit clinical protocol(s) to your IND 072975 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Jynarque (tolvaptan) to ensure the benefits of the drug outweigh the risk of serious and potentially fatal liver injury associated with the use of Jynarque (tolvaptan).

Your proposed REMS must also include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Jynarque will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about the risk of serious and potentially fatal liver injury.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Jynarque can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of serious and potentially fatal liver injury listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers who prescribe the drug must be certified.
- Pharmacies that dispense the drug must be certified.
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions.
- Each patient using the drug is subject to liver function monitoring.
- Each patient using the drug is enrolled in a registry.

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 prescribers and pharmacies that dispense the drug be certified, documentation of safe use conditions, patient liver function monitoring, and a patient registry.

Your proposed REMS, submitted on April 20, 2018, amended and appended to this letter, is approved.
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.

Your REMS must be fully operational before you introduce Jynarque (tolvaptan) into interstate commerce.

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

As required under section 505-1 (g) (3) (A) of the FDCA, assessments of an approved REMS must evaluate the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified.

1) Communication Plan (6-month and 12-month assessment only)
    a. The date(s), number and medical specialty of healthcare providers who were sent the ***Letter for Healthcare Providers*** and the methods of distribution
    b. 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.
    c. Sources of the distribution lists for healthcare providers

2) REMS Program Implementation (6-month and 12-month assessment only)
    a. Product launch date
    b. Date when the JYNARQUE REMS website became active and is fully operational including the online confirmation of patient authorization functionality and the availability of REMS materials
    c. Date prescribers could become certified online, by email, or by fax
    d. Date when the REMS call center is fully operational
    e. Number of unique site visits to the JYNARQUE REMS website during the assessment period.

3) Post -Training Knowledge Assessments (KA) (6-month and 12-month assessment only)
    a. Number of completed post-training knowledge assessment for healthcare providers including method of completion and number of attempts to complete
    b. Summary of the most frequently missed KA questions
    c. A summary of potential comprehension or perception issues identified with the KA

4) REMS Program Enrollment Statistics (per reporting period and cumulatively)
    a. Patients
        i. Number of newly enrolled and active (patients who have received at least one outpatient dispense during the reporting period)) patients with demographics (age, gender)
        ii. Number of patients who have discontinued therapy
    b. Healthcare providers
        i. Number of newly enrolled and active (who have prescribed at least once during the reporting period) certified prescribers with profession (e.g., physician, advanced practice nurse, physician assistant), specialty, and academic credentials
        ii. Number of healthcare providers who were de-enrolled and the reason for the de-enrollment
    c. Pharmacies/Distributors
        i. Number of newly enrolled and active (existing/dispensed a shipment of Jynarque) distributors/certified pharmacies with pharmacy type
        ii. The number of pharmacies/distributors that were de-enrolled and the reason for de-enrollment

5) JYNARQUE Utilization Data (per reporting period and cumulatively)
    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, race, gender)

6) REMS Program Infrastructure and Performance (per reporting period and cumulatively)
    a. Report on ***Patient Status Forms*** including:
        i. Number of patient status forms expected, received, outstanding, and not due as of the cut-off date by the number of active patients.
        ii. Number of ***Patient Status Forms*** not received within 115 calendar days for the first 18 months of treatment and the prescription disposition (discontinued, continued)
        iii. Number of ***Patient Status Forms*** not received within 205calendar days after 18 months of treatment and the resulting prescription disposition (discontinued, continued)
        iv. Number of ***Patient Status Forms*** outstanding at the end of the reporting period (include possible reasons such as lost to follow up or deaths) and outreach strategies to obtain outstanding forms
        v. Number and percent of prescriber responses attesting to patient compliance with required monitoring based on the patient status form
        vi. Number and percent of patients whose physician attested as being complaint with the required monitoring based on the patient status form
        vii. Number of enrolled patients that experienced a treatment interruption, duration of the treatment interruption, and a summary of the root cause analysis and any adverse events resulting from the treatment interruption.
    b. 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. A summary report of corrective actions resulting from issues identified

7) REMS Compliance Metrics
    a. Compliance with the REMS Program
        i. Number of JYNARQUE prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.
        ii. Number of JYNARQUE prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.
        iii. Number of JYNARQUE prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences.
        iv. 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.

v. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.

vi. Number of prescribers, pharmacies and distributors de-certified, reasons for decertification, and actions to address non-compliance.

vii. The number of and reasons for rejected prescription authorizations.

viii. Failures of Rx dispensing authorization due to calls to the REMS Program for authorization when the Call Center was closed or when the prescriber/patient verification portion of the website was down.

ix. A summary of audit activities conducted during the reporting period including but not limited to:

1. An overview of the audit plan for each stakeholder
2. The number of audits performed
3. Summary report of the processes and procedures that are implemented in order to be in compliance with the JYNARQUE REMS requirements
4. A summary report of deviations found, the associated corrective and preventive action (CAPA) plans, and the status of CAPA plans.

8) Evaluation of Knowledge (beginning with the 12-month assessment)

A Knowledge Attitude and Behavior Survey will be conducted with random samples of prescribers who have prescribed, and patients who have been prescribed JYNARQUE (tolvaptan) in order to assess their awareness and understanding of the risk of JYNARQUE. The surveys will also assess prescribers and patients' awareness of the REMS materials, knowledge of the risks associated with JYNARQUE and knowledge of requirements of the REMS. The methodology and protocols for the KAB surveys, and the survey instruments, will be developed after the approval of the REMS. These documents will be provided to the FDA at least 90 days before the surveys are initially administered.

The first KAB assessment of prescribers and patients will be completed for inclusion in the 12 month FDA Assessment Report, and will be repeated annually. Survey results will be provided in each REMS Assessment Report.

The KAB surveys will assess the following:

a. Patient understanding of:

• The risk of serious and potentially fatal liver injury associated with the use of JYNARQUE

• The importance of regular liver testing as described in the ***Patient Guide***

b. Prescriber understanding of:

• 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 PI

• 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) 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 Program Coordinating Center reporting serious and potentially fatal liver injury event and resulting prescription disposition (discontinued, continued)
   d. Adverse event assessments of severe and potentially fatal hepatic injury
      i. 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.
      ii. Include a line listing of all cases that includes: manufacturer control number, narrative, and assessment of causality
   e. A study to evaluate prescriber's adherence to baseline and periodic liver function monitoring as described in the PI

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). 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.

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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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

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 204441S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

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 REVISION 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, 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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

We request that for a period of 5 years, you submit all cases of liver transplant or death related to liver injury from any source as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)). You should provide detailed analyses of these events, as well as review findings of the Independent Liver Safety Data Review Board, in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format).

Provide detailed clinical information and causality assessments, including any review by the Independent Liver Safety Data Review Board, of all serious liver events in your periodic safety report. To identify these cases, use the following MedDRA search terms:

> Preferred terms: acute hepatic failure, hepatic failure, hepatic necrosis, hepatic encephalopathy, ascites, hepatorenal failure, hepatorenal syndrome, hepatitis fulminant, drug-induced liver injury, liver injury
> High level terms: cholestasis and jaundice

These analyses should show cumulative data relative to the date of approval of Jynarque (tolvaptan) tablets as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of serious liver events reported with Jynarque (tolvaptan) tablets should also be provided in the periodic safety report.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
04/23/2018