CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204441Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation 1
Division of Cardiovascular and Renal Products

NDA/BLA #s:	204441
Products:	Jynarque (tolvaptan) tablets
APPLICANT:	Otsuka Pharmaceuticals
FROM:	Mary Ross Southworth, PharmD
DATE:	April 20, 2018

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Jynarque (tolvaptan) to ensure that the benefits of the drug outweigh the risks of hepatoxicity. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with autosomal dominant polycystic kidney disease (ADPKD) is 300,000-600,000 (1:500 to 1:1000); however, the estimate of clinically overt ADPKD is imprecise because some diagnoses are made incidentally (without symptoms) or at the time of death.

B. ADPKD is an inherited systemic disease caused by genetic mutations and is characterized by the presence of numerous fluid filled kidney cysts. The development a growth of these cysts leads to progressive loss of renal function as well as other complications. The clinical course is variable, but for those that progress to end-stage renal disease, organ failure typically develops in the 6th decade of life.

C. Jynarque (tolvaptan) has demonstrated an effect on slowing the rate of decline in renal function in patients at risk of rapidly progressing ADPKD.

D. Jynarque (tolvaptan) has shown effects on delaying progression of renal disease in both early, rapidly progressing disease and in later stages of the disease so the drug could potentially be used chronically by a significant number of ADPKD patients.

E. Three cases meeting the laboratory criteria for Hy's law (ALT> 3x ULN; TB > 2x ULN) were observed in 3/1487 patients in the development program indicating that Jynarque (tolvaptan) has the potential to cause fatal hepatotoxicity. At least one case of liver failure leading to transplant in a patient with ADPKD has been documented in the post-marketing setting in Japan. A precise incidence of severe liver injury in patients taking Jynarque (tolvaptan) is not known.

F. Jynarque (tolvaptan) is not a new molecular entity.

The elements of the REMS will include elements to assure safe use and a communication plan.

The elements to assure safe use include:

- Healthcare providers who prescribe the drug must be specially certified.
- Pharmacies and other facilities that dispense Jynarque (tolvaptan) will be certified.
- Patients will have liver tests monitored appropriately.
- Jynarque (tolvaptan) will be dispensed only with documentation of safe use conditions.
- Patients will be enrolled in a registry to collect data on clinical liver injury events.

The elements of the REMS will also include an implementation system and a timetable for submission of assessments of the REMS.

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/s/

MARY R SOUTHWORTH
04/20/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	204441
PDUFA Goal Date	April 24, 2018
OSE RCM #	2017-2186 & 2017-2184
Reviewer Name(s)	Mona Patel, PharmD, RAC
	Joan E. Blair, RN, MPH, Health Communications Analyst, DRISK
Team Leader	Leah Hart, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	April 13, 2018
Subject	Review of Proposed REMS
Established Name	Tolvaptan
Trade Name	Jynarque
Name of Applicant	Otsuka Pharmaceutical Co., Ltd
Therapeutic Class	Vasopressin V_2-receptor antagonist
Formulation(s)	Tablet
Dosing Regimen	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Jynarque (tolvaptan) to mitigate serious and potentially fatal liver injury in the treatment of autosomal dominant polycystic kidney disease (ADPKD). A proposed REMS was initially reviewed during the review of the original application in 2013, and a proposed REMS was included in the October 24, 2017, resubmission to the August 28, 2013, Complete Response letter issued for efficacy, safety, and bioequivalence issues. Subsequently, the proposed REMS was amended on February 9, and March 30, 2018. The Applicant's proposed REMS consists of a Medication Guide, Communication Plan, elements to assure safe use (ETASU) that prescribers and pharmacies would be certified, documentation of safe use conditions as well as monitoring, an implementation system, and a timetable for submission of assessments.

DRISK and the Division of Cardiovascular and Renal Products (DCRP) agree that a REMS with ETASU is needed to ensure the benefits of Jynarque outweigh its risk of serious and potentially fatal liver injury. The Jynarque REMS will ensure that prescribers and pharmacies are certified, documentation of safe use conditions exists as well as patient monitoring. Additionally, it has been determined that the REMS Program should include a REMS Registry (ETASU F) to further support long term safety and safe use of Jynarque.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Jynarque (tolvaptan) to mitigate serious and potentially fatal liver injury in the treatment to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). Otsuka Pharmaceuticals re-submitted an application (NDA 204441) for Jynarque with the proposed indication of ADPKD. This resubmission is under review in the Division of Cardiovascular and Renal Products (DCRP). A proposed REMS was reviewed during the initial review of the original application in 2013, and a proposed REMS was included in the October 24, 2017, resubmission to the August 28, 2013, Complete Response letter issued for efficacy, safety, and bioequivalence issues. Subsequently, the proposed REMS was amended on February 9, and March 30, 2018. The Applicant's proposed REMS consists of a Medication Guide, Communication Plan, elements to assure safe use (ETASU) that prescribers and pharmacies would be certified, documentation of safe use conditions as well as monitoring, an implementation system, and a timetable for submission of assessments.

On March 22, 2018, the FDA provided initial comments, based on review of the February 9 and February 15, 2018, submissions, and advised the Applicant that the REMS document was still

under review.[1] The Applicant subsequently submitted a REMS amendment on March 30, 2018 which is the subject of this review.[2]

1.1 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed REMS relevant to this review (further detailed regulatory history is available in the DRISK review dated March 22, 2018):

- **February 9, 2018**: The FDA received a REMS Amendment which contained a REMS Document, REMS Supporting Document and REMS Materials.
- **February 15, 2018**: The FDA received a REMS Correspondence which contained a (b) (4) Adverse Event (b) (4) Reporting Form.
- **March 22, 2018**: The FDA sent comments and red-lined REMS Materials to the Applicant based on review of the REMS Amendment submitted on February 9, 2018, and the REMS Correspondence submitted on February 15, 2018.
- **March 30, 2018**: The FDA received a REMS Amendment in response to the March 22, 2018, comments which contained a REMS Document, REMS Supporting Document and REMS Materials.

2 Risk Management Activities Proposed by Otsuka Pharmaceuticals

2.1 REVIEW OF APPLICANT'S PROPOSED REMS

The FDA received a REMS Amendment on March 30, 2018, in response to FDA's comments on the REMS Document, Supporting Document, and red-lined REMS Materials sent to the Applicant on March 22, 2018. The amended REMS Document, REMS Supporting Document, and materials require additional revisions to be acceptable.

2.2 REMS Document

The Applicant's March 30, 2018, REMS submission, included an updated REMS Document as requested by the FDA on March 22, 2018.

Reviewer Comment: The REMS Document was updated with FDA's changes consistent with comments sent to Sponsor on March 22, 2018, however since that time, the REMS Document has undergone final Agency clearance. Further changes are necessary for the REMS Document to be complete. Red-lined changes are appended to this review.

2.2.1 REMS Goals

The Applicant's March 30, 2018, submission included a revised goal statement to align with the FDA's March 22, 2018 recommendations:

The goal of the Jynarque REMS is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that healthcare providers are educated on the following:

    a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque

    b. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

    c. 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

2. Ensuring that healthcare providers adhere to:

    a. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

3. Ensuring that patients are informed about:

    a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque

    b. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

    4. Enrollment of all patients in a registry to further support long term safety and safe use of Jynarque

Reviewer Comment: In the Applicant's March 30, 2018 submission, the proposed REMS goals have been revised to align with FDA's March 22, 2018, recommendations, therefore the proposed REMS goals are acceptable.

3.2.2 Communication Plan

The Applicant's March 30, 2018, submission removed the (b) (4) as requested by the FDA on March 22, 2018.

Reviewer Comment: In the Applicant's March 30, 2018 submission, the Communication Plan has been revised to align with FDA's March 22, 2018, recommendations, therefore the proposed Communication Plan is acceptable.

3.2.3 Elements to Assure Safe Use (ETASU)

The Applicant's March 30, 2018, submission included a REMS registry (ETASU F) as requested by the FDA on March 22, 2018.

Reviewer Comment: In the Applicant's March 30, 2018 submission, the ETASU have been revised to align with FDA's March 22, 2018, recommendations, therefore the proposed ETASU are acceptable.

2.3 REMS MATERIALS

The Applicant's March 30, 2018 submission included the following REMS Program materials:

- *Prescriber Enrollment Form*
- *Prescriber Training*
- *Prescriber Knowledge Assessment*
- *Program Overview*
- *Patient Status Form*
- *Outpatient Pharmacy Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Patient Enrollment Form*
- *Patient Guide*
- *Letter for Healthcare Providers*
- *REMS Website*
- *Liver Adverse Event Case Report Form*

Program Overview

As requested by the FDA on March 22, 2018, a *Program Overview* was submitted to replace the (b) (4).

Reviewer Comment: In the Program Overview, pharmacy requirements should be delineated as outpatient and inpatient requirements as outlined in the REMS Document. See red-lined version of the Program Overview appended to this review.

Patient Status Form

As requested by the FDA on March 22, 2018, this form was revised to capture FDA's comments.

Reviewer Comment: This form should be revised further to only capture if a serious and potentially fatal liver injury event occurred in addition to capturing if liver monitoring was completed. See red-lined version of the Patient Status Form appended to this review.

Liver Adverse Event (b) (4) Reporting Form

As requested by the FDA on March 22, 2018, this form was revised to capture FDA's comments.

Reviewer Comment: This form should be revised further to only capture if a serious and potentially fatal liver injury event occurred. (b) (4)

(b) (4) as outlined in our last review dated March 22, 2018. See red-lined version of the Liver AE (b) (4) Reporting Form appended to this review.

Necessary changes to these materials in addition to editorial and formatting changes made to all materials are reflected in the red-lined versions appended to this review. The attestations were updated on the enrollments forms and are reflected on the red-lined versions appended to this review. Finally, all the REMS Materials will need to be submitted with final formatting and graphics as all FDA has received thus far is content.

2.4 REMS SUPPORTING DOCUMENT

The Applicant's March 30, 2018, REMS submission included an updated REMS Supporting Document to align with FDA changes to the REMS Document and REMS Materials.

Reviewer Comment: The REMS Supporting Document is aligned with the REMS Document and REMS materials. Further changes are necessary for the REMS Supporting Document to be acceptable. The Applicant must incorporate information on the following:

- Methods/processes for a prescriber to complete a Liver Adverse Event (b) (4) Reporting Form
- Details on how the collection of clinical information related to event will occur.
- Process for following up with healthcare provider should a serious and potentially fatal liver injury event go un-reported.
- Role and responsibilities of Prescriber Delegates & the REMS Coordinating Center
- Process for following up on a missing Patient Status Form
- De-certification process for prescribers and pharmacies
- De-enrollment process for patients

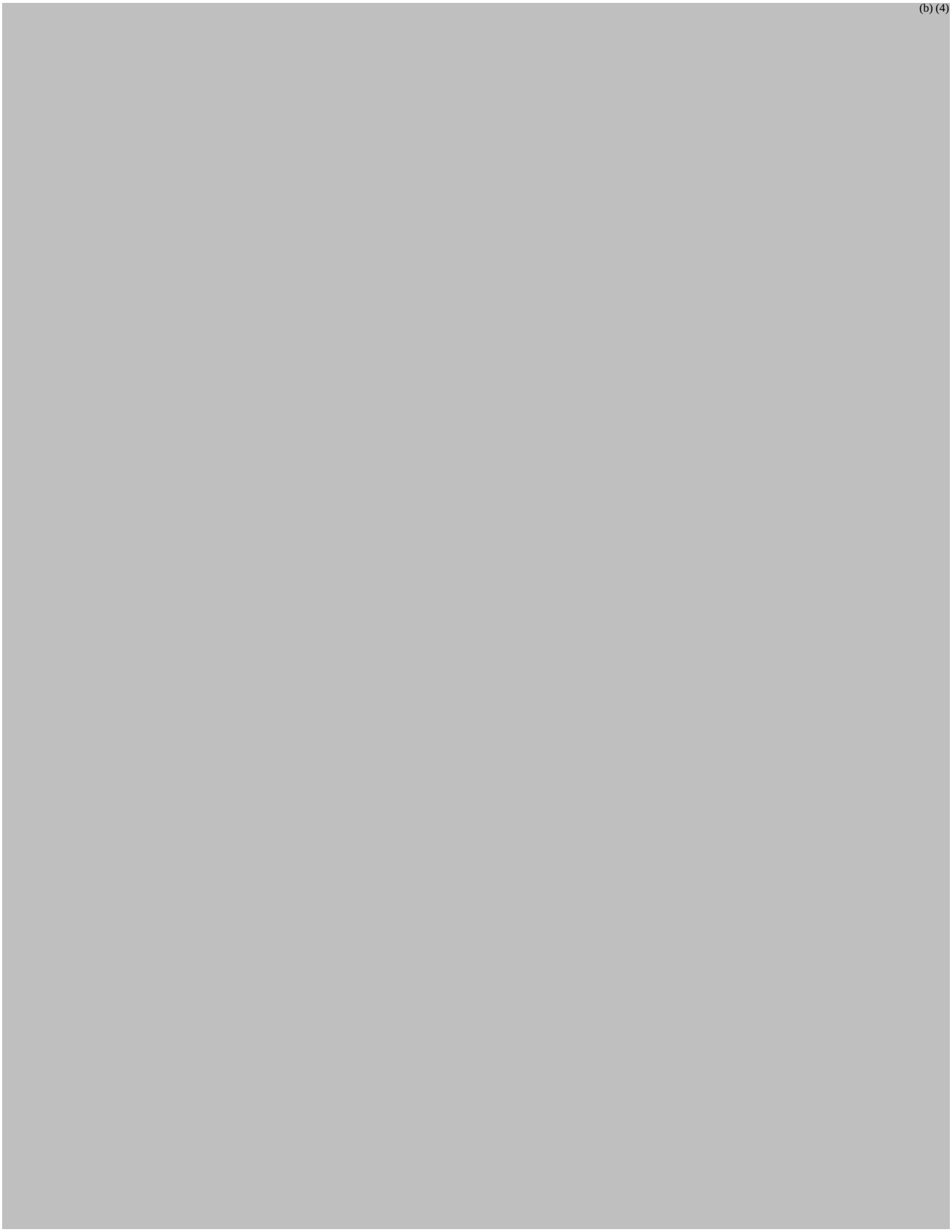
Red-lined changes to the REMS Supporting Document will be sent to the Applicant and are appended to this review.

2.5 REMS ASSESSMENT PLAN

The Applicant's March 30, 2018 REMS submission included an updated proposed REMS Assessment Plan based on FDA changes to the REMS Document and REMS materials for Jynarque as follows:

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. For each JYNARQUE REMS Program Assessment Report the following information will be provided:

(b) (4)


(b) (4)

Reviewer Comment: The assessment plan requires edits to align with the changes to the REMS and not the Applicant's proposal included with the March 30, 2018 submission. The below Assessment Plan will be communicated to the Applicant to include in their REMS Supporting Document (refer to comment in Section 6):

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

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 *JYNARQUE REMS Program 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)
   b. Report on Jynarque Patient Status forms including:

i. Number of Jynarque REMS patient status forms expected, received, outstanding, and not due as of the cut-off date by the number of active patients.
ii. Number of Jynarque REMS 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 Jynarque REMS patient status forms not received within 205 calendar days after 18 months of treatment and the resulting prescription disposition (discontinued, continued)
iv. Number of Jynarque REMS 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.

c. 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 Jynarque 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 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. A 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. 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 Jynarque REMS Patient Status forms that reported a patient experiencing a serious and potentially fatal liver injury event
   b. Number of Liver Adverse Events (b) (4) 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

3 Discussion

The Applicant's amended REMS proposal, as submitted on March 30, 2018, includes the addition of ETASU F and the REMS Program Overview as requested by the FDA on March 22, 2018. The REMS Document and REMS Materials require changes as outlined above to be acceptable. Additionally, the proposal should include an updated REMS Supporting Document. Red-lined versions of the REMS Document and REMS Materials as appended to this review will be sent to the Applicant along with a red-lined version of the REMS Supporting Document.

4 Conclusion & Recommendations

We do not find the Applicant's proposed REMS acceptable. Red-lined versions of the REMS Document and REMS Materials as appended to this review will be sent to the Applicant along with a red-lined version of the REMS Supporting Document.

5 Comments for Applicant

General Comment

The Agency has reviewed the proposed REMS Document, REMS Supporting Document, and REMS Materials submitted on March 30, 2018. Necessary changes to these materials in addition to editorial and formatting changes made to all materials are reflected in red-line on the clean MS Word version of the materials. The attestations were updated on the enrollment forms and are reflected in red-line on the clean MS Word version of the forms. Comments are also noted on the .pdf version of the prescriber training material. See attached red-lined documents. Finally, all the REMS Materials will need to be submitted with final formatting and graphics as all FDA has received thus far is content.

Assessment Plan

The REMS assessment plan, to be included in your REMS Supporting Document, must include, but is not limited to, the following:

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 *JYNARQUE REMS Program 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)

   d) Number of completed post-training knowledge assessment for healthcare providers
   including method of completion and number of attempts to complete
   e) Summary of the most frequently missed KA questions
   f) 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

iii. 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

iv. Number of healthcare providers who were de-enrolled and the reason for the de-enrollment

c. Pharmacies/Distributors

iii. Number of newly enrolled and active (existing/dispensed a shipment of Jynarque) distributors/certified pharmacies with pharmacy type

iv. The number of pharmacies/distributors that were de-enrolled and the reason for de-enrollment

5) Jynarque Utilization Data (per reporting period and cumulatively)

d. 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)

e. Report on Jynarque Patient Status forms including:

viii. Number of Jynarque REMS patient status forms expected, received, outstanding, and not due as of the cut-off date by the number of active patients.

ix. Number of Jynarque REMS patient status forms not received within 115 calendar days for the first 18 months of treatment and the prescription disposition (discontinued, continued)

x. Number of Jynarque REMS patient status forms not received within 205 calendar days after 18 months of treatment and the resulting prescription disposition (discontinued, continued)

xi. Number of Jynarque REMS 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

xii. Number and percent of prescriber responses attesting to patient compliance with required monitoring based on the patient status form

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

xiv. 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.

f. Call Center Report

iv. Number of contacts by stakeholder type (patient/caregiver, prescriber, pharmacy, other)

v. Summary of frequently asked questions (FAQ) by stakeholder type

vi. A summary report of corrective actions resulting from issues identified

7) REMS Compliance Metrics

b. Compliance with the Jynarque 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 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. A 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. 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

f. Number of Jynarque REMS Patient Status forms that reported a patient experiencing a serious and potentially fatal liver injury event

g. Number of Liver Adverse Events (b) (4) Reporting Forms submitted and resulting prescription disposition (discontinued, continued).

h. Number of calls made to REMS Program Coordinating Center reporting serious and potentially fatal liver injury event and resulting prescription disposition (discontinued, continued)

i. 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

j. 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.

Resubmission Instructions:

Submit the following revised REMS materials to your application by 2pm EST April 17, 2018. All content in the materials must align with the Agency cleared REMS Document, the *final* Prescribing Information and Medication Guide, and include content that is consistent across all of the REMS materials and website.

Accept the tracked changes in the MS Word newly redlined documents and only indicate any new changes you propose as redlined changes in your next submission. The next submission to the Gateway should include Clean MS Word, Tracked MS Word (if applicable), and final formatted versions of the following 15 documents:

- ***REMS Document***
- ***REMS Supporting Document***
- ***JYNARQUE REMS Outpatient Pharmacy Enrollment Form***
- ***JYNARQUE REMS Inpatient Pharmacy Enrollment Form***
- ***JYNARQUE REMS Prescriber Training***
- ***JYNARQUE REMS Prescriber Knowledge Assessment***
- ***JYNARQUE REMS Program Overview***
- ***JYNARQUE REMS Prescriber Enrollment Form***
- ***JYNARQUE REMS Patient Status Form***
- ***JYNARQUE REMS Patient Enrollment Form***
- ***JYNARQUE REMS Liver Adverse Events*** (b) (4) ***Reporting Form***
- ***JYNARQUE REMS Patient Guide***
- ***JYNARQUE REMS Dear Healthcare Provider Letter***
- ***JYNARQUE REMS Website Screenshots***
- ***JYNARQUE REMS*** (b) (4)

Your next submission should also include one compiled CLEAN pdf document that includes the REMS Document and all REMS materials, except for the (b) (4) in PDF and the REMS Supporting Document in WORD format.

6 Appendices

6.1 REFERENCES

[1] Patel, Mona. REMS Review for Jynarque, March 22, 2018.

[2] Otsuka Pharmaceuticals. Risk Evaluation and Mitigation Strategy for Jynarque (tolvaptan), March 30, 2018.

7.2 Attachments

REMS Document
Supporting Document
JYNARQUE REMS Outpatient Pharmacy Enrollment Form
JYNARQUE REMS Inpatient Pharmacy Enrollment Form
JYNARQUE REMS Prescriber Training
JYNARQUE REMS Prescriber Knowledge Assessment
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/s/

MONA G PATEL
04/13/2018

JAMIE C WILKINS PARKER
04/13/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	204441
PDUFA Goal Date	April 24, 2018
OSE RCM #	2017-2186 & 2017-2184
Reviewer Name(s)	Mona Patel, PharmD, RAC
	Joan E. Blair, RN, MPH, Health Communications Analyst, DRISK
Team Leader	Leah Hart, PharmD
Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	March 22, 2018
Subject	Review of Proposed REMS
Established Name	tolvaptan
Trade Name	Jynarque
Name of Applicant	Otsuka Pharmaceutical Co., Ltd
Therapeutic Class	Vasopressin V_2-receptor antagonist
Formulation(s)	tablet
Dosing Regimen	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Jynarque (tolvaptan) to mitigate serious and potentially fatal liver injury in the treatment of autosomal dominant polycystic kidney disease (ADPKD). The proposed REMS was reviewed during the initial review of the original application in 2013, and a proposed REMS was included in the October 24, 2017, resubmission to the August 28, 2013, Complete Response letter issued for efficacy, safety, and bioequivalence issues.[1] The Applicant's proposed REMS consists of a Medication Guide, Communication Plan, elements to assure safe use (ETASU) that prescribers and pharmacies would be certified, documentation of safe use conditions as well as monitoring, an implementation system, and a timetable for submission of assessments.

DRISK and DCRP agree that a REMS with ETASU is needed to ensure the benefits of Jynarque outweigh its risk of serious and potentially fatal liver injury. The Jynarque REMS will ensure that prescribers and pharmacies are certified, documentation of safe use conditions exists as well as patient monitoring. Additionally, it has been determined that the REMS Program should include a REMS Registry (ETASU F) to further support long term safety and safe use of Jynarque.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Jynarque (tolvaptan) to mitigate serious and potentially fatal liver injury in the treatment toslow kidney (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) (ADPKD). Otsuka Pharmaceuticals re-submitted an application (NDA 204441) for Jynarque with the proposed indication of ADPKD. This resubmission is under review in the Division of Cardiovascular and Renal Products (DCRP). A proposed REMS was reviewed during the initial review of the original application in 2013, and a proposed REMS was included in the October 24, 2017, resubmission to the August 28, 2013, Complete Response letter issued for efficacy, safety, and bioequivalence issues. The Applicant's proposed REMS consists of a Medication Guide, Communication Plan, elements to assure safe use (ETASU) that prescribers and pharmacies would be certified, documentation of safe use conditions as well as monitoring, an implementation system, and a timetable for submission of assessments.

2 Background

2.1 PRODUCT INFORMATION

Tolvaptan is an aquaretic that competitively blocks the binding of arginine vasopressin to V2 receptors. It was originally approved ((Samsca NDA 22275) in May 2009 for the treatment of

clinically significant hypervolemic and euvolemic hyponatremia, defined as serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Otsuka is currently seeking approval of tolvaptan (NDA 204441) to slow kidney (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

Samsca (tolvaptan) is the only orally available product within this drug class. It is marketed as 15 mg and 30 mg immediate release tablets. The recommended starting dose is 15 mg once daily for the treatment of hyponatremia. The dosage may be increased at intervals ≥ 24 hours to 30 mg once daily and to a maximum of 60 mg once daily as needed to raise serum sodium. The prescribing information (PI) states tolvaptan should be initiated and re-initiated in a hospital because too rapid correction of hyponatremia can cause osmotic demyelination syndrome (ODS). Administration of Samsca should not occur beyond 30 days for this indication.

Jynarque (tolvaptan) for ADPKD will be administered on an outpatient basis and will be available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg immediate release tablets. The proposed initial dosage is 60 mg per day as a split-dose regimen of 45 mg/15 mg (45 mg taken on waking and 15 mg taken 8 hours later) to be titrated upward to a split-dose regimen of 90 mg (60 mg/30 mg) per day then to a target split-dose regimen of 120 mg (90 mg/30 mg) per day as tolerated. Patients should be maintained on the highest tolerable dose for chronic therapy.[a]

NDA 204441 is a 505 (b)(1) application. Tolvaptan was given orphan designation for ADPKD on April 6, 2012 and granted fast track on January 20, 2006. Tolvaptan for ADPKD is currently marketed in 7 regions or countries: European Economic Area, Canada, Japan, Republic of Korea, Switzerland, Australia, and Hong Kong.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 204441 relevant to this review:

- **August 28, 2013**: The FDA issued a Complete Response letter for efficacy and safety-related issues. The FDA instructed Otsuka to include an updated REMS in the resubmission.
- **October 24, 2017**: The FDA received a resubmission which included an updated REMS Document, REMS Supporting Document and REMS Materials.
- **November 21, 2017**: A REMS Oversight Committee meeting was held to provide an update on the proposed REMS for Jynarque.
- **December 5, 2017**: The FDA issued an Information Request requiring changes to the REMS Document, REMS Supporting Document and Materials.

[a] the expected or actual duration of treatment with the drug

- **December 7, 2017**: A teleconference was held with Otsuka Pharmaceuticals to discuss the December 5, 2017 Information Request.
- **December 22, 2017**: The FDA received a REMS Amendment in response to the December 5, 2017, Information Request which contained a REMS Document, REMS Supporting Document and Materials.
- **January 16, 2018**: A teleconference was held with Otsuka Pharmaceuticals to discuss the December 22, 2017, REMS amendment.
- **January 16, 2018**: The FDA sent an Information Request as a follow-up to the January 16, 2017, teleconference which required changes to the proposed REMS program.
- **January 30, 2018**: Information request for assessment of a spontaneous report of a female subject from Japan who developed acute liver failure while on tolvaptan to treat ADPKD that resulted in a liver transplant.
- **February 1, 2018**: Information request for assessment of a female subject from Japan (Samsca Drug Use-Results Survey) and a female subject from Belgium (Extension Study 156-08-271) whose hepatic function had decreased after initiating tolvaptan for ADPKD.
- **February 1, 2018**: The FDA received a safety amendment in response to the January 30, 2018, information request.
- **February 5, 2018**: The FDA received a safety amendment in response to the February 1, 2018, information request.
- **February 7, 2018**: A teleconference was held with Otsuka Pharmaceuticals to inform them of the need for liver monitoring at 14 days after initiation of therapy and the need for a patient registry in the REMS to further support long term safety and safe use of Jynarque
- **February 9, 2018**: The FDA received a REMS Amendment in response to the January 16, 2018, Information Request which contained a REMS Document, REMS Supporting Document and REMS Materials.
- **February 15, 2018**: The FDA received a REMS Correspondence in response to the February 7, 2018 teleconference which contained a (b) (4) Adverse Event (b) (4) Reporting Form.

3 Risk Management Activities Proposed by Otsuka Pharmaceuticals

3.1 Review of Applicant's Proposed REMS

In the October 24, 2017, resubmission, the Applicant proposed a REMS with a (b) (4) Communication Plan, ETASU, implementation plan and a timetable for submission of assessments. The proposed ETASU includes prescriber and pharmacy certification, documentation of safe use conditions, and monitoring. The REMS proposal was complete and included a REMS Document, REMS Supporting Document and Materials. Otsuka subsequently submitted amendments on December 22, 2017, February 9, 2018 and February 15, 2018.

3.2 REMS Document

In October 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry[b] which provided updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) Document for a prescription drug product, including biological drug products. DRISK is providing to the Applicant a draft REMS Document for the Jynarque REMS in this format.

3.2.1 REMS Goals

The Applicant's February 9, 2018 submission includes the following REMS goal:

The goal of the JYNARQUE REMS is to mitigate the risk of (b) (4) injury by:

1. Ensuring that healthcare providers are educated on the following:
    a. the risk of (b) (4) injury associated with the use of JYNARQUE
    b. the requirement for baseline and (b) (4) monitoring (b) (4)
    c. the need to counsel patients about the risk of (b) (4) injury and the need for baseline and (b) (4) monitoring (b) (4)
2. Ensuring that healthcare providers adhere to:
    a. the requirement for baseline and monthly monitoring for the first 18 months of treatment and every 3 months thereafter
3. Ensuring that patients are informed about:
    a. the risk of (b) (4) injury associated with the use of JYNARQUE
    b. the requirement for baseline and (b) (4) monitoring (b) (4)

Reviewer Comment: The proposed REMS goals have been revised to align with the Agency's January 16, 2018 recommendations. However, the REMS goal should be changed further:

The goal of the Jynarque REMS is to mitigate the risk of serious and potentially fatal liver injury *by*:

1. Ensuring that healthcare providers are educated on the following:

[b] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque

b. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

c. 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

2. Ensuring that healthcare providers adhere to:

a. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

3. Ensuring that patients are informed about:

a. the risk of serious and potentially fatal liver injury associated with the use of Jynarque

b. the requirement for monitoring at baseline and periodic monitoring as described in the Prescribing Information

4. Enrollment of all patients in a registry to further support long term safety and safe use of Jynarque

3.2.2 Medication Guide

The Applicant's February 9, 2018 submission proposes (b) (4) as requested by the Agency on January 16, 2018.

Reviewer Comment: (b) (4) This program has a patient directed material, *Patient Guide*, that is focused on the REMS associated risks, as compared with the Medication Guide, which is a patient-directed educational tool that communicates additional risks associated with Jynarque (tolvaptan).

3.2.3 Communication Plan

The Applicant's submission includes a Letter for Healthcare Providers (b) (4) be disseminated within (b) (4) calendar days of the date Jynarque is commercially distributed.

Reviewer Comment: DRISK agrees to having a REMS Program Letter for Healthcare Providers to inform healthcare providers on the new drug approval as there is an existing tolvaptan formulation approved, about the risks associated with tolvaptan in the treatment of ADPKD,

and information about the REMS Program. The Letter for Healthcare Providers must be disseminated within 60 calendar days of the date Jynarque is first commercially distributed. (b) (4)

3.2.4 Elements to Assure Safe Use (ETASU)

The Applicant's February 9, 2018 submission includes ETASU: prescriber certification (A), pharmacy certification (B), documentation of safe-use conditions (D), and monitoring (E).

Reviewer Comment: The Agency continues to agree that the REMS program should include the above elements as outlined in our August 23, 2013, review during the first review cycle of the drug. The initial review cycle also stated that the REMS would require a registry (ETASU F), however the registry was not included with the proposed REMS in the resubmission. Initially, the Agency agreed with the omission of ETASU F from the proposal.

However, with the recent liver failure and hepatic abnormality cases, additional investigation of the serious and potentially fatal liver injury risk is necessary. The REMS should include a REMS registry (ETASU F) to better assist the Applicant via the REMS in becoming aware of liver events, and subsequently collect details on clinical liver injury events (including monitoring up to the event). The REMS registry will also evaluate if the proposed monitoring/discontinuation scheme is adequate (i.e., (b) (4)) to mitigate the risk.

3.2.5 REMS Website

The Applicant's February 9, 2018 submission includes REMS website screenshots

Reviewer Comment: The website screenshots require formatting and content changes. Refer to comments in Section 6.

3.3 REMS APPENDED MATERIALS

The Applicant's February 9, and 15, 2018 submissions include the following REMS Program materials:

- *Prescriber Enrollment Form*
- *Prescriber Training Module*
- *Prescriber Knowledge Assessment*
- (b) (4)
- *Patient Status Form*
- (b) (4) *Pharmacy Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*

- *Patient Prescriber Agreement Form*
- *Patient Guide*
- *Letter for Healthcare Providers*
- (b) (4)
- *REMS Website*
- *Liver Adverse Event Case Report Form (sample form for illustration only)*

Reviewer Comments: The (b) (4) should be replaced by a *Program Overview* that will give a general overview of the REMS program that can be used by prescribers and pharmacies as an educational and informational material. Additionally, the *Liver Adverse Event Case Report Form* can be used by stakeholders as a method (in addition to contacting the REMS program via phone, or reporting via the *Patient Status Form*)to report adverse events suggestive of serious and potentially fatal liver injury at any time. All of the appended materials require formatting and content changes. Refer to comments in Section 6.

3.4 REMS SUPPORTING DOCUMENT

The Applicant's February 9, 2018 REMS submission included a REMS Supporting Document.

Reviewer Comment: The Applicant must submit an amended REMS Supporting Document to align with Agency changes to the REMS Document and appended materials.

4 Discussion

The Applicant's REMS proposal, as submitted on February 9, 2018, includes the Agency's required ETASU. The REMS Document and REMS Materials require changes as outlined above and described in detail in Section 6 below, to be acceptable. Additionally, the proposal should include an updated REMS Supporting Document.

5 Conclusion & Recommendations

We do not find the Applicant's proposed REMS acceptable. Comments for the Applicant are provided in Section 6.

6 Comments for Otsuka

The Agency has reviewed the proposed REMS Document, REMS Supporting Document, and appended materials submitted on February 9, 2018 and February 15, 2018, and has made revisions to, and provided comments on the clean MS Word versions of the materials. Comments are also noted on the .pdf version of the prescriber training material.

6.1 General Comments

-Revise all REMS Materials as needed to reflect:

- the addition of a patient registry
- the revision in the frequency of liver monitoring
- the addition of the following material to the REMS program:
  - ***JYNARQUE REMS Program Overview***
- The revised names of several of the REMS Materials

-Note that the Agency's current thinking has changed regarding both the naming of the DRUGX REMS and referencing the titles of REMS Materials within the content of the REMS Materials. Using the term "Program" as part of the name of the DRUGX REMS is no longer necessary. In addition, repeating the prefix "DRUGX REMS Program" when referencing various materials within the content of materials is redundant, resulting in more text for the REMS participant to read; making the information longer and more difficult to read through.We request that you make these changes within all materials except for the REMS Overview. Also, note that the title that appears at the top of each material will still contain "DRUGX REMS" so that the material is identifiable. We are only requesting this change ***within*** the content of the materials.

- All titles of the materials should be noted in bold and italics to set them apart as important REMS program resources.

-Ensure that all language related to the liver monitoring and reporting requirements are consistently presented throughout all of the REMS Materials as presented in the PI and the REMS Document.

6.2 REMS Document

With the recent liver failure and hepatic abnormality cases, additional investigation of the serious and potentially fatal liver injury risk is necessary. The REMS should include a REMS registry (ETASU F) to better assist the Applicant via the REMS in becoming aware of liver events, and subsequently collect details on clinical liver injury events (including monitoring up to the event). The REMS registry will also evaluate if the proposed monitoring/discontinuation scheme is adequate (i.e., (b) (4)) to mitigate the risk.

- In October 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry[c] which provided updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) Document for a prescription

[c] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

drug product, including biological drug products. DRISK is providing to the Applicant a draft REMS Document for the Jynarque REMS in this format.

REMS Supporting Document

You must submit a revised REMS Supporting Document to align with Agency changes to the REMS Document and appended materials.

REMS Materials

Please note the following specific comments regarding each REMS material. Also see the attached red-lined materials:

JYNARQUE REMS Outpatient Pharmacy Enrollment Form

- Ensure that all attestations are aligned with the revised REMS Document and attached attestations document.
- Note that this enrollment form should use the word "outpatient" vs (b) (4) when referencing outpatient pharmacies in this REMS program..

JYNARQUE REMS Inpatient Pharmacy Enrollment Form

- Ensure that all attestations are aligned with the revised REMS Document and the attached attestations document.

JYNARQUE REMS (b) (4)

- Remove this (b) (4) from the REMS program and replace it with a program overview document. See below.

JYNARQUE REMS Program Overview

- The Agency requests that you create an overview document that describes the requirements of the JYNARQUE REMS Program and the responsibilities of each relevant stakeholder - including prescribers, pharmacies and patients. Please limit the number of pages to a maximum of 6-8.
- The REMS overview should include a cover page and Table of Contents and can include the following subheadings:
    - What is the JYNARQUE REMS?
    - How does the JYNARQUE REMS work?
    - What are the requirements of the JYNARQUE REMS?
    - Prescriber Requirements
    - Pharmacy Requirements
    - Patient Requirements
- The program requirements for each stakeholder group should align with the REMS Document and specific enrollment forms.
- By way of example, we suggest you review the FDA-approved ZINBRYTA REMS Program Overview which may be found at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=357

JYNARQUE REMS Prescriber Training

- Remove the word (b) (4) from the title of this REMS material and to all references to this material.
- It is acceptable to attach the Knowledge Assessment to the training when completed online. With subsequent submissions to the Agency, please include this document (with attached Knowledge Assessment) as part of the REMS website screenshots.
- In addition, create a separate version of this training for completion by stakeholders without going through the REMS website. Include separate pdf versions of this prescriber training and the Knowledge Assessment as two separate resources on the REMS website.
- Update content related to prescriber requirements as outlined in the revised REMS Document.
- Add an additional slide (or more) for each of the following topics:
    - Risk of serious and potentially fatal liver injury associated with JYNARQUE
    - Liver monitoring and reporting requirements
    - Liver adverse event reporting requirements
    - Role of Prescriber Delegate
- By way of example, we suggest you review the FDA-approved ***ZINBRYTA REMS Prescriber Training*** which may be found at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=357 .
- Align content in this training with what is in the new ***JYNARAUE REMS Overview*** material and REMS website.

JYNARQUE REMS Prescriber Knowledge Assessment

- See comments above re: detaching the Knowledge Assessment from the training module for posting as a separate resource on the REMS website.
- Incorporate any revisions to the MS Word version of this document into the online training module/knowledge assessment version.

- Revise the introductory information at the beginning of the knowledge assessment so prescribers know exactly what they need to review prior to taking the knowledge assessment and the need to complete the prescriber enrollment form. See the ***Zinbryta REMS Program Prescriber Knowledge Assessment*** for an example, which can be found here: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=357

JYNARQUE REMS Prescriber Enrollment Form

- Ensure that all attestations are aligned with the revised REMS Document and attestations document, and that all references to the monitoring requirements are consistent with the REMS Document.

JYNARQUE REMS Patient Status Form

- Revisions were made to ensure that healthcare providers understand the difference between when laboratory tests for liver function monitoring are completed and when the prescriber should report the results of this monitoring to the REMS Program.
- Align liver monitoring and reporting frequency content with the final PI.
- A statement was added as a reminder to the prescriber how to report an adverse event for a serious and potentially fatal liver injury.

JYNARQUE REMS Patient Enrollment Form

- Note the revised title of this form, to align with the REMS Document and attestations document. It should be referenced as a Patient Enrollment Form vs. a (b) (4) .
- Note changes made to shorten this form, (b) (4) and to align patient attestations with the revised REMS Document
- Revise this form as needed to ensure it collects all information needed.

JYNARQUE REMS Liver Adverse Events (b) (4) Reporting Form

- The *Liver Adverse Event (b) (4) Report Form* can be used by stakeholders as a method (in addition to contacting the REMS program via phone, or reporting via the *Patient Status Form*)to report adverse events suggestive of serious and potentially fatal liver injury at any time.
- Ensure that this form is complementary with the patient status form and include the data fields from the patient status form.
- The title should be changed from (b) (4) to "Liver."
- Submit a MS Word version of this form for review in your next submission.
- A separate non-REMS form can be used to reflect all data needed to report liver adverse events, abnormal laboratory values, and all cases of liver injury, as necessary for any post-marketing data collection.

JYNARQUE REMS Patient Guide

- Note revisions to use plain language.
- Align all liver function monitoring requirements with the final PI.

JYNARQUE REMS Dear Healthcare Provider Letter

- The Letter for Healthcare Providers must be disseminated within 60 calendar days of the date Jynarque is first commercially distributed. Note changes made to shorten the letter and focus on the REMS Program.

(b) (4)

JYNARQUE REMS Website

- Align website content with what you propose for the new ***JYNARQUE REMS Program Overview*** material. You may also refer to the Zinbryta REMS Website. It can be found at the REMS@ FDA website here https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=357. Website content must also align with the REMS Document and PI.
- Submit website screenshots showing all content and functionality prior to your final submission and after the content is finalized.

JYNARQUE REMS Distributor Enrollment Form

- Although this is not a REMS material appended to the REMS Document, this form should be included in the REMS Supporting Document in your final submission and updated to include similar attestations to those found in the REMS Document (REMS Requirement #5).

Assessment Plan

The assessment plan is till undergoing review and comments will be sent as soon as the Agency has completed the review.

Resubmission Instructions:

Submit the following revised REMS materials to your application within 7 business days. All content in the materials must align with the revised REMS Document, the attached attestations, and the Prescribing Information, and include content that is consistent across all of the REMS materials and website.

In the red-lined MS Word version of the materials, accept the tracked changes you agree to and only show as tracked changes those changes you would like FDA to review. The next submission to the Gateway should include Clean MS Word, Tracked MS Word (if applicable), and final formatted versions of the following 17 documents:

- ***REMS Document***
- ***REMS Supporting Document***
- ***JYNARQUE REMS Outpatient Pharmacy Enrollment Form***
- ***JYNARQUE REMS Inpatient Pharmacy Enrollment Form***
- ***JYNARQUE REMS Prescriber Training***
- ***JYNARQUE REMS Prescriber Knowledge Assessment***
- ***JYNARQUE REMS Program Overview***
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- ***JYNARQUE REMS Patient Guide***
- ***JYNARQUE REMS Dear Healthcare Provider Letter***
- ***JYNARQUE REMS Website***
- ***JYNARQUE REMS*** (b) (4)

7 Appendices

7.1 REFERENCES

[1] Lehrfeld, Kimberly. REMS Review for Jynarque, August 23, 2013.
[2] Clinical Overview 2.5 Jynarque (tolvaptan) Resubmission October 24, 2017

7.2 Attachments

REMS Document
REMS Supporting Document
REMS Program Attestations
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/s/

MONA G PATEL
03/22/2018

JAMIE C WILKINS PARKER
03/22/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	August 23, 2013
Reviewer(s):	Danielle Smith, Pharm.D., M.A., Risk Management Analyst, Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D.. DRISK
Division Director:	Claudia Manzo, Pharm.D. DRISK
Drug Name(s):	Tolvaptan
Therapeutic Class:	vasopressin 2 (V2) receptor antagonist
Dosage and Route:	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg tablets
Application Type/Number:	NDA 204441, NDA 22275
Submission Number:	S-0001, received March 1, 2013
Applicant/sponsor:	Otsuka Pharmaceutical Company, Ltd's
OSE RCM #:	2013-717

CONTENTS

EXECUTIVE SUMMARY

This review documents the Division of Risk Management's (DRISK) recommendations for the proposed REMS requirements for tolvaptan (NDA 204441), submitted by Otsuka Pharmaceutical Company, Ltd.'s (Otsuka), received March 1, 2013 and updated on June 17, 2013.

Tolvaptan was originally approved (Samsca NDA 22275) in May 2009 for the treatment of "clinically significant hypervolemic and euvolemic hyponatremia," defined as serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. The Sponsor (Otsuka) is currently seeking approval to market tolvaptan (NDA 204441) to slow kidney (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

The serious risk to be addressed by a REMS is drug induced liver injury (DILI) which is attributable to tolvaptan and has been observed in a controlled trial in patients with ADPKD. This risk has not been observed in patients utilizing tolvaptan for the approved indication. A REMS is only necessary to ensure the benefits outweigh the risk of DILI associated with tolvaptan for the proposed indication of ADPKD

The minimally necessary requirements for the Tolvaptan REMS include prescriber certification, pharmacy certification, documentation of safe use conditions, a patient registry, an implementation system, and timetable for submission of assessments.

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) recommendations for the proposed REMS requirements for tolvaptan (NDA 204441), submitted by Otsuka Pharmaceutical Company, Ltd.'s (Otsuka), received March 1, 2013 and updated on June 17, 2013.

1.1 BACKGROUND

Tolvaptan is an aquaretic that competitively blocks the binding of arginine vasopressin to V2 receptors. It was originally approved (Samsca NDA 22275) in May 2009 for the treatment of "clinically significant hypervolemic and euvolemic hyponatremia," defined as serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Otsuka is currently seeking approval to market tolvaptan (NDA 204441) to slow kidney (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

Tolvaptan (Samsca) is the only orally available product within this drug class. It is marketed as 15 mg and 30 mg immediate release tablets. The recommended starting dose is 15 mg once daily for the treatment of hyponatremia. The dosage may be increased at intervals ≥ 24 hours to 30 mg once daily, and to a maximum of 60 mg once daily as needed to raise serum sodium. The prescribing information (PI) states tolvaptan should be initiated and re-initiated in a hospital because too rapid correction of hyponatremia can cause osmotic demyelination syndrome (ODS).

Tolvaptan for ADPKD will be available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg immediate release tablets. The proposed initial dosage is 60 mg per day as a split-dose regimen of 45 mg/15 mg (45 mg taken on waking and 15 mg taken 8 hours later) to be titrated upward to a split-dose regimen of 90 mg (60 mg/30 mg) per day then to a target split-dose regimen of 120 mg (90 mg/30 mg) per day as tolerated. Patients should be maintained on the highest tolerable dose.

1.2 REGULATORY HISTORY

The relevant regulatory history specific to the REMS for tolvaptan is as follows:

- **May 19, 2009:** The Agency approved tolvaptan (Samsca NDA 22275) for the treatment of hyponatremia with a REMS to mitigate the risk of ODS during initiation of tolvaptan. The REMS included a (b) (4) and Communication Plan (CP).
- **September 23, 2011:** The Samsca REMS was modified (b) (4) since the risk of ODS occurs during initiation of tolvaptan in a hospital. (b) (4).
- **September 14, 2012:** The Samsca REMS was released after the REMS CP requirement was complete and the 3-year REMS assessment demonstrated that the CP had met its goals.

- **November 13, 2012:** Otsuka submitted a proposed REMS to mitigate the risk of drug induced liver injury (DILI) associated with tolvaptan for the treatment of ADPKD; and thereby notified the Agency that tolvaptan can cause liver injury. The proposed REMS contained a (b) (4) CP with a Dear Healthcare Provider (DHCP) letter and a website and timetable for submission of assessments. The Sponsor's proposed goals of the REMS for tolvaptan for the ADPKD indication were to inform and educate healthcare providers and their patients about the risk of DILI and strategies to mitigate the risk. The initial proposed program did not include any mandatory requirements or restricted distribution.

- **November 27, 2012:** FDA and Otsuka met via teleconference to discuss the risk of DILI identified in the ADPKD development program. FDA advised the Sponsor to issue a DHCP letter describing the potential for hepatotoxicity with the use of Samsca, update IND protocols, etc.
- **January 22, 2013:** Otsuka issued a DHCP letter regarding the potential risk of DILI with the use of Samsca, based on findings from the ADPKD development program.
- **March 1, 2013:** Otsuka submitted NDA 204441, for the proposed indication of ADPKD, which contained a proposed REMS with a (b) (4) prescriber certification, pharmacy certification, implementation system, and timetable for submission of assessments.
- **March 14, 2013:** DCRP sent Otsuka proposed revisions to the Samsca label which included the following:
    - Dosage and administration: Limit to 30 days.
    - Indications for usage: Removed cirrhosis from the indication
    - Warnings and Precautions: Added Section 5.2 to include information regarding liver toxicity and recommend limiting use of tolvaptan to 30 days.
- **March 27, 2013:** Otsuka accepted the Agency's proposed revisions to the label for the approved indication; however, Otsuka proposed the addition of a REMS because "a REMS is warranted at this time to support safe and appropriate use for a subset of patients who require chronic therapy (i.e. > 30 days) in an outpatient setting."
- **March 28, 2013:** DCRP advised the Sponsor to submit a revised REMS for consideration for the approved indication if Otsuka believed it was necessary to ensure the benefits outweighed the risks for use >30 days.
- **April 9, 2013:** FDA approved revised labeling for the approved indication.
- **April 23, 2013:** Otsuka submitted a proposed REMS for the approved indication to allow for treatment longer than 30 days.
- **May 15, 2013:** DCRP requested Otsuka to submit a proposed label and REMS incorporating both indications.

- **June 7, 2013:** DCRP requested Otsuka submit a revised REMS proposal which includes a registry for tolvaptan.
- **June 17, 2013:** (b) (4)
- **July 3, 2013:** Otsuka was provided FDA interim comments set #1.
- **July 18, 2013:** Otsuka submitted a revised REMS. It was under review at the time of the AC.
- **Aug 5, 2013:** The Cardiovascular and Renal Drugs Advisory Committee voted 9-6 not to approve tolvaptan for the treatment of ADPKD. In the discussion of the effectiveness and the burden of the REMS, the general consensus was that the proposed REMS was reasonable given the severity of the risk and although it would be burdensome, it would not be unnecessarily so. However, given the uncertainty about the benefit of the drug and the severity of the risk, the drug should not be approved.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Otsuka Pharmaceutical Company, Ltd Proposed REMS submission for Tolvaptan dated July 17, 2013 (Seq. No. 0036), received July 18, 2013.
- Otsuka Pharmaceutical Company, Ltd Proposed REMS submission for Tolvaptan in response to Information Request dated June 7, 2013 (Seq. No. 0024), received June 17, 2013.
- Otsuka Pharmaceutical Company, Ltd Proposed REMS submission for Tolvaptan (NDA 204441) (Seq. No. 0001), received March 1, 2013.

2.2 ADDITIONAL MATERIALS INFORMING THE REVIEW

- Clinical Review for tolvaptan (NDA 204441), N Beasley and A Thompson July 7, 2013
- Cross-Discipline Team Leader (CDTL) review, S Grant August 2013

3 BENEFIT/RISK CHARACTERIZATION

3.1 PRODUCT EFFICACY

Clinical benefit

One trial was conducted to support the proposed ADPKD indication. The study included 1445 adult patients with rapidly-progressing ADPKD (as indicated by kidney volume ≥ 750 ml), who were randomized 2:1 to treatment with tolvaptan or placebo for 36 months. The primary endpoint was rate of renal volume change from baseline. The secondary endpoint was time to Investigator-reported ADPKD clinical progression events. ADPKD-related clinical progression events were a composite of 1) worsening kidney function (25% reduction in reciprocal serum creatinine during treatment), 2) kidney pain,

3) worsening hypertension, 4) worsening albuminuria, and severe renal pain. This secondary endpoint would be considered the key efficacy endpoint. In order to provide convincing evidence of a treatment benefit the composite secondary endpoint for a single study would need a p-value <0.01. The primary endpoint would provide supportive data. The study met the key efficacy endpoint with a p-value of 0.01, although it was not robust.

Size of intended population and seriousness of the disease

According to a 2008 article (NEJM 359:1477), 300,000 to 600,000 Americans have ADPKD. Hypertension frequently develops during early adulthood (and even during childhood). Pyelonephritis and renal-cyst infections are serious problems requiring aggressive antimicrobial therapy. Kidney failure requiring renal-replacement therapy occurs in approximately 50% of patients and typically develops in the fourth to sixth decade of life.

Anticipated duration of treatment

ADPKD is a slowly progressive disease; therefore, treatment with tolvaptan may continue for decades.

Evaluation of medical need

There is no other pharmacologic therapy approved (or used significantly off-label) to slow kidney (b) (4) in adults with ADPKD. Patients with advanced ADPKD undergo dialysis and transplant to manage their disease.

Expected utilization (outpatient or inpatient)

It is anticipated that tolvaptan will primarily be dispensed for outpatient use for the ADPKD population.

Anticipated prescribers

The primary prescribers are likely to be nephrologists. Nephrologists would not be expected to have unique experience managing DILI.

3.2 SERIOUS RISK OF CONCERN: DRUG-INDUCED LIVER INJURY (DILI)

DILI attributable to tolvaptan has been observed in a controlled trial in patients with ADPKD. Otsuka convened a panel of experts on DILI to review the liver safety database for tolvaptan in the treatment of ADPKD. That panel concluded "that in patients with ADPKD tolvaptan has the potential to cause liver injury capable of progression to liver failure." They continued that "a rough incidence of liver failure can....be estimated as 3/860 x 10, or about 1:3000 patients (who) receive long term treatment with tolvaptan".

The incidence of DILI in the post-market setting is not expected to differ much from that observed in the clinical trial. However, patients are likely to have more serious outcomes in the post-marketing setting if patients are not followed closely and DILI progresses to severe liver injury undetected. In addition, DILI associated with tolvaptan has not been fully characterized and there is the potential that some cases could rapidly progress to serious liver injury (i.e. liver failure, liver transplant or death) despite detection and

prompt discontinuation of tolvaptan. No treatment for idiosyncratic DILI has been demonstrated effective.

Of note, no cases of drug-induced liver injury have been reported in studies of other indications (i.e., hyponatremia and heart failure). However, one case of a patient developing probable mild tolvaptan-induced liver toxicity (transaminase elevations only) that abated following discontinuation of tolvaptan was reported in the medical literature.

In interpreting this information, the following should be considered:

- Relatively few subjects in clinical studies were exposed long term (approximately 1300 subjects exposed to tolvaptan for > 6 months and about 817 exposed for > 1 year; long term exposure is almost exclusively in heart failure subjects at a dose of 30 mg once daily),
- Modest numbers of patients have been prescribed tolvaptan long term in the post-market setting
- Patients with heart failure, cirrhosis and SIADH can have transaminase elevations related to the underlying disease so determining causation of transaminase elevations is problematic.

Therefore the information available is inadequate to conclude that tolvaptan cannot cause DILI in patients being treated for hyponatremia or other conditions.

4 SUMMARY OF THE PROPOSED REMS FOR TOLVAPTAN

The proposed REMS for tolvaptan includes risk management strategies which will mitigate the risk of severe liver failure resulting in liver transplant or death by detecting DILI early at a time when discontinuing treatment may prevent progression to severe liver injury. In addition, the proposed REMS contains a registry which will be utilized to better characterize the risk of hepatotoxicity in patients treated with tolvaptan for ADPKD. The sponsor's original proposed REMS and the FDA's original counter-proposal is summarized in the FDA Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee meeting on August 5, 2013.[1]

Below are the goals and the elements that have been agreed upon with the sponsor for the REMS for tolvaptan: Prescriber certification, pharmacy certification, documentation of safe use conditions and a registry.

4.1 GOAL AND OBJECTIVES OF THE TOLVAPTAN REMS

The goal of the Tolvaptan REMS is to mitigate the risk of serious (b) (4) liver injury by:

1. (b) (4)

[1] See link to this material at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm363342 htm

2. (b) (4)

3.

4.

5.

Rationale:

The key components necessary to mitigate the risk of DILI associated with the administration of tolvaptan include (1) adequate education for healthcare providers and patients; (2) assurance that adequate monitoring is completed and assessed; and (3) data are available to further characterize the risk of DILI. The first 3 goals outlined above are included to ensure the following: Prescribers need to be adequately informed about the potential risk of DILI associated with the use of tolvaptan and how it can be appropriately mitigated (i.e. early detection, prompt discontinuation when DILI is detected). Additionally, patients must be informed about how to recognize signs and symptoms of liver injury and the importance of seeking medical attention if the signs and symptoms do occur. Goal 4 focuses on the need for documentation of safe use conditions. In order to mitigate the risk of progression from liver toxicity to liver failure, FDA recommends prescribers document laboratory monitoring and prescribers verify this safe use condition is met prior to dispensing every prescription. Finally, the last goal is specified since a registry is recommended in order to further characterize this serious risk in the post marketing setting.

4.2 PATIENT DIRECTED MATERIALS

The REMS should include a DILI specific Patient Education Tool (i.e. Patient Information Sheet, patient brochure) which prescribers will be required to review with the patient before initiation of tolvaptan for outpatient use.

The Patient Education Tool will focus on the risk of DILI associated with the administration of tolvaptan. The tool should describe 1) the signs and symptoms associated with liver toxicity and 2) the appropriate actions to take should they occur (i.e. contact the prescriber, discontinue tolvaptan). Prescribers should review the tool with every patient receiving outpatient tolvaptan therapy and provide it to patients as a reference at initiation and periodically while the patient is on outpatient tolvaptan.

In order to ensure a patient has been informed of the risk of DILI, (b) (4) A Medication Guide will be required for tolvaptan, but the tolvaptan MG should not be a component of the REMS.

Rationale:

The important safety information about the risk of DILI, which is the focus of the REMS, will be diluted by other important safety messages in the MG if the MG is the only tool to communicate the risk of DILI. A patient's early recognition and reporting of signs and symptoms of hepatotoxicity is essential to mitigate the risk of DILI because signs and symptoms can present in the interim period between laboratory testing requirements. Therefore, the MG is not the recommended strategy to ensure that patients are educated adequately on how to recognize signs and symptoms of DILI and the recommended actions to take if signs and symptoms are observed.

Rationale:

The (b) (4) *and Patient Education Tool will provide the necessary assurance that patients have received adequate education about the serious risk of hepatotoxicity associated with tolvaptan and assure they are informed of how to potentially mitigate the risk of progression to liver failure by recognizing signs of liver toxicity early.*

4.3 ELEMENTS TO ASSURE SAFE USE

4.3.1 Healthcare Prescriber Certification

All prescribers of tolvaptan need to be certified. Certification includes the following:

- Completion of a *Healthcare Provider Training and Certification Program* educational materials which includes education about:
    - The risk of hepatotoxicity associated with the use of tolvaptan
    - Strategies to enhance early detection and intervention for the risk of hepatotoxicity including the need to:
        - Monitor plasma hepatic transaminases and total bilirubin prior to initiation of tolvaptan and monthly thereafter.
        - Counsel patients on how to self-monitor and recognize signs and symptoms that may suggest liver injury, stop tolvaptan if they experience any signs or symptoms

consistent with liver injury, and immediately report these to their healthcare provider

- Completion of the post-training knowledge assessment questions.
- Submission of a Prescriber Enrollment Form to the tolvaptan REMS program which will include agreements to follow the REMS requirements.

Rationale:

The REMS must include a requirement that all prescribers become trained and certified in the REMS program, in order to ensure that prescribers are aware of the risk of DILI, how to mitigate this risk by fulfilling the REMS requirement to (1) inform patients regarding the risk of DILI and (2) monitor hepatic enzymes and bilirubin monthly.

4.3.2 Documentation of safe use conditions

Prescribers should document that monthly laboratory monitoring has been reviewed and is acceptable to continue tolvaptan treatment every month. Pharmacies will verify this documentation prior to dispensing any prescriptions for tolvaptan in the outpatient setting.

Rationale:

The goal of monthly laboratory monitoring enables prescribers to detect abnormal liver laboratory results early which should result in prompt discontinuation of tolvaptan and thereby prevent progression to liver failure. However, monthly monitoring is not of value if prescribers and patients do not comply with the recommendations. Historically, HCPs' and patients' adherence to routine monitoring decreases over time. Therefore, requiring documentation of routine monitoring through the Tolvaptan REMS program will provide additional assurance that monitoring occurs throughout a patient's tolvaptan treatment.

4.3.3 Pharmacy Certification

The Sponsor will ensure that tolvaptan is acquired and dispensed only through pharmacies that are specially certified.

- Inpatient Pharmacies
    - An authorized designee (e.g., hospital pharmacy director or attending physician) shall be specially trained and certified
    - The pharmacy will only dispense tolvaptan to patients after verifying the healthcare provider is certified in the REMS Program.
    - The pharmacy must have policies and procedures in place to assure no outpatient prescriptions will be dispensed
- Outpatient Pharmacies
    - To become certified, an authorized pharmacy representative must agree to the following on behalf of the pharmacy:

- All pharmacists and staff involved with the dispensing of tolvaptan will be educated about the risk of hepatotoxicity associated with tolvaptan and about the requirements of the REMS.
- The pharmacy will only dispense tolvaptan to patients after verifying the healthcare provider is certified in the REMS Program.
- The pharmacy will only dispense to patients that are enrolled in the registry.
- The pharmacy will verify that the tolvaptan REMS has a record of liver testing confirmation within the prior month for the patient.
- Tolvaptan will only be dispensed with a 30 day supply.

Rationale:

In order to provide assurance that HCPs who prescriber tolvaptan are certified and that the documentation of safe use conditions are being met, pharmacies will be required to verify this prior to dispensing every prescription for tolvaptan.

4.3.4 Registry

The Sponsor will be required to develop and maintain a tolvaptan patient registry.

Rationale:

The patient registry would enroll all outpatients at initiation of therapy and the sponsor will follow up with prescribers about patient discontinuations. In addition, pharmacies and prescribers must agree to mandatory reporting to the registry of any adverse events suggestive of liver injury associated with the administration of tolvaptan in the inpatient and outpatient setting. A standardized adverse event (AE) reporting form would be utilized to collect data on AEs suggestive of liver injury to enable the Agency to further characterize the risk of hepatotoxicity associated with tolvaptan and potentially refine recommendations to mitigate the risk (i.e. actions taken, how the patient was managed, patient outcomes, etc.) The details of the tolvaptan registry have yet to be negotiated with the Sponsor.

5 LIMITATIONS OF A REMS FOR TOLVAPTAN

While the FDA proposed REMS with ETASU contains the minimally necessary requirements to provide some assurance that the benefit of treatment with tolvaptan outweighs the serious risk of hepatotoxicity, the REMS will not prevent all instances of serious liver injury (i.e., liver failure or death) associated with the administration of tolvaptan. Currently available data provides limited information regarding the characterization of DILI associated with the administration of tolvaptan; therefore, such characteristics as patient risk factors, time to onset, etc. have not been adequately identified at this time. Due to these limitations, it is unknown whether the recommended monitoring will be adequate to detect liver injury at a point when it can be mitigated. In addition, no specific intervention, including monthly monitoring, has been shown to

decrease the risk of hepatotoxicity associated with tolvaptan. Monthly monitoring was not utilized in phase 3 clinical trials for tolvaptan, since hepatotoxicity was not recognized as a risk during early clinical development. Furthermore, there is no known, effective treatment for DILI.

6 IMPACT OF A REMS FOR TOLVAPTAN ON BURDEN AND ACCESS

The proposed Tolvaptan REMS program will increase healthcare system burden and permit patient access to tolvaptan for the treatment of ADPKD.

The REMS will add administrative burdens to prescribers and pharmacies. It requires prescribers and pharmacies to enroll and become certified before they can prescribe and dispense tolvaptan. It also requires prescribers to enroll their outpatients in the patient registry. Furthermore, the required documentation of laboratory monitoring will add administrative burden to prescribers who would otherwise be ordering and reviewing laboratory results at their discretion without this additional required step. Verification of REMS requirement by certified pharmacies will increase healthcare burden, as well.

The increased burden to prescribers and pharmacies will potentially impact patient access. The requirement for prescriber certification will likely limit the number of healthcare providers willing to obtain certification since it requires mandatory education and enrollment. Furthermore, many prescribers who have not treated patients with ADPKD in the past may not enroll in the program initially. It is unclear to what extent this will result in a limitation of access to patients who are appropriate candidates for therapy. However, this burden may be offset by eliminating prescribers who are not willing to commit to the necessary monitoring requirements to mitigate the risk of hepatotoxicity.

Furthermore, the required documentation of safe use may result in treatment interruptions because patients may be denied tolvaptan from the pharmacy because of noncompliance with the program requirements.

In order to decrease the impact on burden and access, the proposed REMS includes distinctions based on inpatient and outpatient care settings. Additionally, the REMS utilizes a limited number of tools, each serving multiple purposes (e.g., (b) (4) that enrolls the patient in the REMS registry and documents patients have received adequate education regarding the risk of DILI).

The burdens of a restricting distribution in some manner must be carefully considered in light of the risk of DILI and the drug's benefits. Implementing the proposed components imposes substantial burden for the prescriber, pharmacists, and patients.

7 NON-APPROVAL RECOMMENDATION

The tolvaptan review team does not recommend approval of tolvaptan for the proposed indication to slow kidney (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). The rationale for not approving is documented by Dr. Grant in his August 2013 Cross-Discipline Team Leader (CDTL) review. He concludes "that study 251 does not reliably demonstrate much if any effect of tolvaptan on the progression of renal disease in patients in ADPKD" primarily due to defects in the design and conduct of study 251, the trail intended to demonstrate tolvaptan

effective in the treatment of ADPKD. With regards to the proposed REMS he concludes that "The proposed REMS is likely to substantially reduce the risk of tolvaptan-induced severe liver injury resulting in death or transplantation."

8 DISCUSSION

When considering the need for a REMS for tolvaptan the following factors were taken into consideration:

- Based upon the clinical development program for ADPKD, the Sponsor's expert panel estimates an incidence of 1/3000 patients who will develop liver failure or death associated with the administration of tolvaptan.
- The limited size of the clinical development program does not permit a full characterization of DILI associated with the administration of tolvaptan.
- The demonstrated risk of liver injury associated with the administration of tolvaptan was observed with less than 18 months of use. For patients with ADPKD, the expected benefit (delay in progression to end stage renal disease) may not be realized for many years or even decades on treatment.

Based on the aforementioned considerations, a REMS is required for tolvaptan to ensure the benefits outweigh the risk of DILI for the proposed indication of ADPKD. While the proposed REMS with elements to assure safe use contains the minimally necessary requirements to provide some assurance that the benefit of treatment with tolvaptan outweighs the serious risk of hepatotoxicity, the REMS will not prevent all instances of serious liver injury (i.e., liver failure or death) associated with the administration of tolvaptan.

A successful REMS for tolvaptan will ensure adequate education of patients and HCPs about the risk of hepatotoxicity and will ensure adequate monitoring of patients for drug-induced liver injury. Adequate monitoring for DILI includes patient self-monitoring and monthly hepatic laboratory monitoring. Furthermore, the requirement for prescribers to document monthly monitoring and the evaluation of the results are essential to help ensure that DILI is detected early, possibly prior to patients experiencing symptoms, and evaluated promptly in order to mitigate the risk of progression to severe liver injury. If hepatic injury occurs, reporting of the event and relevant patient specific data to a patient registry is important in order to further characterize this risk.

Finally, prescriber and pharmacy enrollment in the REMS program are required to ensure that the drug is dispensed only when prescribed by certified healthcare providers who understand the risks and appropriate use of tolvaptan.

9 CONCLUSION

If tolvaptan is approved for an indication of ADPKD a REMS is required to ensure the benefits outweigh the risk of DILI.

This review outlines the minimally necessary requirements of a REMS for Tolvaptan including prescriber certification, pharmacy certification, documentation of safe use conditions, a patient registry, an implementation system, and timetable for submission of assessments.

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/s/

KIMBERLY LEHRFELD
08/23/2013

CLAUDIA B MANZO
08/23/2013
concur