

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204441Orig1s000**

**OTHER REVIEW(S)**

RHPM NDA Overview  
April 23, 2018

**NDA 204441**

**Sponsor:** OTSUKA PHARMACEUTICAL DEVELOPMENT AND COMMUNICATIONS INC

**Classification:** 10/Resubmission

**Indication:** A selective vasopressin V2-receptor antagonist indicated to slow kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

**Date of Application:** October 24, 2017

**Goal Date:** April 24, 2018

**Background:**

Tolvaptan is a vasopressin V2 receptor antagonist that was approved on May 19, 2009 (NDA 22275) for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). At the time of approval, tolvaptan was also being developed under IND 72,975 as a treatment for autosomal dominant polycystic kidney disease (ADPKD).

**Summary of Key Regulatory Milestones:**

July 27, 1995	IND for tolvaptan submitted
August 18, 2005	SPA - Clinical submitted
September 29, 2005	SPA - Clinical Agreement granted
January 20, 2006	Fast Track Designation Granted
April 6, 2012	Orphan Designation Granted
July 19, 2012	Pre-NDA Meeting
November 6, 2012	Rolling Review Granted
November 15, 2012	Product Quality/Nonclinical NDA Sections submitted
March 1, 2013	NDA submitted
August 5, 2013	AC meeting
August 28, 2013	Complete Response Letter issued
May 1, 2015	SPA – clinical agreement reached for protocol 156-13- 210 (04/02/2014)
October 24, 2017	NDA resubmitted

On March 8, 2013, the applicant was notified they would receive a priority review although a request for standard review was requested. The Division's reasons were as follows: 1) the development program had been granted fast track, 2) the indication was granted orphan designation, and 3) the applicant had requested and been granted a rolling review of the NDA. Dr. Grant noted all these actions were taken because currently there is no available therapy for delaying the onset of the renal complications of ADPKD. He stated that when the preliminary estimate indicates a drug will provide safe and effective therapy where none exists, the current guidance is that the NDA review of that drug should be classified as priority. Complexity of review is not a criterion for determining the classification of an NDA.

The applicant's clinical development program included 3 ongoing trials of tolvaptan under U.S. IND:

- Protocol 156-08-271 (IND 72,975) is an uncontrolled long-term (24 months minimum) extension study of tolvaptan (maximum dose of 90/30 mg) in patients with ADPKD.
- Protocol 156-09-290 (IND 107,847) is a phase 2, placebo-controlled, 8-week trial of tolvaptan (60/30 mg split dose tablets and MR capsules of 50 mg and 80 mg once daily) in subjects with ADPKD.
- Protocol 156-08-275 is an ongoing placebo-controlled trial of tolvaptan (maximum daily dose of 60 mg once daily) in patients with hyponatremia.

Trial 156-04-251 is the pivotal trial of tolvaptan for the treatment of ADPKD, in which the long-term safety and efficacy of tolvaptan oral split-dose regimens (titrated between 60 mg/day and 120 mg/day) were compared with placebo.

On March 8, 2013, the sponsor was notified of the Division's intent to take tolvaptan to the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) in early August 2013.

On August 5, 2013, both FDA and Otsuka presented at the Advisory Committee meeting and the committee members voted 9-6 against approval.

On August 28, 2013 a Complete Response Letter was issued.

On May 1, 2015, the sponsor requested to amend their April 2, 2014 SPA of a clinical protocol, for a Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease, Version 2.

On October 24, 2017, the applicant resubmitted their NDA with the second confirmatory trial, Protocol 156-13-210, entitled, *"A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney*

*Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease*". Trial 156-13-210 used change in eGFR (from pretreatment baseline to post-treatment follow-up) in subjects with later stage illness (late CKD Stage 2 to early CKD Stage 4) as its primary endpoint.

**Reviews** *(Please note these are summaries and not complete reviews. Please refer to their complete reviews in DARRTS).*

**Joint Division Director's Memo and CDTL Review (April 23, 2018)**

**Reviewer:** Norman Stockbridge, M.D., Ph.D. and Aliza Thompson, M.D.

**Conclusion:** Approval

**Labeling:** Please see review in DARRTS

**Summary:** Please see review in DARRTS

**Medical (April 19, 2018)**

**Reviewer:** Melanie Blank, M.D. (efficacy)  
Nhi Beasley, Pharm.D. (safety)

**Conclusion:** Approval

**Labeling:** Please see review in DARRTS

**Summary:**

Based on evidence from two adequate and well-controlled clinical trials, TEMPO and REPRISE, it can fairly and responsibly be concluded that tolvaptan will have one of the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling, namely to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). (b) (4)

If tolvaptan's safety profile had been reassuring, we think the available data, despite the aforementioned limitations, might have been sufficient to support approval. However, tolvaptan's safety profile was not reassuring. Tolvaptan caused liver injury in patients with ADPKD. There were three subjects with hepatocellular liver injury judged to be at least probably due to tolvaptan ("Hy's Law" cases) out of ~860 subjects with ADPKD treated over a 14-month treatment period. These subjects did not progress to liver failure leading to transplantation or death, but the finding of two or more Hy's Law cases in a clinical trial safety database is a strong predictor of a drug capable of causing such injury. Based on Hy's Law, the rough incidence of liver failure can be estimated as  $3/860 \times 10$ , or

~ 1 in 3000 patients treated with tolvaptan. There are only a handful of marketed drugs with this incidence of liver injury (bosentan for pulmonary hypertension and isoniazid for tuberculosis). Most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of  $\leq 1$  per 10,000.

**Statistical (February 27, 2018)**

**Reviewer:** John Lawrence, Ph.D.

**Conclusion:** Approval

**Labeling:** None

**Summary:**

Two Phase 3 studies have been completed to assess the safety and efficacy of tolvaptan for the treatment of polycystic kidney disease (PKD). The first study was completed in 2012 and has been reviewed (June 2013). This review focuses mainly on the second trial. Based on the collective evidence of both studies, tolvaptan appears to slow the rate of decline of kidney function as measured by the estimated glomerular filtration rate (eGFR). [REDACTED] (b) (4)

[REDACTED] From the one study where all subjects had TKV measured annually, there appears to be a substantial acute hemodynamic effect, but little or no long term chronic effect on TKV. Depending on what model is used in the double-blind phase, there is either no chronic effect or a very small chronic effect. If there were a small effect, it may or may not be a clinical benefit. When using the model that suggests there is a small chronic effect on TKV, there is a very small correlation between chronic effect on TKV and chronic effect on eGFR. The proportion of the treatment effect on eGFR explained by TKV is very small in that trial. This suggests chronic effect on TKV is not a surrogate endpoint for effect on eGFR for this study population. In a long term extension phase of that trial, all subjects were treated with tolvaptan to determine whether there was a sustained difference between the two arms. At the end of this extension phase, the subjects who were treated 3 years longer with tolvaptan in the double-blind phase had no significant difference in TKV from the subjects that had been randomized to placebo. Both studies have been relatively short term (1-3 years) and have shown a modest effect on annualized change in eGFR. If approved, tolvaptan will be used chronically. It is natural to assume that the effect seen in one year (~1 mL/min) will compound each year, so that after 10 years there will be approximately 10 mL/min effect. We don't know if that is true, but we do have evidence from the two trials that tolvaptan works in both early and late stage of disease.

**Pharmacology (February 27, 2018)**

**Reviewer:** Gowra Jagadeesh, Ph.D.

**Conclusion:** Approval

**Labeling:** Recommendations and edits were made on the label.

**Summary:**

There are no approvability issues for tolvaptan based on nonclinical toxicity testing program.

**Clinical Pharmacology Review (April 16, 2018)**

**Reviewer:** Martina Sahre, Ph.D.

**Summary:**

From a clinical pharmacology perspective, the NDA is acceptable, provided agreement on labeling can be reached. See full review in DARRTS.

**1.2 Recommended Phase 4 study commitments**

To date, the applicant has not conducted clinical studies of the identified potential interactions between tolvaptan and BCRP as well as the metabolite DM-4103 with OATP1B1/B3 and OAT3. A post marketing requirement (PMR) for assessing the interactions with BCRP, OATP1B1/B3 and OAT3, in vivo, will be sent to the Applicant. Until the results from these assessments become available, the risk for drug interactions with these transporters will be addressed in labeling.

**1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings**

The reader is referred to previous reviews for tolvaptan for NDA 22,275 and the previously submission of NDA 204,441 for information about clinical pharmacology. The new information the applicant has provided are centered around in vitro transporter interaction assays, a fluconazole drug-drug interaction study (DDI) to assess interaction with a moderate CYP3A inhibitor as well as a new pivotal clinical study (156-13-210, REPRISE) in ADPKD patients with more advanced renal impairment (eGFR between 25-65 mL/min/1.73 m<sup>2</sup>).

**Labeling:**

**3.4.1 Contraindication for strong CYP3A4 Inhibitors**

 (b) (4)  
contraindication for  
strong CYP3A4 inhibitors:

- Exposures after administration of a strong CYP3A4 inhibitor were characterized in a dedicated DDI study with ketoconazole in which a half-maximal ketoconazole dose (200 mg) was used. Typically, a 400 mg dose is administered. Therefore, there is potential for greater increases in exposure than what the study indicated.
- Most medications that constitute strong CYP3A4 inhibitors would be short-term treatments, for which tolvaptan treatment could be interrupted.

— [Redacted] (b) (4)

### 3.4.2 Dose adjustment for moderate CYP3A4 Inhibitors

While the applicant also did not study the highest dose during coadministration with fluconazole, at least the high fluconazole dose was administered on the day before administration with tolvaptan. The applicant approaches dose reduction for this group of comedications by a halving the doses as shown in Table 8. The sponsor justifies this by stating that moderate CYP3A4 inhibitors are defined as those with increases in exposure (AUC ratio) greater than 2-fold, and therefore a halving of dose would be the appropriate means. This discounts that the definition for a CYP3A4 inhibitor of moderate strength lies within a range (2-<5-fold), and is usually adjusted by the clinical data evidence, i.e. here the 3-fold increase in AUC. That said, the dose for tolvaptan can be down-titrated. Further, given the available tablet strengths, 15, 30, 45, 60, 90 mg, a dose adjustment to a third of the original initial dose is not possible. Therefore, the dose adjustment is considered acceptable.

**Table 8. Dose adjustment for moderate CYP3A4 inhibitors**

<i>Regular daily split dose</i>	<i>Adjusted split dose</i>
90/30 mg	45/15 mg
60/30 mg	30/15 mg
45/15 mg	15/15 mg

### 3.4.3 Transporter Interaction Data

The applicant had not added transporter interaction or metabolite information to their label and an Information Request was sent to the applicant, to which they responded on 3/29/2018. The applicant proposed to add the following language to the label:

[Redacted] (b) (4)  
*In vitro studies indicate that tolvaptan or its oxobutyric metabolite may have the potential to* [Redacted] (b) (4)  
[Redacted] (b) (4)  
[Redacted] (b) (4)  
[Redacted] (b) (4)

(b) (4)  
[redacted]. Therefore, this type of language should not be added to the label.

The following edits are proposed:

*Tolvaptan is a substrate of P-gp and an inhibitor of P-gp and BCRP. The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3. In vitro studies indicate that tolvaptan or the oxobutyric acid metabolite of tolvaptan may have the potential to increase exposure of drugs that are substrates to these transporters* (b) (4)  
[redacted] [see Drug Interactions (7.2), (7.3)].

### Sections 7.2 and 3

#### 7.2. OATP1B1/3 and OAT3 Transporter Substrates

*The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3. Patients who take JYNARQUE, should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g. statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide) [see Clinical Pharmacology (12.3)].*

#### 7.3 BCRP Transporter Substrates

*Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin) [see Clinical Pharmacology (12.3)].*

#### 3.4.4 Metabolite Data

Given that at least one metabolite has the potential to interact with transporters, the applicant was asked to provide language in the label detailing metabolism of tolvaptan. The applicant responded that information was not added, because the metabolites are not considered active. Considering the potential transporter interaction, the statement in the sentence before should be detailed further. While there may not be metabolites that show effect on the pathways that are hypothesized to be important for the clinical effect of tolvaptan, given the potential for transporter interaction, they are not inert. The guidance for Drug Labeling, 2017 clearly states that metabolism of a drug should be summarized, where necessary. Therefore, this reviewer recommends editing the proposed language by the applicant as follows:

“Fourteen metabolites have been identified in plasma, urine and feces; all but one were also metabolized by CYP3A and none are considered to be pharmacodynamically active. (b) (4) radiolabeled tolvaptan (b) (4) a minor component in plasma representing 3% of total plasma radioactivity; (b) (4) the oxobutyric acid metabolite (b) (4) present at greater than 52.5% of total plasma radioactivity with all others present at lower concentrations than tolvaptan. The oxobutyric acid metabolite shows a plasmahalf-life of ~180 h.”

### **Biopharmaceutics Review (March 7, 2018)**

**Reviewer:** Zhuojun Zhao, Ph.D.

**Conclusion:** Approval

**Labeling:** None

**Summary:**

During the review of the original NDA 204441 submission, (b) (4) for the bioequivalence trial 156-11-295. FDA subsequently advised that the BE trial conducted on the 90-mg tablets would need to be repeated because of this deficiency.

In the resubmission, instead of conducting a new BE study, the Applicant requests waiver of bioequivalence study for both 45-mg and 90-mg tablets based on the Teleconference with the Agency on September 11, 2017. The information provided in the resubmission to support the biowaiver request for 45 and 90 mg strengths include:

**Composition proportionality:** The new 45- and 90-mg strengths were designed to be immediate release tablets that were quantitatively proportional with the currently approved 60-mg tablets. The 45-mg tablet is exactly 0.75 times and the 90-mg tablet is exactly 1.5 times the 60-mg tablet. (b) (4)

**Dissolution similarity:** The similarity factors (f<sub>2</sub>) calculated for the dissolution profiles for 1 x 45 mg vs 1 x 60 mg and 1 x 90 mg vs 1 x 60 mg obtained using the QC dissolution method were 65 and 57, respectively, demonstrating the dissolution equivalency of the approved 60-mg tablets and the proposed commercial 45- and 90-mg tablets.

**Dose Proportionality:** Per Samsca® label, the area under the curve (AUC) increases proportionally with dose after single doses of up to 480 mg and multiple doses up to 300 mg once daily. Based on the provided supportive information, the bio-waiver request for 45 and 90 mg is granted.

<sup>1</sup> DARRTS: REV-QUALITY-21 (Primary Review), final date 07/10/2013

<sup>2</sup> \\cdsesub1\evsprod\nda204441\0000\m3\32-body-data\32p-drug-prod\tolvaptan-tablets\32p2-pharmdev\formulation-development-

**Product Quality (February 16, 2018 and March 23, 2018)**

**Reviewer:** Thomas Wong, Ph.D.

**Conclusion:** Approval

**Labeling:** None

**Summary:**

NDA 204441 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

**Risk Evaluation and Mitigation Strategy (REMS)(August 23, 2013)**

**Reviewers:** Mona Patel, Pharm.D. RAC  
Joan E. Blair, RN, MPH, Health Communications Analyst

**Labeling:** None.

**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 (b) (4) 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.

**Patient Labeling Review (Med Guide) (April 9, 2018)**

**Reviewer:** Puja Shah, Pharm.D., RAC  
Morgan Walker, PharmD, MBA, CPH

**Labeling:** None.

**Summary:** The MG is acceptable with our recommended changes. Please see DARRTS for full review.

**Action:**

An Approval Letter will be drafted for Dr. Stockbridge's signature.

---

Anna Park

Senior Regulatory Management Officer  
April 23, 2018

APPEARS THIS WAY ON ORIGINAL

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

/s/  
-----

ANNA J PARK  
04/24/2018



**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency Templates  
Version: 2018-01-24**

Date: 04/18/2018

Reviewer(s): Marie Bradley, PhD, MSc.PH, MPharm  
Division of Epidemiology II

Team Leader (Acting): Efe Eworuke, PhD  
Division of Epidemiology II

Division Director: Lockwood Taylor, PhD  
Division of Epidemiology II

Subject: ARIA Sufficiency Memo

Drug Name(s): Tolvaptan

Application Type/Number: Non NME NDA 204441

Applicant/sponsor: Otsuka

OSE RCM #: 2017-2184



**EXECUTIVE SUMMARY** (place "X" in appropriate boxes)

<b>Memo type</b>	
-Initial	
-Interim	
-Final	X
<b>Source of safety concern</b>	
-Peri-approval	X
-Post-approval	
<b>Is ARIA sufficient to help characterize the safety concern?</b>	
-Yes	
-No	X
<b>If "No", please identify the area(s) of concern.</b>	
-Surveillance or Study Population	
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

## **1. BACKGROUND INFORMATION**

### **1.1. Medical Product**

Tolvaptan is a selective vasopressin V2 receptor antagonist, which blocks renal collecting ductular arginine-vasopressin (AVP) V2-receptors to inhibit reabsorption of free water from glomerular filtrate in the kidneys. It was approved by the FDA (NDA 022275) in 2009 (SAMSCA®) for treatment of clinically significant hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], in patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

In 2013 the sponsor (Otsuka) submitted a new NDA 204441 for tolvaptan (Jynarque) which proposed a higher dosing regimen to slow the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease (ADPKD). This genetically transmitted disease affects about 600,000 persons in the United States and is the fourth most common cause of end-stage renal disease, after diabetes, hypertension, and glomerulonephritis. Around 50% of ADPKD patients develop kidney failure by 4<sup>th</sup> to 5<sup>th</sup> decade of life. The development program for use of tolvaptan in ADPKD was granted orphan drug designation 6 April 2012, despite having a prevalence (approx. 600,000) greater than that usually specified for orphan drug status in the US, where the upper limit is normally 200,000.

It is unclear exactly when the sponsoring company became aware of the problems of possible tolvaptan-induced liver injury in ADPKD patients, but the issue was discussed with FDA in July 2012 when the accumulated long-term data from pivotal clinical trial 156-04-251 were being evaluated in preparation for submission of NDA204441. Despite this discussion, the sponsor proceeded with submission of the NDA 204441 in 2013 and proposed a risk evaluation and mitigation strategy (REMs) based on the findings of the three Hy's law cases. FDA responded to this submission with a complete response (CR) in 2013 mostly related to efficacy, specifically missing data, inappropriate primary endpoints, small effect size and unconvincing sustained effect. In response to the CR, the sponsor conducted another efficacy trial in ADPKD and tested a strategy of monthly liver test monitoring for 18 months, followed by every 3 months.

The sponsor resubmitted their NDA on Oct 24, 2017, and there were no Hy's law cases in the most recent trial data and this submission comprised a REMS for monthly liver testing. DCRP have since become aware of a case of liver failure and transplant in a patient taking tolvaptan for ADPKD in the post-marketing setting in Japan where tolvaptan was approved for ADPKD in 2014.

### **1.2. Describe the Safety Concern**

#### **Safety of tolvaptan use in ADPKD**

Tolvaptan is suspected of inducing hepatic toxicity when used for the treatment of ADPKD. During the tolvaptan clinical development program for ADPKD, imbalances in the number of drug induced liver injury (DILI) events between the treatment and placebo arms were observed. Three cases of DILI that met the Hy's law criteria were observed among ADPKD subjects exposed to tolvaptan for less than 9 months, and no cases were seen in the placebo group. Those pre-clinical studies also found a notable increase in the frequency of moderate to severe elevations (often up to ten the

upper limit of normal [ULN]) of serum aminotransferase (AT) enzyme activity, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), markers of liver injury, in patients treated with tolvaptan, compared to those receiving placebo. The sponsor (Otsuka) convened a special consulting committee of academic hepatologists to review the clinical data and render an opinion as to whether they believed tolvaptan to be the probable cause of several cases of serious (but not fatal) liver injury and dysfunction. The report of the expert hepatology consultants finalized in October 2012 concluded that long-term treatment with tolvaptan carried a risk of liver failure in about 1 per 3000 treated patients. They opined that the risk of liver injury would probably be lowered with more frequent monitoring of serum liver tests but would not likely be eliminated.

## **DILI**

The FDA guidance entitled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” states that DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years and that finding one Hy’s Law case in the clinical trial database is worrisome; finding two cases is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in AT activities in serum reflecting release of ALT or AST from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug’s potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that can cause hepatocellular injury extensive enough to reduce the liver’s functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. Hy’s Law states that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Thus, a finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2x upper limit of normal (ULN), identifies a drug likely to cause severe DILI (fatal or requiring transplant).

Hy’s Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by an incidence of 3-fold or greater elevations above the ULN of ALT or AST compared to the (non-hepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum total bilirubin (TBL) to >2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase [ALP]).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.<sup>1</sup>

## **Safety of tolvaptan use for hyponatremia (SAMSCA®)**

Since its approval for hyponatremia in 2009, only one report of liver test abnormalities associated with tolvaptan has been published<sup>2</sup>. This occurred in a 75-year-old man with SIADH who showed sharp rises in serum ALT, AST and Gamma-glutamyl transferase (GGT) levels 24 days after starting tolvaptan at 15 mg/day then increasing to 30 mg/day. Stopping the drug led to reversal of the abnormalities after 11 and 23 days. No symptoms or functional abnormality of bilirubin

concentration or prothrombin time were reported, but the authors considered the injury clearly related to tolvaptan.

The liver injury observed in the tolvaptan development program for ADPKD has not been seen among patients using the drug for hyponatremia, perhaps due to the lower doses used but also suggesting a mechanistic link between ADPKD and susceptibility to tolvaptan-induced liver injury. However, there is no evidence that the polycystic renal disease of ADPKD in itself would increase the risk for hepatotoxicity with tolvaptan but the need for longer duration and higher doses of drug treatment for this indication may be implicated. ADPKD patients differ from those using tolvaptan for hyponatremia in a least one respect, a genetic inheritance of PKD1 or PKD2 genes that lead to renal tubular cyst development and slow growth. It is not known whether this might also confer some increased risk of hepatocellular injury. However, the liver injury observed in the clinical development program for tolvaptan in ADPKD was not that of a slow cyst-growth obstructive type, but of rapid, although delayed and seldom immediate, injury to the hepatocytes in affected individuals.

A labeling revision in April 2013 limited use of SAMSCA to 30 days, at up to 60 mg/day, removed the indication for use in patients with cirrhosis, and referred to tolvaptan-induced liver toxicity. Around the same time, the sponsor sent an urgent letter to all healthcare providers “**IMPORTANT DRUG WARNING**” of the potential risk of liver injury with use of SAMSCA® based on data from the ADPKD trials.

**1.3. FDAAA Purpose (per Section 505(o)(3)(B))**

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	x
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

**1.4. Statement of Purpose**

The Division of Cardiovascular and Renal products (DCRP) are currently reviewing the NDA 204441 (non-NME) for tolvaptan (Jynarque) and consulted the Division of Epidemiology-II (DEPI II) to determine the sufficiency of ARIA for identifying and estimating the rates of DILI among tolvaptan users with ADPKD if the drug is approved for use in the US. They are also interested in monitoring biomarkers predictive of DILI such as elevated liver enzymes, specifically (ALT or AST) and elevated TBL in tolvaptan users.

Based on the Hy’s laws DILI cases identified among tolvaptan users in the clinical development program for ADPKD, the lack of cases in the placebo group and the post-market case of liver failure and transplant seen in Japan, the conditions for a PMR under FDAAA are satisfied. FDA seeks to answer the question on signal detection: “Can Sentinel surveillance help identify Hy’s law DILI cases among tolvaptan users in the post marketing setting if the drug is approved in

the US?" This information will be used to provide more precise estimates of DILI incidence in tolvaptan users in the post-market setting.

DCRP are also strongly considering a mandatory registry of tolvaptan treated patients as part of the REMS proposed by the sponsor to collect data on liver testing and details on clinical liver events. This registry could be used to measure incidence rates of DILI as a PMR.

### **1.5. Effect Size of Interest or Estimated Sample Size Desired**

- Not applicable as no estimate of risk will be examined.

## **2. SURVEILLANCE OR DESIRED STUDY POPULATION**

### **2.1 Population**

Adult patients with a diagnosis of ADPKD

### **2.2 Is ARIA sufficient to assess the intended population?**

ADPKD is a rare disease. Prevalence in the US is estimated to be between 1 in 400 (including observed and estimated autopsy cases) and 1 in 1000 (clinically diagnosed cases only) (3). There are currently approximately 600,000 cases of ADPKD in the US. Despite this, ARIA may be sufficient for identifying a population of patients with ADPKD.

## **3 EXPOSURES**

### **3.1 Treatment Exposure(s)**

The exposure of interest is tolvaptan use (Jynarque) for the treatment of ADPKD. The drug will be administered initially at 45 mg QAM and 15 mg QPM titrated to 90 mg/30 mg per day. A second tolvaptan product SAMSCA® used for hyponatremia will not be included as it is used at a lower dose and for a limited time and has not, to date, been associated with hepatotoxicity.

### **3.2 Comparator Exposure(s)**

Currently there is no approved treatment for ADPKD, therefore an active comparator is not available. If tolvaptan is approved, patients who receive it for treatment of ADPKD are likely to be systematically different from those who choose not to use the drug rendering them poor comparators. There are therefore challenges in identifying an ideal comparator.

### **3.3 Is ARIA sufficient to identify the exposure of interest?**

ARIA may be sufficient to identify patients exposed to tolvaptan for treatment of ADPKD but this will depend on uptake of the new treatment.

## 4 OUTCOME(S)

### 4.1 Outcomes of Interest

The outcome of interest is DILI, indicated by liver injury (elevated transaminase enzymes- AST and ALT) and altered liver function (elevated TBL). The identification of DILI cases in ARIA would require an algorithm to identify evidence in the claims data of both liver injury and altered liver function. These would be indicated by laboratory test results for liver function tests which provide information on levels of liver enzymes and bilirubin. Currently the results of laboratory tests are unavailable in most Sentinel data partners. In addition, based on the data from pivotal clinical trial 156-04-251, a panel of expert hepatologists concluded that long-term treatment with tolvaptan carried a risk of liver failure in about 1 per 3000 treated. As this is such a rare event, it is unlikely that Sentinel would capture a large enough sample of users to detect many events. A panel of hepatologists would likely be required to confirm DILI events in ARIA.

### 4.2 Is ARIA sufficient to assess the outcome of interest?

No, ARIA was judged to be insufficient to assess DILI. The main concern is that accurate evaluation of DILI will require laboratory test results that are currently unavailable in most Sentinel data partners. In the absence of this laboratory data, ICD-9-CM diagnostic codes could be used to identify liver injury. However, the validity of using only ICD-9-CM diagnostic codes to identify cases of severe acute liver injury in Sentinel has been shown to be poor.<sup>3</sup> In addition, a recent systematic review and meta-analysis on the performance of algorithms used to identify DILI in health record databases found that the PPV of DILI detection algorithms was low, ranging from 1.0% to 40.2%, with a pooled estimate of 14.6% (95%CI 10.7-18.9).<sup>4</sup>

## 5 COVARIATES

### 5.1 Covariates of Interest

N/A

### 5.2 Is ARIA sufficient to assess the covariates of interest?

N/A

## 6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

### 6.1 Surveillance or Study Design

A prospective cohort design is required to adequately assess the rate(s) of specific outcomes. DCRP is strongly considering a mandatory registry for patients using tolvaptan for ADPKD, pending drug approval, from which they anticipate DILI incidence rates can be measured.

### 6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

No

## 7 NEXT STEPS

ARIA is insufficient to evaluate the safety of tolvaptan (Jynarque) in the post-marketing setting. The sponsor has proposed a REMS for Jynarque requiring liver testing prior to commencing the drug and monthly thereafter for the duration of therapy and certification of prescribers and



pharmacies. DCRP is also strongly considering a mandatory REMS registry in which each patient prescribed Jynarque will be invited to enroll to collect data on liver testing and details on clinical liver events. The aim of the registry would be fully characterizing the hepatotoxicity risk with tolvaptan, including measuring incidence rates of DILI and to refine recommendations to mitigate the risks of DILI occurring.

The following observational PMR for tolvaptan, if approved, has been proposed:

1.A prospective observational study among patients enrolled in the tolvaptan (Jynarque)Risk Evaluation and Mitigation Strategies (REMS) registry, with the primary objective of determining the incidence rates of drug-induced liver injury. All patients enrolled in the registry should be followed for the duration of tolvaptan treatment and for at least 6 months following discontinuation of treatment. The protocol should specify at least two appropriate comparator populations to which the observed incidence rates will be compared. The identification of a comparator population may be difficult given ADPKD is a rare disease with no currently available treatments. Those who initiate new treatments may be substantially different compared to those who do not. All data would be prospectively collected and verified using medical laboratory results.

#### **References:**

1. FDA. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) July 2009
- 2.Cabello Muriel A, Marin Pozo JF, Alcalá Sanz A, Carrillo Ortiz D. Alteración hepática tras tratamiento con tolvaptán. [*Hepatic change after treatment with tolvaptan*] Farm Hosp. [*Farmacia Hospitalaria*] 2011;35(2):94-6. (Spanish)
- 3.Lo Re V 3rd, Haynes K, Goldberg D, Forde KA, Carbonari DM, Leidl KB, Hennessy S, Reddy KR, Pawloski PA, Daniel GW, Cheetham TC, Iyer A, Coughlin KO, Toh S, Boudreau DM, Selvam N, Cooper WO, Selvan MS, VanWormer JJ, Avigan MI, Houstoun M, Zornberg GL, Racoosin JA, Shoabi A. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. *Pharmacoepidemiol Drug Saf.* 2013;22(8):861-72.
- 4.Tan EH, Low EXS, Dan YY, Tai BC. Systematic review and meta-analysis of algorithms used to identify drug induced liver injury (DILI) in health record databases. *Live*;38(4):742-753.

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

/s/  
-----

MARIE N BRADLEY  
04/19/2018

EFE EWORUKE  
04/19/2018

LOCKWOOD G TAYLOR  
04/20/2018

MICHAEL D BLUM on behalf of JUDITH W ZANDER  
04/20/2018

MICHAEL D NGUYEN  
04/20/2018

ROBERT BALL  
04/20/2018

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: April 9, 2018

To: Norman Stockbridge, MD  
Director  
**Division of Cardiovascular and Renal Products  
(DCaRP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA, CPH  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Puja Shah, Pharm.D., RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (tolvaptan)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 204441

Applicant: Otsuka Pharmaceutical Development and Commercialization, Inc.

## 1 INTRODUCTION

On October 24, 2017, Otsuka Pharmaceutical Development and Commercialization, Inc. submitted for the Agency's review a resubmission of their New Drug Application (NDA) 204441 for TRADENAME (tolvaptan) tablets. This resubmission is in response to the Agency-issued Complete Response (CR) letter received by the Applicant on August 28, 2013. The purpose of this resubmission is to address the deficiencies identified in the CR letter and provide a proposed Prescribing Information (PI) and Medication Guide (MG) for TRADENAME (tolvaptan) tablets.

TRADENAME (tolvaptan) tablets is indicated <sup>(b)</sup><sub>(4)</sub> slow kidney function decline <sup>(b)</sup><sub>(4)</sub> in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCaRP) on February 13, 2018 for DMPP and OPDP to review the Applicant's proposed MG for TRADENAME (tolvaptan) tablets.

## 2 MATERIAL REVIEWED

- Draft TRADENAME (tolvaptan) tablets MG received on October 24, 2017, and received by DMPP and OPDP on March 22, 2018.
- Draft TRADENAME (tolvaptan) tablets PI received on October 24, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 22, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

MORGAN A WALKER  
04/09/2018

PUJA J SHAH  
04/09/2018

LASHAWN M GRIFFITHS  
04/10/2018

# Internal Consults

\*\*\*\*Pre-decisional Agency Information\*\*\*\*

**Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.**

To: Joan E. Blair, Health Communications Analyst,  
Division of Risk Management (DRISK),  
Office of Surveillance and Epidemiology (OSE)

From: Puja Shah, Regulatory Review Officer, OPDP

CC: James Dvorsky, Team Leader, OPDP  
Darrell Lyons, Safety Regulatory Project Manager, OSE  
Leah Hart, Team Leader, DRISK  
Mona G. Patel, Risk Management Analyst, DRISK  
Doris Auth, Associate Director, DRISK  
Jamie Wilkins-Parker, Deputy Director, DRISK  
Carole Broadnax, OPDP  
Michael Wade, OPDP  
CDER-OPDP-RPM

Date: April 9, 2018

Re: NDA 204441  
JYNARQUE (tolvaptan) tablets for oral use  
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)  
Materials (Submission date: March 29, 2018)

---

## **Materials Reviewed**

OPDP has reviewed the following proposed REMS materials for [TRADE NAME]:

- Healthcare Provider (HCP) REMS Materials:
  - Jynarque REMS Prescriber Enrollment Form
  - Jynarque REMS Patient Enrollment Form
  - Jynarque REMS Outpatient Pharmacy Enrollment Form
  - Jynarque REMS Inpatient Pharmacy Enrollment Form
  - Jynarque REMS Program Overview
  - Jynarque REMS Prescriber Training
  - Jynarque REMS Prescriber Knowledge Assessment
  - Jynarque REMS Individual Patient Status Form
  - Jynarque REMS Liver Adverse Events (b) (4) Reporting Form
  - Jynarque REMS Dear Healthcare Provider Letter
  
- Direct-to-Consumer (Patient) REMS Materials:
  - Jynarque REMS Patient Guide
  
- Jynarque REMS Website

The version of the draft REMS materials used in this review were sent from DRISK (Joan E. Blair) via email on March 30, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Jynarque.

### **General Comment**

Please remind Otsuka Pharmaceuticals, that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link [www.JYNARQUErems.com](http://www.JYNARQUErems.com), and toll free number 1-866-244-9446. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind Otsuka Pharmaceuticals that the REMS specific website should not be the sole source of approved REMS materials.

OPDP notes that the Jynarque Prescribing Information (PI) and Medication Guide are still being reviewed and modified. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved Jynarque PI and Medication Guide.

## REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Jynarque REMS Prescriber Enrollment Form
- Jynarque REMS Patient Enrollment Form
- Jynarque REMS Outpatient Pharmacy Enrollment Form
- Jynarque REMS Inpatient Pharmacy Enrollment Form
- Jynarque REMS Prescriber Knowledge Assessment
- Jynarque REMS Individual Patient Status Form
- Jynarque REMS Liver Adverse Events (b) (4) Reporting Form

## Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Jynarque REMS Patient Guide
  - **Risk**
    - OPDP notes the following presentation regarding the communication of the signs and symptoms of the Boxed Warning of hepatotoxicity (bolded emphasis original; underlined emphasis added):

### **“What are the signs and symptoms of serious liver injury?”**

You or your family member should contact your healthcare provider right away if you have any of the following symptoms:

- Feeling (b) (4) tired
- . . .

(b) (4)

We note that the Medication Guide for Jynarque does not include the word (b) (4) (b) (4)

(b) (4)  
We recommend deleting the word (b) (4) to be consistent with the Medication Guide.

Additionally, the presentation regarding the signs and symptoms of the REMS related risk of hepatotoxicity are inconsistent with the Medication Guide. According to the Medication Guide for Jynarque (bolded emphasis original; underlined emphasis added):

(b) (4). Stop taking TRADENAME and contact your healthcare provider right away if you (b) (4) any of the following symptoms:

- feeling tired
- (b) (4) loss of appetite
- nausea
- . . .
- yellowing of the skin and white part of the eye
- dark urine”

(b) (4)  
We recommend revising this presentation to be consistent with the Medication Guide.

- Jynarque REMS Dear Healthcare Provider Letter
- Jynarque REMS Prescriber Training
- Jynarque REMS Website
- **Risk**
  - OPDP notes the use of the following claims in several instances throughout the aforementioned REMS materials (emphasis added):
    - “Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of liver injury **can mitigate**, ...”
    - “Discontinuation in response to laboratory abnormalities, signs and symptoms of liver injury . . . can **reduce the risk** of severe hepatotoxicity.”
    - “**To reduce the risk** of significant or irreversible liver injury, ...”
    - “**To mitigate the risk** of liver injury...”

- “The goal of JYNARQUE REMS is **to mitigate the risk** of serious and potentially fatal liver injury by: ...”

These and similar claims may misleadingly imply a guarantee that discontinuing Jynarque treatment and the use of this REMS will mitigate the REMS related risk of hepatotoxicity. We recommend including the word “help” (e.g., “can **help** mitigate...”, “To **help** reduce the risk...”, “to **help** mitigate the risk...”, etc.) to qualify these claims and to avoid the promotional implication of a guarantee of risk avoidance. Please note that OPDP made similar comments to the Division of Cardiovascular and Renal Products (DCaRP) regarding similar phrasing in the Jynarque PI.

- Jynarque REMS Prescriber Training

- **Risk**

- The Jynarque REMS Prescriber Training presents the following claim regarding the specific time intervals of the laboratory testing requirements (emphasis added):

- “Blood testing for hepatic transaminases and bilirubin is required prior to initiation of JYNARQUE therapy, (b) (4) then monthly...”

This claim omits important material facts regarding the specific time intervals at which laboratory testing is required. Specifically, the Jynarque PI states (emphasis added):

“Measure ALT, AST and bilirubin before initiating treatment, **at 2 weeks and 4 weeks after initiation**, then monthly...”

We recommend revising this claim to clearly communicate the specific time intervals of the lab testing requirements, consistent with the PI.

- Jynarque REMS Prescriber Training
- Jynarque REMS Program Overview

- **Risk**

- These REMS materials include the following claims regarding the liver function monitoring (bolded emphasis original; underlined emphasis added):

- **“Monitor** your JYNARQUE patients on an ongoing basis” (Jynarque REMS Prescriber Training and Jynarque REMS Program Overview)
- “The need for required blood testing before my first dose and regularly during treatment” (Jynarque REMS Program Overview)

The use of the words “ongoing” and “regularly” are vague and may undermine the REMS related risk of hepatotoxicity and the requirement to monitor liver function at very specific time points. We recommend revising these claims (e.g. “The need for required blood testing before my first dose and at specific intervals during treatment”).

- Jynarque REMS Dear Healthcare Provider Letter

- **Risk**

- This REMS material includes the following claim regarding the Jynarque REMS Patient Status Form (emphasis added):
  - “During treatment, prescribers must also **regularly** complete and submit the Patient Status Form.”

The use of the word “regularly” is vague and may undermine the REMS related risk of hepatotoxicity and the important requirement to complete the Jynarque REMS Patient Status Form at very specific time points. Specifically, the Jynarque REMS Patient Status Form states the following (emphasis original):

**“During treatment, this form must be completed and submitted as follows:**

- every 3 months for the first 18 months of treatment
- and every 6 months thereafter.”

We recommend including this important information to clearly communicate the difference between the specific time intervals of the completion of laboratory tests and the submission of the Jynarque REMS Patient Status Form.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.





105 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

PUJA J SHAH  
04/09/2018

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** April 6, 2018

**To:** Anna Park, RPh, Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, MS, Associate Director for Labeling, DCaRP

**From:** Puja Shah, Pharm.D., RAC, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for JYNARQUE (tolvaptan) tablets for oral use

**NDA:** 204441

---

In response to DCaRP's consult request dated February 13, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for JYNARQUE (tolvaptan) tablets for oral use.

**PI/Medication Guide:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DCaRP (Anna Park) on March 22, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 26, 2018, and we our comments are provided below.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or Puja.Shah@fda.hhs.gov.

40 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

PUJA J SHAH  
04/06/2018

## Memorandum - Preliminary Response to Consultation Request

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
 OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 21 February 2018

FROM: John R. Senior, M.D., Office of Surveillance and  
 Epidemiology (OSE)

TO: Bach Nhi Beasley, Pharm.D., Safety Reviewer, Division of  
 CardioRenal Products (DCRP), Office of New Drugs (OND)  
 Norman Stockbridge, M.D., Director,  
 Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCRP  
 Aliza Thompson, M.D., Medical Reviewer, DCRP

VIA: Robert Ball, M.D., Deputy Director, OSE  
 Gerald Dal Pan, Director, OSE

SUBJECT: Review of a case of suspected **tolvaptan**-induced liver failure requiring liver transplantation in Japan, reported by the sponsoring company Otsuka on 17 September 2017, with comments on approvability (NDA 20441) of tolvaptan for the slowing progression of autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan, as (SAMSCA® Otsuka), was approved 19 May 2009 for short-term, in-hospital treatment of hyponatremia with symptomatic hyponatremia or serum Na <125 mEq/dl, with retention of fluid in patients with heart failure, cirrhotic ascites, and the syndrome of inappropriate antidiuretic hormone (SIADH) in patients, or were resistant to fluid intake restriction, or for clinically significant hyper- or eu-volemic hyponatremia. New consultation request received 7 February 2018, with request for response by 21 February.

### Documents reviewed:

- 1) Current 2018 consultation request, as below;
- 2) Consultation request 2 April 2013 from Dr. Aliza Thompson via Ms. Lori Wachter (DCRP) and Ms. Cherye Milburn (OSE), requesting response by 1 July 2013, OSE tracking #2013-1420;
- 3) Otsuka proposal for Risk Mitigation Plan dated 13 November 2012, including report from consulting hepatologist Paul B. Watkins dated 28 October 2012 (“A review of the liver safety database for tolvaptan in; the treatment of Autosomal Dominant Polycystic Kidney Disease”);
- 4) Previous consultation request 29 November 2012, alerting us that the sponsor (Otsuka) had identified a potentially serious signal for liver injury in ADPKD studies, with possible impact on labels for approved indications, prior to our receipt of data for the new PKD work, with partial consultation responses dated 3 and 13 February 2013;
- 5) Memorandum to file, 13 December 2012 from Dr. Mary Ross Southworth
- 6) Otsuka letter to Healthcare Providers, 22 January 2013, **IMPORTANT DRUG WARNING** of significant liver injury associated with SAMSCA;

- 7) Approved labeling for tolvaptan (SAMSCA, Otsuka) for treating euvolemic or hypervolemic hyponatremia, last updated 3 May 2013.
- 8) (b) (4) consultation response 28 June 2013, expressing concerns
- 9) . . . and many other submissions from and responses to Otsuka on the more than 20 years this drug has been under consideration, plus a burst of recent literature on ADPKD as a lifetime disease.

---

The consultation request, from Mary Ross Southworth of DCRP/OND was transmitted to me on 7 February by Darrell Lyons of DRISK/OSE, requesting response by 21 February.

*Tolvaptan is a vasopressin 2 receptor antagonist approved in the US for the treatment of hyponatremia (NDA 22,275). The sponsor is seeking approval of a higher dosage regimen of tolvaptan to slow the rate of kidney function decline in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). This application received a Complete Response in 2013 for reasons primarily related efficacy. Dr. Senior from the Office of Surveillance and Epidemiology completed a consult review in June 2013 where he reviewed potential cases of liver injury from the cirrhosis, heart failure, hyponatremia and ADPKD development program. In addition, a Hepatic Adjudication Committee convened after the first ADPKD trial was completed also reviewed potential cases of liver injury. The HAC's best estimate of the potential for tolvaptan to cause serious liver injury resulting in transplant or death was based on 3 chemical Hy's Law cases in 860 patients treated with tolvaptan, an estimate of 1/3000. After the Complete Response, the sponsor conducted another efficacy trial in ADPKD and tested a strategy of monthly liver test monitoring for 18 months, followed by every 3 months. When the sponsor resubmitted their application (Oct 24, 2017, submission 55), there were no Hy's law cases in the most recent trial. We have become aware of a case of liver failure and transplant in a patient taking tolvaptan for ADPKD in the postmarketing setting in Japan that is fairly well-documented. Please review the following case and address the following questions:*

- 1) What is my assessment of the causal relationship between tolvaptan and liver failure in this case?**
  - 2) Do I agree with the assessments of the Hepatic Adjudication Committee members?**
- 

The current request follows a long series of back-and-forth communications between the sponsor and the DCRP and within the DCRP about this drug, dating back to an IND in 1995 for its former name OPC-41061 before the generic name tolvaptan was established. Although concerns have been raised for many years about the potential hepatotoxicity of tolvaptan, this case appears to be the first discovered or reported in which a nearly fatal outcome occurred. My opinion as an FDA hepatologist was requested concerning the likelihood in this case of causality by tolvaptan, but I feel strongly that that the implications call for my opinion on approvability of tolvaptan for treating ADPKD., that I shall address with disclaimer and confidentiality after discussion of the case report.

Otsuka is seeking approval of a higher dosage regimen of tolvaptan for slowing progression of renal function decline in patients with ADPKD. This approval was not granted in 2013, based on three cases of apparent tolvaptan-induced serious liver injury ("Hy's Law" cases), since which additional studies were conducted. Otsuka then resubmitted a new request 24 October 2017 for tolvaptan treatment of patients with ADPKD.

The information provided for case (b) (6) was received from an unstated Japanese physician on (b) (6), concerning a 37-year-old Japanese single mother diagnosed in (b) (6) as having ADPKD. She was said to have a medical history of alcohol use and smoking up to age 20, hepatic cyst, ovarian cystectomy, and urticaria, in addition to ADPKD.

She was reported to weigh 47 kg and was 1.63 m tall (body mass index 17.7 (103.4 lb\_5'4") on an unspecified date. There was "no problem" with her thyroid. She was not given any medication other than tolvaptan. No information was given about the status of function or injury of either her kidneys or liver before tolvaptan was administered, except for one measurement on [REDACTED] of serum ALT of 7 IU/L (normal range 4-44), total bilirubin 0.3 mg/dL (normal range 0.2-1.3), AST 14 IU/L (normal range 5-40), ALP 135 IU/L (normal range 120-340), but no renal function tests were reported. She was said on that same day to be mildly anemic with blood hemoglobin 11.5 g/dL (normal range 12-16), slightly low serum cholesterol 125 mg/dL (normal range 150-219), and protein 6.6 g/dL (normal range not given). By the time tolvaptan was initiated in [REDACTED] her hemoglobin had normalized to 12.6 g/dL, protein had risen to 6.9 g/dL, and cholesterol stayed a bit low at 130 mg/dL.

*It is not stated how ADPKD was diagnosed, nor why the physician felt that treatment with tolvaptan should be started at that particular time.*

Tolvaptan administration was started in hospital on [REDACTED] at 15 mg/day orally, then increased to 22.5 mg daily on [REDACTED], 30 mg/day on [REDACTED], 45 mg daily on [REDACTED] 60 mg/daily on [REDACTED]. Monthly monitoring of serum enzymes (ALT, AST, ALP) and TBL (total bilirubin) was started when she had been escalated to the 60 mg daily dose in [REDACTED] and remained about constant in [REDACTED] but on [REDACTED] the ALT rose to 69 and AST to 45 IU/L, both slightly elevated above the normal range without symptoms, interpreted as "acute hepatic failure (false hepatic coma type)" and tolvaptan dose was reduced to 45 mg/day on [REDACTED]. Recheck on [REDACTED] showed even more increase in ALT to 142 and AST to 82 IU/L, and tolvaptan was stopped, the patient was advised to rest. A computed tomography scan showed only the hepatic cyst but no evidence of liver atrophy or parenchymal disorder.

*The diagnosis of hepatic failure on [REDACTED] was not justified by the findings, and it is unclear what the physician meant by false hepatic coma type, when she was asymptomatic and the serum bilirubin was still normal.*

On [REDACTED] the ALT spiked to 1293, AST to 860, with small increases in TBL and AP within the normal range, her prothrombin time fell to 59% (normal range 80-120, and her international ratio rose to 1.36, accompanied by symptoms of anorexia, nausea, and malaise. Blood ammonia was normal at 19 (normal range 36-86), and she was not grossly jaundiced (TBL 0.9-2.5 on [REDACTED]) but rose to 3.8 mg/dL on [REDACTED] and blood ammonia rose to 102 on [REDACTED]. She was hospitalized on [REDACTED], over family objections, and was seen by an unidentified hepatologist who stated that liver transplantation would be necessary, based on finding TBL 5.2 mg/dL, blood ammonia 83 mcg/dL prothrombin time 22%, PT ratio 2.82, despite falling ALT and AST and no response to monoammonium glycyrrhizinate injections or domperidone.

*The treating physician was clearly not able to decide properly what should be done, but had started testing for other causes of hepatic failure, such as tests for viral infections Ebstein-Barr virus, hepatitis B and C and A viruses, all of which were negative.*

The patient was transferred to a liver transplant hospital, unspecified, on [REDACTED], with serum bilirubin 8.4 mg/dL and was transplanted on [REDACTED], with no reports of what went on during that admission.

*The details of medical history and laboratory findings, and clinical interpretation of findings, were not well summarized or reported in the jumbled account submitted, It was not stated what*

*records were reviewed, who was reporting (?the local physician) or how decisions were being made, but the records from the re-hospitalization and transplant center were especially skimpy in thi regards, I agree with the two external reviewers (Alpers, Freston, and Lewis) that the information provided is incomplete and unsatisfactory, but still think that the liver failure in this patient was probably and very likely caused by tolvaptan.*

The explanted liver showed measurements of 19.5 x 13 x 7 cm in size, but no weight was given. Cysts were found immediately beneath the liver capsule, shedding of hepatocytes, bile-filled cholangioles, with marked zonal necrosis, consistent with diagnosis of acute liver necrosis caused by a drug.

*The description of the findings was wordy but not what would be expected from a transplant center, and it is unclear who wrote it. The external reviewers were not satisfied that that the findings were not presented, and may still feel that the report is not of good quality, as do I. It may well be that the report was written in Japanese and suffers in translation, but it is regrettable that a full report was not received from the transplant hospital. The reporter who actually wrote this narrative summary does not appear to be as knowledgeable as might be desired.*

Following liver transplantation, rejection by the recipient was noted on liver biopsy. Steroid pulse treatment was started on (b) (6), two weeks post-transplant and rabbit anti-human thymocyte immunoglobulin given, with plasma exchange (b) (6). Repeat liver biopsy on (b) (6) showed improvement and she was reported to be discharged from hospital on (b) (6).

*The reported concluded in (b) (6) that this represented a case of tolvaptan-induced liver failure for which transplantation was needed to preserve the patient's life. No other cause had been found. No evidence of benefit to her kidneys was reported, nor would have been expected in so short a time, but that option is foreclosed by th verous serious liver damage.*

---

Comment: In answer to the two questions asked I can only agree with the external consultants who all felt the information provided was incomplete, that other possible causes were at least reasonably excluded, and that it was very likely that tolvaptan had caused the liver damage and failure threatening her life and necessitating transplantation. Dr. Lewis was somewhat reluctant to assess this a strongly because of no literature reports of severe liver injury, no other deaths or transplants attributed to tolvaptan, despite its being approved since 2009 for short-term therapy of hyponatremia in euvolemic or hypervolemic patients. It remains unclear whether the safety of tolvaptan in those patients was due to decreased susceptibility or to the shorter duration of treatment limited to 30 at up to 60 mg/day and requirement for hospitalization in the labeling.

***Disclaimer: I understand that under current legislation authorizing FDA regulations for the approval of new drugs, or old drugs for new indications, my opinions do not reflect those prevalent at the agency, that I am neither expert in nephrology or law, nor in the financial adverse effects on good patient care. I submit them only for internal discussion in the hope that this case may raise issues for internal debate and discussion that others may make public and seek to inform the ultimate decision makers, voters, consider the implications of approving drugs for treatment of inherited diseases that they do not cure or correct.***

Having said that, so what? Can we, *should* we, simply approve tolvaptan for treatment of ADPKD, as has been done in Japan and several other countries in the world, and add the FDA approval for tolvaptan as the best if not ideal treatment for delaying progression of ADPKD? The worldwide monopoly would understandably but regrettably would be likely to encourage the sponsoring company to do. Our responsibility is primarily to patients, and not to pleasing sponsors or their backers, but I understand that goes beyond what our agency is empowered to do. In this particular case, it could be argued that tolvaptan is the best known treatment for slowing progression of the renal dysfunction that occurs *very slowly* in some people who inherit the genetic defect, so that almost half of those who do so will progress to end-stage renal disease<sup>1</sup> by age 70, a few in childhood, and most after age 50. The problems are, as I had summarized five years ago and will repeat, that we really don't know yet exactly who should be treated, when to start, at what dose, for how long. Screening all children, or even those with some parental history of the disease, using expensive imaging techniques would be prohibitively costly and difficult to enforce.

A cluster of articles<sup>3-5</sup> in this month's influential New England Journal of Medicine followed another pair<sup>6-7</sup> in November 2017 in the same journal, including an endorsement by the editor, Julie Ingelfinger. The sponsor had also reported results of an extension trial in Japan<sup>8</sup> of the TEMPO study done at Mayo Clinic<sup>9</sup> that was reported in July 2017. These and many other publications that have appeared, particularly in the past year, should be read and digested by the current reviews and decision makers. I also need more time to understand and digest all that has been written, findings of studies, and implications.

## REFERENCES

- 1) SE, Chapman AB, Torres VE, Ouyang J, Czerwiec FS. Pharmacokinetics and pharmacodynamics of tolvaptan in autosomal dominant polycystic kidney disease; phase 2 Potts JW, Mousa SA. Recent advances in management of autosomal-dominant polycystic kidney disease. *Am J Health-Syst Pharm.* 2017 Dec 1;74(23):1059-68.
- 2) Senior JR. Consultation response 28 June 2013. DARRTS NDA 204441, 23 June 2013.
- 3) De Tymowski C, Legrand M. Tolvaptan in later-stage polycystic kidney disease, *N Engl J Med.* 2018 Feb 1; 378(5):488.
- 4) Pazmino PA. Tolvaptan in later-stage polycystic disease. *N Engl J Med.* 2018 Feb 1; 378(5):488-9.
- 5) Torres VE, Gansevoort RT, Czerwiec FS. Tolvaptan in later-stage polycystic disease. *N Engl J Med.* 2018 Feb 1; 378(5):489-90.
- 6) Torres VE, Chapman AB, Duvuyst O, Gansevoort RT, Perrone RD, Koch G, Ouyang J, McQuade RD, Blais JD, Czerwiec FS, Sergyeva O, REPRISE Trial Investigators. Tolvaptan in later-stage polycystic disease. *N Engl J Med.* 2017 Nov 16 377(20):1930-42.
- 7) Ingelfinger J. Tolvaptan and Autosomal-Dominant Polycystic Kidney Disease. *N Engl J Med.* 2017 Nov 16 377(20):1988-9
- 8) Muto S, Okada T, Yasuda M, Tsubouchi H, Nakajima K, Horie S. Long-term safety profile of tolvaptan in autosomal dominant polycystic kidney disease patients; TEMPO extension Japan trial. *Drug Health Patient Saf* 2017 Oct 25; 9:93-104.
- 9) Duvuyst O, Chapman AB, Shoaf, Czerwiec, Blais JD. Tolerability of aquaresic-related symptoms following tolvaptan for autosomal dominant polycystic kidney disease; results from TEMPO 3.4 *Kidney Int Rep.* 2017 Jul 21; 2(6):1132-40.
- 10) Torres VE, Chapman AB, Duvuyst O, Gansevoort RT, Perrone RD, Danduand A, Ouyang J, Czerwiec FS, Blais, JD, TEMPO 4.4 trial investigators. *Nephrol Dial Transplant.* 2017 Mar 31; Epub ahead of print

*Following submission of this preliminary consultation, I spoke with the DCRP Director and associates to express my concerns, not only about this one case, but about the reliability of the risk evaluation and mitigation system (REMS) on which the sponsor is depending. It did not appear to work in this case, and raises the question of whether it is a solution to the problem, particularly with such a marginal efficacy benefit in slowing the growth of renal cysts and even less effective slowing of serum creatinine increase used to estimate glomerular filtration rate and renal function.*

*I wanted to take some additional time for thought about whether or not the REMS program worked in this case and check carefully on what the treating physician in Japan did or did not do in following the REMS instructions promulgated by the sponsor. I was allowed some extra time, until 12 March, for this, and attach the supplemental comments below on the subsequent pages.*

*See the supplemental consultation remarks below.*

**Memorandum - Addendum**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 12 March 2018

FROM: John R. Senior, M.D., Office of Surveillance and Epidemiology (OSE)

TO: Mary Ross Southworth, Pharm.D., Deputy Director for Safety, Division  
Of CardioRenal Products (DCRP)  
Bach Nhi Beasley, Pharm.D., Safety Reviewer, (DCRP)  
Aliza Thompson, M.D., Medical Reviewer, DRCR  
Norman Stockbridge, M D., Director, DRCP

VIA: Robert Ball, M.D., Deputy Director, OSE  
Gerald Dal Pan, Director, OSE

SUBJECT: The consultation request of 7 February 2018, originally sent to Dr. Mark Avigan, by Darrell Lyons of OSE, was referred subsequently to me because of previous consultations in 2013. Tolvaptan was approved in Japan for the treatment of autosomal-dominant polycystic kidney disease (ADPKD), but not in the United States, where only the indication for its short-term, limited use for treating eu- or hypervolemic hyponatremia as SAMSCA<sup>®</sup> was approved. After failing to obtain approval for using tolvaptan at higher dose for ADPKD, Otsuka conducted another fairly large trial (TEMPO, in 129 centers worldwide, under leadership of V. E. Torres. No cases of serious hepatotoxicity were found in that study, but DCRP has recently become aware of a new case in Japan, not from a controlled study but from post-marketing experience, resulting in the new consultation request to which I replied on 21 February. In that preliminary memorandum I agreed with the three external reviewers that the patient's hepatic failure and need for transplant was probably caused by tolvaptan, despite many deficiencies in the reporting of details about the case by the prescribing and treating physician in Japan.

In preparation for the planned meeting with representatives of the sponsor on 20 March, this response was requested by 12 March 2018. This supplemental commentary pertains to the case in question, that of the Japanese woman who was treated with tolvaptan as labeled there.

It should be noted that the treating physician in Japan followed very well the rules and precautions promulgated by Otsuka. Tolvaptan dosing 15 mg/day was started in hospital on [REDACTED] (b) (6), and gradually increased after a week to 22.5 mg/day, then at roughly monthly intervals to 30, 45, and 60 mg/day. Monitoring of liver injury tests was carried out and prompt action taken when the serum ALT rose sharply on [REDACTED] (b) (6), then was stopped completely 2 weeks later. Despite very prompt stopping of tolvaptan administration the patient's liver function (bilirubin retention and coagulation abnormalities) deteriorated despite falling levels of the acute injury markers, with progressive necrosis of liver cells and atrophy of the whole liver. Despite considerable effort, no other cause could be found than tolvaptan toxicity. Shown on the next page is a time-course data table, as used in DISH illustrating the sequence of abnormalities observed.

APPEARS THIS WAY ON ORIGINAL

Reported case	(b) (6) from (b) (6) woman 37 treated for ADPKD with SAMSCA (tolvaptan)	(liver tests table)							
		mg/day	4-44	5-40	34-104	0.2-1.3	80-120		36-86
date	comment	dose	ALT	AST	ALP	BLT	PT%	INR	NH <sub>3</sub>
(b) (6)	x=ADPKD; how??		7	14	135	0.3			
	poor nutrition, slender BMI 17.17 ht=1.63 m, wt 47 kg								
			8	17	152	0.3			
			8	14	125	0.3			
			13	18	138	0.3			
	start TLV in hospital; ??why now	15							
		15	22	20	155				
	increase dose at home	22.5							
		22.5	21	24	148	0.3			
	increase to 30	30							
		30	16	17	129	0.3			
	increase to 45	45							
		45	10	15	139	0.3			
	increase to 60	60							
		60	10	15	136	0.2			
	"hepatic failure" ???	60	69	45	140				
	no symptoms; decrease to 45	45							
	stop TLV	45	142	82	147	0.3			
	CT hepatic cysts; advised to rest	0							
	queasy, anorexic; CT liver atrophy	0	<b>1293</b>	<b>860</b>	<b>302</b>	0.9	59	1.36	19
	IV Neominophagen x3 days								
	"tests improved"		<b>609</b>	<b>236</b>	<b>290</b>	1.2	53	1.45	
	"acute hepatic failure" (INR up)		<b>573</b>	<b>303</b>	<b>307</b>	<b>2.1</b>	<b>44</b>	<b>1.64</b>	12
	refusing hospitalization;								
	omperidone, laxative; EBV negative		<b>635</b>	<b>405</b>	<b>332</b>	<b>2.5</b>	<b>43</b>	<b>1.65</b>	
	restart Neominphgen		<b>636</b>	<b>417</b>	<b>312</b>	<b>3.8</b>	<b>33</b>	<b>1.97</b>	13
	gative EBV tests	c	<b>609</b>	<b>434</b>	<b>270</b>	<b>3.9</b>	<b>27</b>	<b>2.37</b>	54
			<b>537</b>	<b>302</b>	<b>344</b>	<b>4.3</b>	<b>27</b>	<b>2.42</b>	69
	ospitalized; seen by hepatologist		<b>426</b>	<b>232</b>	<b>305</b>	<b>5.2</b>	<b>22</b>	<b>2.82</b>	83
	CT hepatic atrophy		<b>379</b>	<b>210</b>	<b>325</b>	<b>5.4</b>	<b>21</b>	<b>2.90</b>	102
			<b>313</b>	<b>153</b>	<b>316</b>	<b>6.5</b>	<b>22</b>	<b>2.87</b>	84
			<b>293</b>	<b>143</b>		<b>8.4</b>	<b>20</b>	<b>3.09</b>	72
			<b>275</b>	<b>145</b>	<b>295</b>	<b>8.7</b>	<b>22</b>	<b>2.87</b>	72
	egative tests for Wilson's, hemochromatosis, AIAT, AI								
	to liver transplant hospital		<b>228</b>	<b>228</b>		<b>8.4</b>			
	CT severe hepatic atrophuy; cysts								
	fresh frozen plasma for INR								
	transplanted successfully		<b>239</b>	<b>667</b>	<b>249</b>	<b>5.2</b>			30
	explant zonal necrosis; 19.5x13x7								
	steroids, rabbit Ig for rejection								
	plasma exchange								
	biopsy showed improvement								
	dx probably TLV-induced								
	reported discharged from hospital								

The table shown above (in Excel) shows very clearly that the treating physician responded quickly to changes in the liver injury tests by first reducing the dose from 60 to 45 mg/day, then stopping it completely two weeks later. That proved to be already too late, for the liver functional failure and necrosis of hepatocytes continued nevertheless, progressing to the patient's transfer to another hospital specializing in liver transplantation on advice of a consulting hepatologist about a month after tolvaptan administration had been stopped.

As the consultants (Drs. David Alpers, Jim Lewis, and Jim Freston) have said, this is an important case, and should not be dismissed lightly by the sponsor. If practicing physicians cannot use this drug safely, despite following all the rules recommended by the sponsor, it should be considered that it is questionable that it be allowed to be used. In this case, of course, there was no benefit shown for treating the ADPKD, and in fact no information was provided to show that she even had the disease or how renal function deterioration might have been slowed.

It is now clear that ADPKD is a lifelong problem, but there is no practical way yet shown for how best to detect it, other than very costly imaging studies used to screen young people, often needing repeated testing to show trends as disease v-e-r-y s-l-o-w-l-y progresses, not in weeks or months but in decades. Even if treatment were started earlier, what daily dose of tolvaptan should be used? Would a lower dose be tolerated and still effective in slowing progression of the bilateral renal cyst development that is more sensitive and precedes rise in serum creatinine on which the estimated glomerular filtration rates are based? It was not stated in this case whether and how the decision was made.

Issues on which DCRP has wanted feedback but that remain unresolved include::

- **Based on the time-course of serum transaminase elevations observed, is it likely that periodic monitoring of liver enzymes would minimize the risk of developing significant liver injury?**

*Monitoring of serum enzyme activities in labeling assumes that it will be done and the results both interpreted and acted upon appropriately. Reality has shown repeatedly that this is not done consistently or for long by many physicians or patients, especially if negative results keep coming. If it isn't done, it won't minimize risk of detecting more serious liver injury and subsequent dysfunction. Therefore, experience has shown it isn't likely to work. Even when done as recommended by Otsuka, the current case in the Japanese woman shows that it still may not work. Although the treating physician stopped the drug promptly it was already too late.*

- **What do we know about dose-response as it relates to DILI in general? Duration of therapy? Because of the low exposure to tolvaptan for hyponatremia (both in the clinical trials and postmarketing) it is not surprising that we have not seen cases, but the sponsor asserts that this may be because the dose and duration of therapy for hyponatremia is lower and shorter, and therefore this risk may not apply to this population. Is this consistent with our experience with other drugs?**

*After drugs have been evaluated during development to detect and eliminate compounds likely to cause predictable dose-related hepatotoxicity, the form of idiosyncratic DILI seen in humans both before and after marketing tends to be rare, dependent more on individual characteristics of the people being treated (therefore "idiosyncratic"), and less clearly on the dose. This is due to the increased susceptibility of a few people to show liver injury at doses well tolerated by most people, for reasons not yet known. This susceptibility is actually dose-related but often at a far lower range of dosing. We cannot at present identify those individuals likely to show initial*

*susceptibility to liver injury or who cannot adapt to repeated exposure; only observation will tell us. Genetic biomarkers of susceptibility are only in their infancy, and are still far too general for individual prediction. The current statistical approach that averages many patients to compute a hypothetical person does not appreciate the individual variation in response to the drug, both for efficacy and susceptibility to harmful effects just doesn't work. There have been at least two rather clear situations in which duration of dosing showed very definite effects: fialuridine and bromfenac. Both drugs seemed to be tolerated for short times but then showed very severe, even irreversible and fatal liver failure on prolonged exposure.*

**- Is there any reason to think that patients with ADPKD would be at increased risk for hepatotoxicity with tolvaptan?**

*Not from the polycystic renal disease itself, but from the need for very long or life-time drug treatment administered in hope of slowing the inexorable progression of this genetic disorder. Treatment could conceivably to be started in childhood when the diagnosis might be made by finding hypertension or hematuria in a child, confirmed by testing for genetic markers PKD1 or PKD2. There could possibly be a duration-related factor of importance, in addition to perhaps a requirement for higher doses. This is something that will need to be considered and explored, in comparing the data for the short-term use of SAMSCA for correction of hyponatremia, and the very long-term need for (b) (4) in hope of slowing progress.*

The current case calls into question the whole concept of risk evaluation and mitigation strategy (REMS) that the sponsor has relied upon. It didn't work, despite following all the rules:

- a. A Medication Guide provided to patients before starting tolvaptan, educating them on the need for liver function testing prior to starting therapy, regular monthly testing for the first 18 months, and the need to self-monitor for signs or symptoms, prompt reporting, and interruption of treatment followed by immediate retesting.
- b. A Communication Plan for healthcare providers likely to prescribe tolvaptan for ADPKD treatment, conveying to them the risk of potential hepatotoxicity especially within the first 18 months, and periodically thereafter, and to re-educate patients on the same points listed above, plus a Dear Healthcare Provider Letter within 60 days of approval and every (b) (4) years.
- c. Copies of the letters were sent to appropriate professional and patients' organizations, and posted at a Tolvaptan ADPKD REMS website, with full prescribing information and the Medication Guide.
- d. Additional voluntary safety measures were developed by Otsuka, as necessary (but not specified).to ensure effective education of both patients and prescribers.
- e. Otsuka agreed to submit REMS assessments to FDA at 18 months, 3 and 7 years after initial approval.

Increase of renal size has appeared to precede and be more sensitive than measures of renal function, now limited by the very insensitive creatinine clearance and derivative manipulations. Reduced incidence rates of a combined (declining renal function (serum creatinine concentration, renal pain, progressive hypertension, and albuminuria) biomarker showed 0.439/year in patients on tolvaptan, compared to 0.500/year on placebo, driven mainly by renal function and renal pain. Renal function, calculated by Cockcroft-Gault or Modification of Diet in Renal Disease formulae also slightly favored tolvaptan – 2.61 vs -3.80 for placebo, as 100/serum creatinine, mg/dL.

It is appreciated that Otsuka has worked long and hard for about 30 years in discovering OPC-61041-Tolvaptan-SAMSCA and trying to develop it for clinical use, but our regulatory concern is

primarily for patients being treated and their physicians who know them best and use informed judgement in prescribing and treating them. Otsuka has not shown clearly that the long term chances of benefits of tolvaptan for ADPKD outweigh its risks of harm in terms of how many patients, by how much, for how long, not to mention at what cost. I do not recommend approval, not because of just one more case, but because granting a monopoly to Otsuka as the only FDA-approved treatment for ADPKD might be a serious mistake.

John R. Senior, MD  
OSE/CDER  
12 March 2018

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

/s/  
-----

JOHN R SENIOR  
03/13/2018

---

## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

---

**Date of This Memorandum:** March 8, 2018  
**Requesting Office or Division:** Division of Cardiovascular and Renal Products (DCRP)  
**Application Type and Number:** NDA 204441  
**Product Name and Strength:** Jynarque (Tolvaptan) tablets, 15 mg, 30 mg, 45 mg, 60 mg, 90 mg  
**Applicant/Sponsor Name:** Otsuka Pharmaceutical CO LTD (Otsuka)  
**FDA Received Date:** February 26, 2018  
**OSE RCM #:** 2017-2185-1  
**DMEPA Safety Evaluator:** Sarah Thomas, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD, BCPS

---

#### 1 PURPOSE OF MEMO

The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container labels and carton labeling for Jynarque under NDA 204441 (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

#### 2 CONCLUSION

Upon review of the revised container labels and carton labeling, we note Otsuka incorporated most of our recommendations except for the blister card text design recommendation. Per Otsuka's February 23<sup>rd</sup> communication to the Division, Otsuka wishes to preserve the current proposed location of the text in the blister card text design because there are no complaints or medication errors in Canada where an identical card text design has been used for close to 3 years and relocating the text on the blister card will require significant changes to the design and packaging process. We find Otsuka's rationale acceptable.

---

<sup>a</sup> Thomas S. Label and Labeling Review for tolvaptan (NDA 204441). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 FEB 16. RCM No.: 2017-2185.

The revised container labels and carton labeling for Jynarque are acceptable from a medication error perspective. We have no further recommendations at this time.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

SARAH E THOMAS  
03/08/2018

CHI-MING TU  
03/08/2018

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Memo**

**Date:** March 6, 2018

**Reviewer:** Paolo Fanti, MD  
Medical Officer  
Division of Pharmacovigilance – I (DPV-I)

**Safety Evaluator Team Leader:** Mihaela Popescu Jason, PharmD, BCPS  
DPV-I

**Medical Officer Team Leader:** Allen Brinker, MD  
DPV-I

**Deputy Division Director:** Monica Munoz, PharmD, MS, BCPS  
DPV-I

**Product Name:** Jynarque (tolvaptan)

**Subject:** Hepatic Adverse Events

**Application Type/Number:** NDA 204441

**Applicant/Sponsor:** Otsuka America Pharm

**OSE RCM #:** 2017-2184

# 1 INTRODUCTION

## 1.1 Background Information and Regulatory History

This memo evaluates the FDA Adverse Event Reporting System (FAERS) for post-marketing cases of hepatic adverse events with the use of tolvaptan. DPV-I noted several hepatic adverse events reported with the use of tolvaptan during datamining activities as part of routine pharmacovigilance. Considering Otsuka's re-submission of tolvaptan for treatment of progressive kidney disease in adult patients with autosomal dominant polycystic kidney disease (ADPKD) and the known risk of tolvaptan-induced liver toxicity in the TEMPO 3:4 pivotal trial<sup>a</sup>, DPV-I initiated this review of the FAERS database for hepatic adverse events in ADPKD patients treated with tolvaptan.

Tolvaptan is an orally administered aquaretic that competitively blocks the binding of arginine vasopressin to V-2 receptors which results in inhibition of water reabsorption in the renal collecting ducts.<sup>1</sup> Tolvaptan was approved for the treatment of clinically significant hypervolemic and euvoletic hyponatremia on May 19, 2009.

The application for tolvaptan use in the treatment of ADPKD patients is currently under FDA evaluation. However, tolvaptan is already approved for this indication in Japan, the European Union, Canada, South Korea, Switzerland, Hong Kong, and Australia. Of note, the sponsor's initial application for the ADPKD indication was not approved by FDA in 2013 based on the TEMPO 3:4 study<sup>a</sup> results which did not adequately demonstrate efficacy and raised concerns about hepatotoxicity. The FDA advised the sponsor to conduct an additional efficacy trial to test the hypothesis that tolvaptan slows the loss of renal function in ADPKD, provide additional information about tolvaptan-induced hepatotoxicity, and implement a risk evaluation and mitigation strategy (REMS) with the overall scope of "evaluating the efficacy of this strategy to significantly decrease the incidence of tolvaptan-induced liver injury progressing to death or transplantation (at least in the USA)".<sup>2</sup> The REMS, as implemented by the sponsor in the latter efficacy trial and in foreign postmarketing activities, included monitoring for signs and symptoms of liver toxicity during the first 18 months of treatment, and the organization of an independent Hepatic Adjudication Committee (HAC) to blindly evaluate reports of liver toxicity. Additionally, though there were no liver injury cases reported in clinical studies or post-marketing reports of non-ADPKD subjects at the time of initial approval, the tolvaptan label for the hyponatremia indication was updated in April 2013 to include the risk of liver injury in the WARNINGS AND PRECAUTIONS section and to restrict therapy duration to 30 days.

The sponsor's current NDA re-submission includes an annual Data Safety Update Report which describes three cases in the active treatment arm as Hy's Law cases [i.e., drug-induced liver injury (DILI) with propensity to life-threatening liver failure] by the HAC.<sup>3</sup> The sponsor also provided results of the additional placebo-controlled double-blind randomized pivotal trial 156-13-210<sup>b</sup>, including results of the REMS. The sponsor concluded that the study results support

---

<sup>a</sup> Study ID 156-04-251. A Phase 3, Multi-Center, Double-Blind, Placebo-Controlled, Parallel-Arm Trial to Determine Long Term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease.

<sup>b</sup> Study ID: 156-13-210. A Phase 3b, Multi-center, Randomized-withdrawal, Placebo-controlled, Double-blind, Parallel-group Trial to Compare the Efficacy and Safety of Tolvaptan (45 to 120 mg/day, Split-dose) in Subjects with Chronic Kidney Disease Between Late Stage 2 to Early Stage 4 Due to Autosomal Dominant Polycystic Kidney Disease

tolvaptan’s efficacy in the treatment of ADPKD. No new cases of DILI consistent with Hy’s Law were reported in trial 156-13-210 and the sponsor stated that there was a “rough incidence of liver failure estimated as 1:3000 patients who receive long term treatment with tolvaptan”. The sponsor also noted that implementation of the REMS minimized the risk of DILI with no detection of Hy’s Law cases. Of note, the sponsor recently submitted a spontaneous report where a Japanese patient receiving tolvaptan for ADPKD developed acute liver failure requiring liver transplantation (FAERS Case# 14032572, Section 3).

In February 2018, representatives from the Office of Surveillance and Epidemiology (OSE) and Division of Cardioresenal Drugs (DCRP) met to discuss Risk Evaluation and Mitigation Strategy (REMS) components after drug approval. The following provisions are currently under consideration: registration of prescriber and pharmacy, limitation of dispensing to 30-day supply, and mandatory registry for all patients receiving the drug. Additionally, the risk of hepatotoxicity will be listed in a boxed warning and prescribers will be advised to monitor liver function at baseline, 2 weeks after initiation of treatment, monthly for the first 18 months, and every 3 months thereafter for the duration of treatment.<sup>4</sup>

## 2 METHODS AND MATERIALS

DPV searched the FAERS database with the strategy described in Table 1.

<b>Table 1. FAERS Search Strategy*</b>	
Date of Search	February 1, 2018
Time Period of Search	No limits <sup>†</sup>
Search Type	Quick Query
Product Active Ingredient	Tolvaptan
MedDRA Search Terms (Version 20.1)	PTs: Hepatic Function Abnormal, Hepatitis Fulminant, Hepatitis Acute, Drug-Induced Liver Injury, Acute Hepatic Failure, Liver Transplant
Outcome	Serious
Case Selection Criteria <sup>†</sup>	Reports were limited to those that included terms “polycystic kidney” in the case narrative or “polycyst” and “cyst” in the medical history.
* See Appendix A for a description of the FAERS database.	
<sup>†</sup> Our case selection criteria focused on identifying cases of DILI in patients receiving tolvaptan treatment for ADPKD. A preliminary evaluation of cases for both the hyponatremia and the ADPKD indications revealed that cases where tolvaptan was used for hyponatremia treatment were confounded by concomitant disease states and the liver injury was more likely attributable to hepatic congestion or shock liver.	

For the purpose of this review, we utilize the term “DILI case” (in lieu of a “Hy’s Law case”) to describe any case of liver injury with DILIN Severity Grade 3 or higher,<sup>5</sup> and with causality assessed as Probable, Highly Likely, or Definite.

### 3 RESULTS

We identified 22 FAERS cases reporting peak serum alanine aminotransferase (ALT)  $\geq 5X$  upper limit of normal (ULN) in ADPKD patients exposed to tolvaptan after excluding duplicates, cases with limited clinical information, and cases reporting peak (ALT)  $< 5X$  ULN.<sup>6,7</sup>

Most cases were reported from Japan (n=20). There were 17 females and five males, with median age 51.3 years old (range 35-64). The time-to-onset of the ALT rise was  $3.5 \pm 1.1$  months, and time-to-ALT-peak was  $4.5 \pm 1.5$  months. Six cases had peak total bilirubin (Tbili)  $\geq 2X > ULN$  and presented clinical signs and symptoms of acute liver injury, including nausea, vomiting, abdominal pain, ascites, jaundice, and/or encephalopathy. These six cases qualified as DILI cases, as defined above, with one describing extensive work-up.<sup>7</sup> The best documented case is summarized below and the other five DILI cases are summarized in **Appendix C**.

#### **FAERS Case #14032572-10; initial FDA received date: January 16, 2018.**

**MCN#** (b) (6) **(spontaneous report)**

A 37-year-old Japanese woman had a medical history of ADPKD (diagnosed 2 years prior), urticaria, liver cyst, ovarian cystectomy, tobacco use, and former alcohol use in her teens. She did not use prescription or over-the-counter medications, toxic substances, dietary supplements, or illicit drugs, and did not have symptoms of  $\alpha 1$ -antitrypsin deficiency. She was initiated on tolvaptan 15 mg daily and dose was gradually increased over three months to 60 mg daily. After four months of treatment, ALT was 10 IU/L [normal (nl) range: 4 - 44 IU/L] and AST 15 IU/L (nl range: 5 to 40 IU/L). After five months of treatment, ALT and AST rose to 69 IU/L and 45 IU/L, respectively, which led to tolvaptan dose reduction to 45mg daily. Two weeks later ALT and AST were 142 IU/L and 82 IU/L, respectively, which led to drug discontinuation. Blood total bilirubin and AlkPhos were normal at the time. Computed tomography scan showed hepatic cysts and “no findings of hepatic parenchymal disorder or hepatic atrophy”. Two weeks after tolvaptan discontinuation and six months after drug initiation, the patient developed malaise, jaundice without encephalopathy, ALT 1293 IU/L, AST 860 IU/L, bilirubin 2.1 mg/dL (nl range: 0.2 to 1.3 mg/dL), which prompted outpatient treatment with monoammonium glycyrrhizinate, domperidone, and a laxative. In the two subsequent weeks, bilirubin rose to 8.4 mg/dL, the prothrombin time-international normalized ratio (PT-INR) rose to 2.82, ALT and AST decreased to 131 and 228 IU/L, respectively, creatinine was 1.05 mg/dL (estimated GFR 51 ml/min, based on J-MDRD), and a computed tomography scan of the abdomen showed “liver parenchyma with atrophy and cysts”, and kidneys with “polycystic appearance and with left renal densities suspicious of possible renal cancer”. Tests were negative for hepatitis A, B, C, and E virus, Epstein-Barr virus, cytomegalovirus, autoimmune disease, hemochromatosis, and Wilson's disease. At the end of six months after tolvaptan initiation, the patient was hospitalized with “transplant criteria score 10 out of 10” based on drug-induced etiology and underwent successful cadaveric-donor liver transplantation. On post-operative day (POD) #9, she developed acute rejection, which responded to intravenous steroids and anti-human thymoglobulin, followed on POD# 25 by possible humoral rejection which responded to plasma exchange and infusion of high-dose intravenous immunoglobulin (IVIG) 50g/day. Tolvaptan lymphocyte stimulation test was negative while on transplant immunosuppressive therapy. Macroscopic pathology of the removed native liver was remarkable for “areas of brown discoloration just under the capsule in both left and right lobe”. Histologically, the “discolored

areas showed marked shedding of hepatocytes, bleeding, and strong cholangiolar hyperplasia”. Otherwise, the “parenchyma was characterized by nodular aggregates of hepatocytes, modest interstitial fibrosis, and mild lymphocyte and histocyte infiltration”. The findings were interpreted by the pathologist as consistent with drug-induced liver disorder. HAC adjudicated the causal relationship [Drug-Induced Liver Injury Network (DILIN) criteria]<sup>8</sup> as “Probable”.

**Reviewer’s Comments:** *The case describes an ADPKD female patient with early-stage chronic kidney disease who developed irreversible acute hepatic failure requiring organ transplantation despite relatively young age, absence of obvious concomitant illnesses, no use of other medications, negative serologies and history for other causes of acute liver disease, frequent monitoring of symptoms, signs and transaminases, prudent escalation of tolvaptan dose over three months, prompt reduction and then discontinuation of tolvaptan upon laboratory evidence of liver injury, and appropriate supportive management after drug discontinuation. Given the strong temporal association, the work-up for alternative causes, and the histology of the explanted liver, the case meets strict Hy’s Law criteria and DPV assesses the causal relationship with tolvaptan as “highly likely”.<sup>8</sup> Of note, Dr. John Senior (OSE hepatologist) is assessing this case in a separate review.*

#### 4 REVIEWER’S COMMENTS

We identified 22 FAERS cases reporting peak serum ALT  $\geq$  5X ULN in ADPKD patients exposed to tolvaptan; six of these cases meet criteria for DILI, with one of these cases being very well documented. The latter case describes acute liver failure resulting in organ transplantation despite prompt intervention by the treating physician. This enhances prior observations of potential hepatotoxic severity associated with tolvaptan use where patients with elevations in ALT and bilirubin improved following drug discontinuation.<sup>9</sup> Based on the currently available information, DPV-I agrees with DCRP’s request to the sponsor to strengthen previous REMS provisions.<sup>4</sup> However, DPV believes the addition of a transaminase laboratory test 2 weeks after start of tolvaptan, followed by monthly laboratory tests for the first 18 months of exposure will not prevent all DILI cases caused by tolvaptan. Even though a REMS with monthly monitoring of transaminases was implemented in the clinical trials and in the postmarketing experience, two of the six DILI cases describe patients who progressed to liver failure, including one patient who progressed to liver transplantation. The most concerning case (FAERS 14032572) notes that providers diligently monitored the patient with monthly labs, increased the frequency of clinical and laboratory checks to bi-weekly after the first occurrence of abnormal transaminases, and promptly reduced and then discontinued tolvaptan based on transaminases. Despite this, the patient progressed to acute liver failure requiring liver transplantation. Additionally, FAERS Case #s 11342440 and 12412451 (see Appendix C) describe two patients who were monitored closely but progressed to experience both ALT and bilirubin elevation. In our case series, hepatic adverse events occurred within the first six months of product exposure. Therefore, it would be prudent to consider bi-weekly lab monitoring for the first six months of treatment. However, DPV-I is aware of the challenge in implementing this approach.

It is important to note that 17 out of the 22 FAERS cases identified with ALT  $\geq$  5X ULN describe female patients. Furthermore, five out of the six DILI cases, including the two progressing to liver transplantation and to death, were in female patients. Prior to the

information discussed in this memo, Dr. John Senior's review of hepatotoxicity with the use of tolvaptan in 2013<sup>9</sup> described three DILI cases, all in females participating in clinical trial 156-04-251. If this observation of a net preponderance of DILI in women accurately predicts future trends, then absolute frequency of death or transplant in women with ADPKD who take tolvaptan could potentially approximate 1:1500. This imbalance of DILI and Hy's Law cases in female patients is concerning and this potential risk factor should be further investigated.

Additionally, DPV-I notes that three of the six DILI cases identified were not adjudicated by HAC (FAERS Case #s 11342440, 12412451, 14033179). It would be prudent to submit an information request to the sponsor to ensure the totality of data related to hepatic adverse events has been evaluated by HAC.

Lastly, DPV-I's causality assessment differs from the HAC with more cases being considered possible, probable, and highly likely by DPV. For example, FAERS report #11910274 (see Appendix C), was adjudicated as "Possible" by DPV-I and "Unlikely" by HAC. The case resulted in death and is confounded by disseminated intravascular coagulopathy (DIC), AKI, suspected infected hepatic cyst, and bacteremia. However, due to missing clinical details (including the liver function tests four months after drug initiation, date and results of procedures and radiological tests done before and during the hospitalization, workup for source and treatment of the bacterial infection, and workup for other causes of acute liver injury), it is challenging to assess whether the hepatic failure is the cause or a complication of the other medical events. As noted above, it would be prudent to submit an information request to the sponsor to collect more information for these cases.

## References

1. Otsuka Pharmaceutical Co. SAMSCA (tolvaptan) PRESCRIBING INFORMATION. 2009 (Initial U.S. Approval). 06/2017 (Last Revision).
2. Stockbridge N. Complete Response. NDA 204441. In: HHS/FDA/CDER/OND/DCRP, ed. <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af802e9e7a>: Document Archiving, Reporting and Regulatory Tracking System (DARRTS); 2013, August 28.
3. Otsuka Pharmaceutical Co. NDA 204441 Resubmission Safety Update of Tolvaptan (OPC-41061). Vol 0055 (59) 10/24/2017 ORIG-1/Resubmission/Class 2: In: Global Submit Review; 2017.
4. Otsuka Pharmaceutical Co. NDA 204441. Resubmission Information Request #18 REMS Teleconference. Vol 0074 (78) 02/15/2018 ORIG-1 /REMS Correspondence: In: Global Submit Review. 2018.
5. Hayashi PH. Drug-Induced Liver Injury Network Causality Assessment: Criteria and Experience in the United States. *International journal of molecular sciences*. 2016;17(2):201.
6. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89(6):806-815.
7. Food and Drug Administration. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. In: U.S. Dept Health and Human Service, ed. <https://www.fda.gov/downloads/Guidances/UCM174090.pdf>: Office of Communications, Division of Drug Information. Center for Drug Evaluation and Research. Food and Drug Administration. 2009.
8. Lee WM, Squires RH, Jr., Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. *Hepatology*. 2008;47(4):1401-1415.
9. Senior JR. Hepatology Consult. Hepatic safety of tolvaptan (NDA 204441), proposed for slowing progression of autosomal dominant polycystic kidney disease (ADPKD). In: HHS/FDA/CDER/OPE, ed. <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af802db1d0>: Document Archiving, Reporting and Regulatory Tracking System (DARRTS); 2013, June 28.
10. Cabañas R, Calderón O, Ramírez E, et al. Sensitivity and specificity of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms causality assessment. *Clinical and Experimental Allergy*. 2018.
11. Lee JH, Seeff L. Uloric (febuxostat). Serious Liver Injury including Liver Failure. In: Document Archiving, Reporting, and Regulatory Tracking System (DARRTS): CDER; 2012, November 7.

## 5 APPENDICES

### APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

#### **FDA Adverse Event Reporting System (FAERS)**

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonization. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## Appendix B. Causality Assessment Scale of Drug-Induced Liver Injury, Based on the DILI Network<sup>6</sup>:

- **Definite:** >95% likelihood. The evidence for the drug causing the injury is beyond a reasonable doubt.
- **Highly likely:** 75%-95% likelihood. The evidence for the drug causing the injury is clear and convincing but not definite.
- **Probable:** 50%-74% likelihood. The preponderance of the evidence supports the link between the drug and the liver injury.
- **Possible:** 25%-49% likelihood. The evidence for the drug causing the injury is equivocal but present.
- **Unlikely:** <25% likelihood. There is evidence that an etiological factor other than a drug caused the injury.
- **Unassessable:** Insufficient information to assess causality.

## APPENDIX C. FAERS DILI CASES

### 1. FAERS Case# 11910274; initial FDA received date: January 12, 2016.

MCN# [REDACTED] (b) (6) (Protocol ID 15600-003, Samsca drug use-results survey)

51-year-old Japanese female with body weight of 46 kg, and medical history of ADPKD diagnosed in 1995, stage 3a CKD, hepatic cyst, hepatic artery embolization in two occasions, repair of retinal detachment, and repair of enterocele when 2-years-old. Concomitant medications included octotiamine. The patient started tolvaptan (unknown dose) on time 0 (T-0) with baseline laboratory values including ALT 14 IU/L (ULN 31 IU/L), AST 23 IU/L (ULN 31 IU/L), GGT 46 IU/L (ULN 45 IU/L), T-Bili 0.6 mg/dL (ULN unknown), INR 1.1 (ULN 1.3), SCr 1.2 mg/dL (ULN unknown). Four months after T-0, GGT was 48 IU/L and SCr 1.2 mg/dL. Five months after T-0, the patient developed abdominal pain with a suspected diagnosis of gastroenteritis but one week later tolvaptan was discontinued, followed by lethargy on the following day. Two days later, she was admitted to hospital with laboratory values including ALT 79 IU/L, AST 162 IU/L, AlkPhos 445 IU/L, Tbili 2.8 mg/dL, PTT 41 (ULN 38), INR 2.1, fibrin D-Dimers 54 (ULN 0.1), and SCr 3.3 mg/dL. One day after admission, ALT was 278 IU/L, AST 508 IU/L, Tbili 3.3 mg/dL, and SCr 3.34 mg/dL, followed by progressive ascites, hepatic failure, AKI, and DIC. She was started on ursodeoxycholic acid and received plasmapheresis during the first two days after admission. A blood culture was positive for *Klebsiella*. A CT scan of the abdomen was significant for “thickened hepatic cyst wall suspicious of infected cyst” and her consciousness waxed and waned throughout the hospitalization. Two weeks after admission, the patient experienced cardiac arrest, acute respiratory failure, acute hepatic failure, and acute kidney injury, and she died the next day. HAC adjudicated the causal relationship (DILIN criteria<sup>8</sup>) as “Unlikely”.

*Reviewer comments: This female patient experienced acute liver failure followed by death, with plausible temporal association between tolvaptan initiation and onset of liver injury. No concomitant hepatotoxic drugs were administered. Presence of abdominal symptoms before the hospital admission and evidence of acute liver failure at the time of admission suggest that the patient developed unrecognized DILI before hospitalization. The case is confounded by concomitant DIC, AKI, suspected infected hepatic cyst, and bacteremia. Due to missing clinical details (i.e., liver function tests four months after T-0, and date and results of: procedures and radiological tests done before and during the hospitalization, workup for source and treatment of the bacterial infection, and workup for other causes of acute liver injury) it is challenging to assess whether the hepatic failure is the cause or a complication of the other medical events. Based on the current available information, this case meets DILI criteria and DPV-I assesses the causal relationship<sup>8</sup> as “Possible”.*

### 2. FAERS Case # 11342440; initial FDA received date: August 5, 2015.

MCN# [REDACTED] (b) (6) (Protocol ID 15600-003, Samsca drug use-results survey)

55-year-old Japanese female with medical history of ADPKD diagnosed in 2000, stage G3a CKD, and hypertension. No history of alcohol use, strenuous physical activity, diabetes mellitus, or pollinosis. Family history is significant for mother with kidney disease. Concomitant medications included telmisartan. At time 0 (T-0), the patient started tolvaptan 45 mg orally daily, with baseline blood profile including ALT 13 IU/L, AST 17 IU/L, and Tbili 0.36 mg/dL

(ULN unknown for all tests). One month after T-0, transaminases were unchanged. However, two months after T-0, the patient developed bloating and lower abdominal pain, followed one week later by diagnosis of drug-induced hepatitis secondary to tolvaptan by a hepatologist. Approximately 75 days after T-0, the patient was hospitalized with ALT 777 IU/L, AST 552 IU/L, Tbili 1.58 mg/dL, and tolvaptan was discontinued. One week after admission, ALT peaked to 1281 IU/L and AST to 1183 IU/L. Two weeks after admission, Tbili peaked to 3.6 mg/dL. Thereafter, the transaminases progressively decreased and approximately 105 days after T-0, ALT was 72 IU/L, AST 68 IU/L, and Tbili 1.7 mg/dL. HAC adjudication for causal relationship is not available.

**Reviewer comments:** *This female patient experienced DILI with 32-fold increase of ALT, 3-fold increase of Tbili and abdominal symptoms consistent with liver disease. The temporal association between tolvaptan initiation and onset of liver injury (i.e., two months) supports a drug-event association, in the absence of exposure to other hepatotoxic drugs. There was a positive dechallenge but it's uncertain whether the liver transaminases normalized completely. This case meets DILI criteria but workup for non-drug-related causes of liver injury is unknown, therefore the case doesn't meet Hy's Law criteria. DPV-I assesses the causal relationship<sup>8</sup> as "Probable".*

### **3. FAERS Case # 12412451; initial FDA received date: May 27, 2016.**

MCN# [REDACTED] (b) (6) (Protocol ID 15600-003, Samsca drug use-results survey)

50-year-old Japanese male with medical history of ADPKD, stage 4 CKD, HTN, subarachnoid hemorrhage, epilepsy, aggressive behavior secondary to cerebrovascular disorder, hyperuricemia, and constipation. His family history is significant for CKD in mother and siblings, and intracranial hemorrhage in the mother. Concomitant medications included nifedipine, olmesartan, febuxostat, sodium bicarbonate, kremezin, lactulose, tiaprilide, zonisamide, lubiprostone, yokukansan (angelica acutiloba root, atractylodes lancea rhizome, bupleurum falcatum root, cnidium officinale rhizome, glycyrrhiza spp. root, poria cocos sclerotium, uncaria spp. hook). At T-0, the patient was started on tolvaptan 15 mg daily, with baseline laboratory values including ALT 16, AST 10, and Tbili 0.4 mg/dL (ULN unknown for all tests). Tolvaptan was then progressively increased to 60 mg daily. The transaminases were stable and unremarkable one week and three months after T-0, but increased five months after T-0, with ALT 51 IU/L, AST 25 IU/L, and Tbili 0.4 mg/dL. Six months after T-0, the transaminases peaked with ALT 510 IU/L, AST 207 IU/L, and Tbili 6.2 mg/dL, followed by discontinuation of tolvaptan and olmesartan after one day, and by hospital admission after two days. The patient remained hospitalized for four days with epigastric pain and vomiting, and was diagnosed with acute hepatitis and high BUN. A drug lymphocyte stimulation test (DLST) was positive for olmesartan. One week after the hospitalization, the transaminases improved with ALT 250 IU/L, AST 88 IU/L, and Tbili 4.6 mg/dL, and three months later they normalized with ALT 8 IU/L, AST 8 IU/L, and Tbili 0.9 mg/dL. HAC adjudication for causal relationship is not available.

**Reviewer comments:** *This male patient experienced DILI with 12-fold increase of ALT, 6-fold increase of Tbili, and abdominal symptoms consistent with liver disease. The temporal association between tolvaptan initiation and onset of liver injury (i.e., five months) supports a*

*drug-event association. Additionally, there was a positive dechallenge. It is important to note that olmesartan is a confounder because it was administered and discontinued concomitantly with tolvaptan, is labeled for the risk of increased transaminases and bilirubin in the “Postmarketing” section of the label, and had a positive DLST result. However, the diagnostic value of the DLST is highly debated.<sup>10</sup> Additional confounding medications include febuxostat<sup>11</sup> (labeled for the risk of hepatic failure under the “Warnings and Precautions” section of the label) and traditional herb remedies which could be associated with hepatotoxicity. However, the contribution of these two drugs to DILI is less likely since both were initiated before tolvaptan treatment and they were continued after tolvaptan and olmesartan discontinuation. This case meets DILI criteria and DPV-I assesses the causal relationship<sup>8</sup> as “Probable”.*

**4. FAERS Case # 12960304; initial FDA received date: November 21, 2016.  
MCN# [REDACTED] (b)(6) (spontaneous physician report)**

48-year-old Japanese female with medical history of ADPKD, stage 3b-4 CKD, and subarachnoid hemorrhage. No history of alcohol consumption, hepatitis virus infection, or circulating autoantibodies. Concomitant medications included spironolactone, febuxostat, losartan, amlodipine. At T-0, the patient was started on tolvaptan 60 mg daily, with baseline laboratory values including ALT 10 IU/L, AST 19 IU/L, Tbili 0.9 mg/dL (ULN unknown for all tests). During the following 6 weeks, tolvaptan dose was increased to 120 mg daily. On week 10 after T-0, the transaminases were markedly abnormal with ALT 853 U/L, AST 766 U/L, ALP 666 U/L, Tbili 2.0 mg/dL, direct bilirubin 1.0 mg/dL, albumin 3.8 mg/dL, platelets  $25.4 \times 10^4$ /mcL, normal eosinophil number, negative HBV/HCV, CMV, and EBV. Abdominal ultrasound showed “ascites, without biliary duct calculus or dilatation”. Abdominal CT scan showed “uneven and irregular liver surface and hepatic atrophy, consistent with chronic and acute liver disorder”. Tolvaptan and all other medications were stopped and ursodeoxycholic acid was started. On week 12 after T-0, the patient experienced general malaise and jaundice, and on week 13 after T-0, was hospitalized with fatigue, itching, jaundice, ALT 437 U/L, AST 650 U/L, ALP 481 U/L, and Tbili 7.1 mg/dL. There was no other organ abnormality or infection. The patient recovered slowly and 10 weeks after hospital admission, ALT was 19 U/L, AST 29 U/L, and Tbili 0.9 mg/dL. HAC adjudicated the causal relationship<sup>8</sup> as “Probable”.

**Reviewer comments:** *This female patient experienced DILI with plausible time relationship with start of tolvaptan, 21-fold increase of ALT, 7-fold increase of Tbili, abnormal liver imaging, jaundice and ascites. There was a positive dechallenge. The case is confounded by concomitant use of febuxostat (labeled for the risk of hepatic failure under the “Warnings and Precautions” section of the label), spironolactone (labeled for the risk of hepatotoxicity under the “Adverse Reactions” section of the label) and amlodipine (labeled for the risk of hepatitis and increased transaminases under the “Postmarketing” section of the label). It’s challenging to assess the contribution of these concomitant medications to the adverse events as they were administered prior to the initiation of tolvaptan. This case meets DILI criteria and DPV-I assesses the causal relationship<sup>8</sup> as “Possible”.*

**5. FAERS Case # 14033179; initial FDA received date: October 2, 2017.**

**MCN# (b) (6) (spontaneous physician report)**

58-year-old Japanese female with medical history of ADPKD diagnosed in (b) (6), right cerebellar hemorrhage in (b) (6), left putamen hemorrhage, HBV carrier status, and hypertension. Concomitant medications included enalapril, amlodipine, and magnesium. The patient initiated treatment with tolvaptan 60 mg daily at T-0, with baseline laboratory profile including ALT 8 IU/L, AST 11 IU/L, Tbili 0.3 mg/dL, AlkPhos 253 IU/L, and GGT 44 IU/L (ULN unknown for all tests). During six weeks after T-0, tolvaptan was progressively increased to 120 mg daily. Eight weeks after T-0, the transaminases had increased to ALT 266 IU/L, AST 175 IU/L, Tbili 0.6 mg/dL, AlkPhos 339 IU/L, and GGT 61 IU/L, and tolvaptan was discontinued. On week 12, the transaminases peaked with ALT 715 IU/L, AST 627 IU/L, Tbili 1.0 mg/dL, ALP 696 IU/L, and GGT 233 IU/L, and the patient started ursodeoxycholic acid. On week 14, Tbili peaked at 2.4 mg/dL, followed by gradual improvement of the transaminases. On week 15, ALT was 106 IU/L, AST 65 IU/L, Tbili 1.6 mg/dL, ALP 581 IU/L, and GGTP 126 IU/L. HAC adjudication for causal relationship is not available.

**Reviewer comments:** *This female patient experienced DILI with 17-fold increase of ALT and 2-fold increase of Tbili, and with plausible time relationship with start of tolvaptan. There was a positive dechallenge but it's uncertain whether the liver transaminases normalized completely. The case is confounded by concomitant use of enalapril (labeled for the risk of hepatitis under the "Postmarketing" section of the label) and amlodipine (labeled for the risk of hepatitis and increased transaminases under the "Postmarketing" section of the label) although these drugs were ongoing at the time of tolvaptan initiation and were not discontinued at the time of the AE. This case meets DILI criteria and DPV-I assesses the causal relationship<sup>8</sup> as "Probable".*

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

/s/  
-----

PAOLO FANTI  
03/06/2018

MIHAELA P JASON  
03/06/2018

ALLEN D BRINKER  
03/06/2018

MONICA MUNOZ  
03/06/2018



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

---

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of New Drugs  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

M E M O R A N D U M

**From:** Elizabeth L. Durmowicz, MD, Medical Officer  
Division of Pediatric and Maternal Health Staff (DPMH)  
Office of Drug Evaluation IV (ODE IV)  
Office of New Drugs (OND)

**Through:** Mona Khurana, MD, Pediatric Team Leader  
John J. Alexander, MD, MPH, Deputy Director  
DPMH, ODE IV, OND

**To:** Division of Cardiovascular and Renal Products (DCaRP)  
Office of Drug Evaluation I, OND

**Subject:** Pediatric Labeling Review

**Applicant:** Otsuka Pharmaceutical Company, Ltd.

**Drug:** Jynarque<sup>1</sup> (tolvaptan)

**Indication (approved):** No approved indication for this NDA<sup>2</sup>

---

<sup>1</sup> The Division of Medication Error Prevention and Analysis issued a letter to the applicant on January 24, 2018 stating that the proposed proprietary name, Jynarque, was determined conditionally acceptable.

<sup>2</sup> Samsca<sup>®</sup> (tolvaptan 15 mg, 30 mg, and 60 mg tablets) was approved for the treatment of clinically significant hypervolemic and euvolemic hyponatremia in adults in 2009 under NDA 22275

**Indication (proposed):** To slow kidney function decline (b) (4) in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

**Dosage Form:** Immediate Release Oral tablets (15 mg, 30 mg, 45 mg, 60 mg, 90 mg)

**Proposed Dosing:** Initial daily dose: 60 mg; Target dose: 120 mg  
Initial and target daily doses to be achieved via dose-titration based on split dose administration<sup>3</sup>

**Consult Request:** DCaRP requested pediatric labeling recommendations, specifically recommendations for Subsection 8.4, to warn of the risk of acute liver failure associated with use of tolvaptan to discourage off-label use in pediatric patients.

**Materials Reviewed:**

- Samsca<sup>®</sup> (tolvaptan, NDA 022275) last approved labeling June 01, 2017<sup>4</sup>
- Resubmission Safety Update of Tolvaptan (NDA 204441). Issue date September 26, 2017 (eCTD Sequence#: 0027; Module 5.3.5.3)
- REMS Strategy (NDA 204441) submitted February 9, 2018 (eCTD Sequence#: 0071)
- DPMH Maternal Health Review (NDA 204441). DARRTS entry February 21, 2018
- Pharmacology/Toxicology Review (NDA 204441, original submission). DARRTS entry July 15, 2013
- Pharmacology/Toxicology Review (NDA 204441, resubmission). DARRTS entry February 27, 2018

**Brief Regulatory Background of NDA 204441**

The applicant submitted NDA 204441 seeking marketing approval for tolvaptan use “to slow kidney disease in adults at risk of rapidly progressing ADPKD” in March 2013. FDA issued a Complete Response (CR) letter citing insufficient evidence of efficacy in August 2013.

---

<sup>3</sup> Split-dosing: 30mg/15 mg, 45mg/15mg, 60mg/30mg, 90/30mg. The second dose is administered 8 hours after the first.

<sup>4</sup> Most recent labeling retrieved from [FDALabel](#) (Access date February 14, 2018)

The applicant conducted a second efficacy trial to address the deficiencies identified in the CR, and the applicant resubmitted NDA 204441 in October 2017 seeking approval for tolvaptan use “to slow kidney function decline [REDACTED] (b)(4) in adults at risk of rapidly progressing ADPKD”. The Prescription Drug User Fee Act (PDUFA) goal date for this application is April 24, 2018.

FDA agreed to the applicant’s request for orphan drug designation, and granted orphan drug designation to tolvaptan for treatment of ADPKD on April 6, 2012.

Tolvaptan was first approved for patients with ADPKD in Japan in March 2014 and is approved and marketed to slow the progression of kidney enlargement in patients with ADPKD in 40 countries, including Australia, Canada, European Economic Area, Japan, Hong Kong, Republic of Korea, and Switzerland.<sup>5,6</sup> Tolvaptan is not approved in any country for any pediatric indications.<sup>7</sup>

### **Brief Tolvaptan Background**

Tolvaptan (OPC-41061) is a selective vasopressin V2 receptor antagonist. Clinical development of tolvaptan for the treatment of ADPKD identified cases of serious, idiosyncratic liver injury. Liver injury was not identified in nonclinical studies of tolvaptan.

FDA approved tolvaptan on May 19, 2009 as Samsca<sup>®</sup> under NDA 022275 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia in adults. DCaRP required studies of tolvaptan in the treatment of this indication in pediatric patients six years to 17 years of age under the Pediatric Research Equity Act (PREA) and issued a Written Request (WR) for studies of tolvaptan on June 15, 2011. The applicant was not able to complete the pediatric studies due to enrollment challenges. The PREA requirements were released and the WR was rescinded on July 19, 2017. No cases of drug induced liver toxicity associated with Samsca<sup>®</sup> have been reported.

### **Brief Review of ADPKD**

ADPKD is a multi-system hereditary disease characterized by the presence of cysts in both kidneys and in other organs as well as vascular and cardiac abnormalities. The renal

---

<sup>5</sup> Per the Maternal Health Review for this application. DARRTS entry February 21, 2018.

<sup>6</sup> Otsuka web site. <http://www.otsuka.co.jp/en/pharmaceutical-business/products/> (Accessed March 1, 2018)

<sup>7</sup> Email correspondence from Otsuka (Marina Tran) to Anna Park, RHPM, DCaRP (March 2, 2018)

manifestations of this disease consist of reduced renal function, hypertension, renal pain, and hematuria and are due to progressive development and enlargement of bilateral renal cysts. The disease occurs in one in every 400-1,000 live births.<sup>8</sup> The majority of patients remain asymptomatic until adulthood; however, data suggest that renal injury begins *in utero*, and 2-5% of patients present in childhood with a broad phenotypic spectrum, including severe neonatal presentations.<sup>9</sup> Treatment is symptomatic and aimed at modifying risk factors which could adversely impact disease progression, but no drug or biologic treatment is approved by FDA to reverse the pathogenesis of ADPKD.<sup>10</sup>

***DPMH Comment:***

*If approved for treatment of ADPKD in adults, tolvaptan is likely to be used off-label in pediatric patients not only for this indication, but also possibly for other renal diseases, such as autosomal recessive polycystic kidney disease and cystinuria, and cardiac conditions, such as congestive heart failure. If the safety profile of tolvaptan can be better characterized in adults and reassurance provided that pediatric patients would not be uniquely susceptible to increased toxicity of this drug (based on the known pharmacology), then DPMH recommends further discussions with the sponsor to encourage pediatric development of tolvaptan under a Written Request (WR). A WR can include studies of more than one indication for which this drug is likely to provide public health benefits in pediatrics. Because this product has orphan status, pediatric studies cannot be required under PREA.*

**Use of Tolvaptan in Pediatric Patients**

The European Medicines Agency (EMA)<sup>11</sup> has an agreed upon Pediatric Investigation Plan (PIP) to study tolvaptan in pediatric patients four weeks to less than 18 years of age for treatment of dilutional hyponatremia and polycystic kidney disease (both ADPKD and Autosomal Recessive Polycystic Kidney Disease).

The applicant has an ongoing pediatric trial in ADPKD being conducted outside the United States. This trial, Trial 156-12-298, is a phase 3b, 2-part, multicenter, one year randomized, double-blind, placebo-controlled trial of the safety, pharmacokinetics,

---

<sup>8</sup> Sommerer C, Zeier M. [Clinical Manifestation and Management of ADPKD in Western Countries](#). *Kidney Dis.* 2016;2:120127.

<sup>9</sup> De Rechter S, Breyssem L, Mekahli D. [Is Autosomal Dominant Polycystic Kidney Disease Becoming a Pediatric Disorder?](#) *Front Pediatr.* 2017;20:5:272. doi: 10.3389/fped.2017.00272. eCollection 2017.

<sup>10</sup> I searched DARTS for NDAs with indication “autosomal dominant polycystic kidney disease” on February 22, 2018.

<sup>11</sup> PIP#: EMEA-001231-PIP02-13-M04 available on the [EMA Web site](#) (Accessed February 16, 2018)

tolerability, and efficacy of tolvaptan followed by a two-year open-label extension in pediatric patients with ADPKD. The applicant submitted preliminary safety data (cutoff date April 18, 2017) from 12 pediatric patients enrolled as part of this NDA resubmission. Per the clinical safety reviewer,<sup>12</sup> “no concerning AEs or liver related AEs” in the 12 pediatric patients were reported by the applicant. The applicant did not report any deaths, serious AEs, treatment emergent AEs leading to discontinuation, or potentially clinically significant elevations in hepatic laboratory data or AEs in five liver Standardized MedDRA Queries (SMQ) in Trial 156-12-298<sup>13</sup>.

**DPMH Comment:**

*I reviewed clinicaltrials.gov<sup>14</sup> and the literature<sup>15</sup> to identify pediatric tolvaptan use and reports of liver toxicity associated with tolvaptan use in pediatric patients. My review of clinicaltrials.gov identified that tolvaptan is currently being investigated in pediatric patients for the treatment of congestive heart failure (CHF), ADPKD, cystinuria and urolithiasis. My literature review identified 12 publications (i.e., two retrospective observational studies and eight case reports) in which tolvaptan was used to treat pediatric patients for hyponatremia,<sup>16</sup> nephrotic edema,<sup>17</sup> ADPKD,<sup>18</sup> and CHF.<sup>19,20</sup>*

---

<sup>12</sup> Personal correspondence with Bach Nhi t Beasley (February 15, 2018)

<sup>13</sup> The five liver SMQs include: Cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; noninfectious hepatitis; liver-related investigations, signs, and symptoms; and liver-related coagulation and bleeding disturbances.

<sup>14</sup> I searched clinicaltrials.gov for “intervention/treatment”: “tolvaptan” with “Child (birth-17)” as a filter on February 16, 2018.

<sup>15</sup> I searched PubMed on February 22, 2018 using combinations of the following terms: “tolvaptan”, “Samsca”, “OPC-41061”, “Jinarc” AND “liver”, “hepat”, “adverse” AND “child”, “pediat”; “tolvaptan” AND pediat”; “OPC-41061” and “pediat”.

<sup>16</sup> Tuli G, Tessaris D, De Sanctis L, Matarazzo P. [Tolvaptan utilization in children with chronic hyponatremia due to inappropriate antidiuretic hormone secretion \(SIADH\)](#). Three case reports and review of the literature. *J Clin Res Pediatr Endocrinol*. 2017;9(3):288-292. doi: 10.4274/jcrpe.4531. Epub 2017 May 17.

<sup>17</sup> Bockenbauer D. [Draining the edema: a new role for aquaretics?](#) *Pediatr Nephrol*. 2014; 29:767–769. doi:10.1007/s00467-014-2763-1

<sup>18</sup> Olalekan K, Fox A, Gilbert R. [Tolvaptan Use in Severe Neonatal Autosomal Dominant Polycystic Kidney Disease \(ADPKD\): The Pharmaceutical Challenge](#). *Arch Dis Child*. 2016;101(9):e2. doi: 10.1136/archdischild-2016-311535.61.

<sup>19</sup> Higashi K, Murakami T, Ishikawa Y, et al. [Efficacy and safety of tolvaptan for pediatric patients with congestive heart failure](#). Multicenter survey in the working group of the Japanese Society of Pediatric Circulation and Hemodynamics (J-SPECH).. *Int J Cardiol*. 2016; 15;205:37-42. doi: 10.1016/j.ijcard.2015.12.003. Epub 2015 Dec 15.

<sup>20</sup> Regen RB1, Gonzalez A, Zawodniak K, et al. [Tolvaptan increases serum sodium in pediatric patients with heart failure](#). *Pediatr Cardiol*. 2013;34(6):1463-8. doi: 10.1007/s00246-013-0671-y.

*The published literature on tolvaptan use in pediatric patients is limited. Based on the limited data in the literature, pediatric use appears to be small and relatively well-tolerated. The literature publications did not identify serious toxicity concerns associated with pediatric tolvaptan use.*

*Given that tolvaptan is being investigated for several indications, if DCaRP decides to issue a pediatric WR for tolvaptan, the WR could include studies of more than one indication, if the studies may produce health benefits in the pediatric population. Review of tolvaptan use in pediatric patients by the Office of Safety and Epidemiology (OSE) may inform the indications to include in a potential WR.*

*Although DPMH did not identify safety concerns associated with pediatric tolvaptan use in the literature, we recommend consultation with OSE to conduct a pharmacovigilance review for adverse event (AE) reports, especially liver toxicity reports, associated with tolvaptan use in pediatric patients.*

## **Discussion of the Potential Toxicity of Tolvaptan in Pediatric Patients**

### Nonclinical Data

Per the Nonclinical Reviewer,<sup>21</sup> the applicant conducted a juvenile rat study to support pediatric clinical trials of tolvaptan for the treatment of hyponatremia, and submitted new juvenile studies in the original submission and resubmission of this NDA. The nonclinical data did not identify a risk of liver toxicity in juvenile animals, and the Pharmacology/Toxicology Midcycle Meeting Review for this application cycle states that juvenile animals are not uniquely sensitive to the toxicity associated with tolvaptan.

### Clinical Pharmacology Data

Per the Clinical Pharmacology Reviewer,<sup>22</sup> FDA does not have any data that would inform “whether there is more or less risk” of liver toxicity in pediatric patients treated with tolvaptan compared to adult patients.

### ***DPMH Comment***

*The FDA Nonclinical and Clinical Pharmacology reviewers for the tolvaptan applications have not identified that tolvaptan use in pediatric patients would be more likely to result in liver toxicity compared to use in adult patients. My review of*

---

<sup>21</sup> Personal correspondence with Gowra G. Jagadeesh (February 15, 2018)

<sup>22</sup> Personal correspondence with Martina Sahre (February 15, 2018)

*documents in DARRTS under the tolvaptan IND for the treatment of hyponatremia (IND 054200), did not identify a review of pediatric clinical pharmacology data.*

#### Pregnancy and Lactation Data

The DPMH Maternal Health Team concluded that the risks of tolvaptan use in pregnancy, lactation, and reproduction cannot be determined due to insufficient evidence. The Maternal Health Review Team and Nonclinical Review team concluded that use in pregnancy “May Cause Fetal Harm”. Although tolvaptan did not cause developmental toxicity in rats or in rabbits at maternally non-toxic doses (i.e., exposures approximately 4-times and 1-time, respectively), effects on embryo-fetal development occurred in both species at maternally toxic doses. Reproductive toxicity findings were observed in animals at exposures similar to the human exposure at the maximum recommended daily dose (i.e., 90 mg, followed by 30 mg).

The Maternal Health Team recommends that women not breastfeed during treatment with tolvaptan. Tolvaptan was present in rat milk (up to a 15 times higher concentration in maternal milk than plasma). Although the clinical relevance of these data is unclear due to species-specific differences in lactation physiology, the Maternal Health Team recommends that women not breastfeed due to the concern for potential serious adverse reactions in the breastfed infant.

#### ***DPMH Comment***

*Although limited, the data available to evaluate risk of tolvaptan use during pregnancy and lactation do not suggest that tolvaptan use in pediatric patients would be more hepatotoxic than use in adults.*

#### **Strategies to Mitigate Liver Toxicity Use of Tolvaptan in Treatment of ADPKD**

The applicant’s planned risk management strategies include labeling (i.e., a boxed warning, Warnings and Precautions, and hepatic monitoring recommendations), a Risk Evaluation and Mitigation Strategy (REMS), enhanced pharmacovigilance activities, and voluntary measures to ensure safe and appropriate use. The goal of the REMS is to mitigate the risk of serious liver injury associated with tolvaptan use. The REMS will include [REDACTED] <sup>(b) (4)</sup> Elements to Assure Safe Use (ETASU) which will include mandatory prescriber training, registration and certification, a Dear Healthcare Provider Letter, and specialty pharmacy certification to dispense only to certified prescribers.

#### ***DPMH Comment:***

*Given that healthcare providers and pharmacies will need to be certified; the ETASU may help prevent off-label use in pediatric patients.*

## **DPMH Discussion of Pediatric Labeling**

Because this product will not be approved in pediatric patients, pediatric use information in labeling would typically be limited to the inclusion of a pediatric use statement<sup>23</sup> in the Pediatric Use subsection (8.4) to state the lack of establishment of safety and effectiveness in pediatric patients (or in a specific pediatric age group(s)) for the treatment of ADPKD. However, even in the absence of pediatric approval, if use of a drug in the pediatric population is associated with a specific hazard, then labeling regulations require the hazard be described in subsection 8.4 and, if appropriate, in sections 4 and 5.

DPMH has not identified concerns that tolvaptan would be ineffective in pediatric patients or that pediatric patients would be at greater risk for increased frequency or severity of tolvaptan associated liver toxicity compared to adult patients. If DCaRP agrees with this assessment, the applicant's proposed language for the Pediatric Use subsection of labeling, "Safety and effectiveness of TRADENAME in pediatric patients have not been established." is acceptable and appropriate. No additional labeling language is needed.

However, if DCaRP has concerns that tolvaptan use would be ineffective or unsafe in pediatric patients or in a specific pediatric age group(s), describe the concern(s) in the Pediatric Use subsection; and if appropriate, summarize the concerns in the BOXED WARNING, CONTRAINDICATIONS, and/or the WARNINGS AND PRECAUTIONS sections, and cross-reference the applicable section/subsection that also summarizes the risk.<sup>24</sup>

### **DPMH Labeling Recommendations:**

Unless DCaRP determines that use of tolvaptan in pediatric patients (or a subgroup of pediatric patients) with ADPKD would be ineffective or unsafe, the applicant's proposed labeling for Pediatric Use (8.4), "Safety and effectiveness of TRADENAME in pediatric patients have not been established." is acceptable.

DPMH does not recommend including additional language in labeling to prevent off-label use.

---

<sup>23</sup> 21 CFR 201.57(c)(9)(iv)(E) or (F)

<sup>24</sup> 21 CFR 201.57(c)(9)(iv)(E) and (F)

**DPMH Additional Recommendation:**

- Consult OSE pharmacovigilance team to conduct a postmarketing safety review of AEs associated with tolvaptan use in pediatric patients.
- Consider requesting an OSE drug use review to identify off-label use of tolvaptan in pediatric patients.
- If the risks of tolvaptan do not outweigh its potential benefits in pediatric patients for the treatment of ADPKD or other indications, DCaRP may wish to encourage pediatric development of tolvaptan by issuing a WR. DCaRP is encouraged to consult DPMH for assistance in issuing a WR.

**Appendix:** Summary of Pediatric Trials of Tolvaptan (per review of clinicaltrials.gov February 16, 2018)

- Study of the Safety and Effectiveness of Samsca<sup>®</sup> (tolvaptan) in Children and Adolescents with Euvolemic or Hypervolemic Hyponatremia (NCT02012959)<sup>25</sup> and Follow Up Extension Study (NCT02020278).

Terminated due to recruitment challenges.

- A Trial of Tolvaptan in Children and Adolescent Subjects with Euvolemic and Hypervolemic Hyponatremia (NCT02442674)

Withdrawn due to inability to meet trial objectives.

- Safety, Pharmacokinetics, Tolerability and Efficacy of Tolvaptan in Children and Adolescents with ADPKD (NCT02964273)

Recruiting in Belgium, Germany, Italy and the United Kingdom. Sponsor: Otsuka

- Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of tolvaptan in Pediatric Congestive Heart Failure (CHF) Patients with Volume Overload (NCT03255226)

Recruiting in Japan. Sponsor: Otsuka

- TCUPS- Tolvaptan Use in Cystinuria and Urolithiasis: A Pilot Study (NCT02538016)

Recruiting patients 12 years to 25 years in Boston, MA. Research IND

- Observational Study in Unites States (U.S.) patients ADPKD (12 years to 70 years) completed (per clinicaltrials.gov update April 2015).

Additional trials that may have enrolled or are enrolling pediatric patients are a dose finding trial conducted in Japan, postmarketing surveillance studies of tolvaptan in Korea, Japan and Germany.

---

<sup>25</sup> Conducted at sites in the United States

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

/s/  
-----

ELIZABETH L DURMOWICZ  
03/05/2018

MONA K KHURANA  
03/06/2018

JOHN J ALEXANDER  
03/06/2018



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

---

Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Memorandum**

**Date:** February 21, 2018                      **Date Consulted:** December 7, 2017

**From:** Kristie Baisden, DO, Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Tamara Johnson, MD, MS, Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health

**To:** Anna Park, Regulatory Project Manager (RPM)  
Division of Cardiovascular and Renal Products (DCRP)

**Drug:** JYNARQUE (tolvaptan)

**NDA:** NDA 204441 (Class 2 resubmission)

**Indication:** Slow kidney function decline [REDACTED] <sup>(b) (4)</sup> in adults at risk of rapidly progressing Autosomal Dominant Polycystic Kidney Disease (ADPKD).

**Applicant:** Otsuka Pharmaceutical Company, Ltd.

**Subject:** Pregnancy and Lactation labeling

**Materials Reviewed:**

- NDA 204441 resubmitted on October 24, 2017
- Applicant's response to IR for PLLR literature review, submitted on January 4, 2018
- DPMH review of conivaptan by Miriam Dinatale, MD, July 6, 2016. DARRTS Reference ID: 3956057

**Consult Question:** "DCRP requests DPMH assistance with PLLR labeling review"

## INTRODUCTION

On October 24, 2017, Otsuka Pharmaceutical Company, Ltd. (Otsuka), submitted a response to the Complete Response (CR) letter previously issued on August 28, 2013, for JYNARQUE (NDA 204441). The proposed indication for JYNARQUE (tolvaptan) is to slow kidney function decline in adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD). On December 7, 2017, DCRP consulted DPMH to provide input on the labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR). This consult provides pregnancy and lactation labeling recommendations to DCRP for JYNARQUE (tolvaptan) based on DPMH's review of the published literature and Otsuka's pharmacovigilance database for tolvaptan.

## REGULATORY HISTORY

- Tolvaptan, a vasopressin V2 receptor antagonist, was first approved in the U.S. for the treatment of hyponatremia on May 19, 2009, under the tradename of SAMSCA (NDA 022275, which was also submitted by Otsuka).
- On March 1, 2013, Otsuka submitted an original NDA 204441 for JYNARQUE (tolvaptan) via the 505 (b) (1) pathway for the new indication to slow kidney function decline in ADPKD. Orphan Drug designation was previously granted on April 6, 2012.
- On August 28, 2013, the Agency issued a CR letter, due to insufficient evidence of efficacy for tolvaptan in ADPKD treatment.
- On October 24, 2017, Otsuka submitted information in response to the CR letter.
- Tolvaptan is currently approved and marketed to slow the progression of cyst development and renal insufficiency in ADPKD in the following regions: Canada, Japan, European Economic Area, Republic of Korea, Switzerland, Australia, and Hong Kong.
- On December 5, 2017, the Agency sent the applicant an information request (IR) for a published literature review regarding the effects of tolvaptan on pregnancy, lactation, and fertility. The applicant's response was received on January 4, 2018, and found to be adequate for the PLLR labeling review.

## BACKGROUND

### Tolvaptan Drug Characteristics<sup>1</sup>

- *Drug Class:* A selective vasopressin receptor antagonist
- *Mechanism of action:* Blocks the binding of vasopressin to the V<sub>2</sub>-receptor in the kidney causing an increase in urine water excretion, an increase in free water clearance, a decrease in urine osmolality, and inhibition of ADPKD cyst growth.
- *Administration:* Oral tablet taken twice daily as a split-dose (30/15 mg, 45/15mg, 60/30mg, or 90/30mg) with titration as tolerated to a maximum daily dose of 120mg.
- *Molecular weight:* 448 Daltons
- *Protein binding:* >98%
- *Half-life:* Dose dependent, ranging 3 hours (15mg dose) to 12 hours (120 mg dose).
- *Bioavailability:* Dose dependent, approximately 56% (42-80%) after a 30mg oral dose.
- *Serious adverse reactions:* Idiosyncratic Hepatic Toxicity, Hyponatremia, Dehydration, Hypovolemia, Urinary Outflow Obstruction, and Uric Acid Increases.

---

<sup>1</sup>JYNARQUE (NDA 204441) proposed package insert

- *Risk Evaluation Mitigation Strategy (REMS):* Regular liver function monitoring is required by a REMS program due to the risk of liver toxicity, which has been observed with tolvaptan use in the ADPKD population.
- *Common Adverse reactions:* Thirst, Polyuria, Nocturia, Pollakiuria, and Polydipsia

*Reviewer's Comment*

*The maximum approved human dose of tolvaptan for the treatment of hyponatremia is 60mg/day; whereas, the maximum recommended human dose of tolvaptan for the treatment of ADPKD is doubled to 120mg/day.*

*The applicant's rationale for the twice daily split-dose regimen for ADPKD includes:*

- *Animal studies indicated constant inhibition of AVP is needed to prevent cyst growth and the single dose trial indicated doses <60mg had an insufficient effect for the full 24hours.*
- *Low doses given twice daily were investigated to minimize urine output related adverse events such as pollakiuria, polyuria, and nocturia.*
- *A split-dose regimen was further investigated to avoid nocturia, with the first dose given upon awakening and second dose given 8 to 9 hours later.*

Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Pregnancy

- *Incidence:* 1:400 to 1:1,000.
- *Prevalence:* Unknown in the general asymptomatic obstetric population because a renal ultrasound is not typically performed in pregnancy.<sup>2</sup>
- *Disease description:* A genetic cause of chronic renal failure in children and adults, characterized by fluid-filled cysts in the kidney and other organs (e.g., liver, pancreas, etc.). The leading cause of end-stage renal failure, hemodialysis, and renal transplant.<sup>3</sup>
- *Clinical manifestations:* Abdominal mass, Chronic Flank or Back Pain, Gross Hematuria, Urinary Tract Infection, Hypertension, and Nephrolithiasis.
- *Current treatment:* There is no available drug therapy that specifically targets the ADPKD pathophysiology. Existing therapy targets symptoms such as pain, infection, and hypertension. Hemodialysis and kidney transplant are used in end stage renal disease secondary to ADPKD.<sup>4</sup>
- *Pregnancy outcomes:* Increased risk of complications such as hypertension, proteinuria, edema, urinary tract infection, pyelonephritis, renal dysfunction, pre-eclampsia, and premature birth. <sup>5</sup> Poor renal function and uncontrolled blood pressure before pregnancy are associated with worse outcomes; whereas normal renal function and well controlled blood pressure before pregnancy are associated with more favorable outcomes.

---

<sup>2</sup> Min Wu, MD et al. Pregnancy Outcomes in Autosomal Dominant Polycystic Kidney Disease: A Case-Control Study. J Maternal Fetal Neonatal Med. 2016 Mar; 29 (5): 807-812.

<sup>3</sup> Neeta Vora, MD et al. Reproductive Issues for Adults with Autosomal Dominant Polycystic Kidney Disease. American Journal of Kidney Diseases. Volume 51, Issue 2, Feb 2008, pages 307-318.

<sup>4</sup> Chapman, A et al. ADPKD: Executive Summary from A Kidney Disease Improving Global Outcomes Controversies Conference. International Society of Nephrology (2015) 88, 17-27.

<sup>5</sup> Cabiddu, G et al. A best practice position statement on pregnancy in chronic kidney disease. J Nephrol. 2016; 29(3): 277-303.

## Current State of the Tolvaptan Labeling<sup>6</sup>

The currently approved SAMSCA (tolvaptan) labeling is from June 1, 2017, and is not in the PLLR format. Sections relevant to pregnancy, lactation, and fertility are summarized below:

- *USE IN SPECIFIC POPULATIONS*: Based on animal data, may cause fetal harm (8.1). Discontinue drug or nursing considering the importance of the drug to the mother (8.3).
- *Pregnancy (8.1)*: Category C. No adequate and well controlled studies in humans. Reduced fetal weights and delayed ossification in rats (162 times MRHD based on BSA). Increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations in rabbits (324 times MRHD based on BSA).
- *Nursing mothers (8.3)*: Tolvaptan is excreted in rat milk. Breastfeeding during treatment is not recommended because of the potential for serious adverse reactions in infants.
- *Fertility (13.1)*: Male and female rats treated with oral tolvaptan had fewer corpora lutea and implants than control, but only at the highest dose level.

PLLR Labeling for another drug in the class, conivaptan, includes similar lactation information as the tolvaptan label. For further details, see the DMPH review by Miriam Dinatale, MD.<sup>7</sup>

## **REVIEW**

### ***PREGNANCY***

#### Nonclinical Experience

In pregnant rats, oral administration of tolvaptan at 10, 100, and 1000mg/kg/day during organogenesis was associated with reduced fetal weight and delayed ossification of the fetuses at the maternally toxic highest dose (17 times the human exposure at the 90/30mg dose based on AUC). Radioactive tolvaptan was distributed to fetal tissues in pregnant rats.

In pregnant rabbits, oral administration of tolvaptan at 100, 300, and 1000mg/kg/day during organogenesis was associated with abortions, embryo-fetal death, fetal microphthalmia, brachymelia, and skeletal malformations at the maternally toxic highest dose (2.6 times the human exposure at the 90/30mg dose based on AUC). Maternal toxicity occurred at all doses.

For further details, see the previous Nonclinical Review by Xavier Joseph, DVM<sup>8</sup> and the current Nonclinical Review by Gowra Jagadeesh, PhD.

#### *Reviewer's Comment*

*The applicant is relying on the previous nonclinical studies performed for the initial tolvaptan approval in 2009. No new reproductive toxicity studies were performed for this submission. Therefore, the current nonclinical team recalculated the human exposure multiples based on the area under the curve (AUC) rather than the body surface area (BSA) which was reported in the previous nonclinical review<sup>8</sup> and the current SAMSCA (tolvaptan) labeling.<sup>6</sup> Aforementioned, it is important to note that the AUC recalculations were also adjusted for the higher maximum recommended dose of tolvaptan for ADPKD treatment (120mg), which is twice the maximum recommended dose of tolvaptan for hyponatremia treatment (60mg).*

---

<sup>6</sup> Drugs@FDA: SAMSCA (tolvaptan) FDA approved label. Accessed 12/27/17.

<sup>7</sup> DPMH review of conivaptan for PLLR conversion by Miriam Dinatale July 6, 2016. Reference ID: 3956057.

<sup>8</sup> Xavier Joseph, D.V.M. Pharm/Tox NDA (022275) Review. 7/12/13. Reference ID: 3340528.

*DPMH discussed the clinical significance of the above animal findings with the Nonclinical Review Team. Considering the reproductive toxicity findings were observed in animals at exposures similar to the human exposure at the 90/30mg dose, the Nonclinical Review Team agreed with the applicant's proposed labeling statement "May Cause Fetal Harm". The Nonclinical Review Team noted the reproductive toxicity effects seen in rats and especially in rabbits were quite severe and may have been independent of the effects seen on maternal body weights and food consumption.*

#### Applicant's Review of Literature

A search was performed in BIOSIS Previews, Embase, and MEDLINE up to December 11, 2017 using the keywords OPC-41061, tolvaptan, Samsca, and Jinarc in relation to "pregnancy" and "congenital anomaly". Per the applicant, only 2 out of the 497 articles retrieved contained any relevant information. Both articles were from the nonclinical literature and have already been reviewed in the above nonclinical section. No relevant clinical reports of tolvaptan use in pregnancy were found in the applicant's literature search.

#### DPMH's Review of Literature

A search was performed in PubMed, Embase, Micromedex<sup>9</sup>, TERIS<sup>10</sup>, Reprotox<sup>11</sup>, and Briggs<sup>12</sup>, using the terms "tolvaptan and pregnancy," "tolvaptan and pregnant women," "tolvaptan and pregnancy and birth defects," "tolvaptan and pregnancy and congenital malformations," "tolvaptan and pregnancy and stillbirth," "tolvaptan and spontaneous abortion," and "tolvaptan and pregnancy and miscarriage."

One case report<sup>13</sup> described a postpartum exposure to tolvaptan in a 39-year-old female who developed SIADH with hyponatremia due to a postpartum hemorrhage during C-section from a placenta accreta. The patient's sodium level normalized after a 15mg dose of oral tolvaptan was administered.

Briggs<sup>12</sup> reports there are no human data regarding the use of tolvaptan in pregnancy. However, animal reproduction studies suggest low risk because the toxic effects occurred in the presence of maternal toxicity at doses significantly higher than the human dose.

#### Review of the Pharmacovigilance Database

##### ***Clinical Trials (ADPKD)***

Pregnancy was an exclusion criteria for participation in all 22 of the tolvaptan clinical trials. Randomized patients who were sexually active and of childbearing potential were required to maintain two forms of adequate contraception. Tolvaptan was discontinued in the patients who became pregnant during clinical trials. Pregnancies that occurred within 30 days of the last dose of tolvaptan were reported to the sponsor's Pharmacovigilance Department. The pregnancy course was followed to completion and the maternal and fetal outcomes were reported.

---

<sup>9</sup>Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 12/27/17.

<sup>10</sup>TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 12/27/17.

<sup>11</sup>Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 12/27/17.

<sup>12</sup>Briggs, GG, Freeman, RK, & Yaffe, SJ. (2017). *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

<sup>13</sup> Snow et al. Managing severe peripartum hyponatremia: A case report. *Obstetric Med* 2014, Vol 7 (4) 171-173.

Infant outcomes were followed for a minimum of 6months. Table 1 summarizes the 17 pregnancies that occurred in tolvaptan-treated clinical trial participants across the ADPKD program (see below).

*Reviewer’s Comment*

*The applicant stated that reporting pregnancy in the partner of a tolvaptan treated trial participant was not required because nonclinical fertility studies did not indicate an effect of tolvaptan on sperm. However, spontaneous reports of pregnancy in the partner of a trial participant were captured.*

*A total of 7 partner pregnancies were reported during clinical trials with outcomes including: 1 spontaneous abortion and 6 live births without birth defects. This reviewer agrees with the applicant that partner pregnancies are unlikely to be as clinically meaningful in evaluating the risks of tolvaptan use in pregnancy. The pregnancies of actual trial participants are more clinically meaningful because these patients had a direct drug exposure which is quantifiable. However, the data collected from pregnant trial participants also has limitations such as the discontinuation of tolvaptan in this population, the inability to control for maternal disease and concomitant medication confounders, the limited number of cases, etc.*

*Overall, only 2 pregnancies occurred in the placebo treated clinical trial participants across the ADPKD program. The outcomes of the placebo treated pregnancies included 1 spontaneous abortion and 1 elective abortion.*

**Table 1: Pregnancies in Tolvaptan Treated Trial Participants Across the ADPKD Program**

Patient ID#	Age (years)	Dose (mg)	Exposure Timing	Pregnancy Outcome (M=maternal, F=fetal)	Reviewer’s Comments
<b>Trial 156-04-251: Phase 3b, Randomized, Double-blind, Placebo-controlled, Safety and Efficacy in ADPKD</b>					
(b) (6)	34	90/30	1 <sup>st</sup> trimester (Preconception to 10wk EGA)	<b>Term Live Birth (NSVD)</b> M: Pregestational Diabetes F: Healthy infant, Weight normal, Apgars normal, No birth defects	
	38	60/30	Not reported	<b>Elective abortion</b> at unknown EGA (LMP not reported)	Reason for elective abortion not reported.
	30	60/30	1 <sup>st</sup> trimester	<b>Elective abortion</b> at ~6wk EGA. Histopathology: normal	Reason for elective abortion not reported.
	25	90/30	1 <sup>st</sup> trimester	<b>Elective abortion</b> At ~6-8wk EGA (LMP uncertain)	Reason for elective abortion not reported.
	41	45/15	1 <sup>st</sup> trimester (Discontinued 1 month prior to miscarriage)	<b>Spontaneous abortion</b> at ~9wk EGA (Ultrasound showed a non-viable embryo)	Concomitant med: irbesartan, methyldopa.  Agree with investigator advanced maternal age is a risk factor for miscarriage.
	37	45/15	1 <sup>st</sup> trimester	<b>Elective abortion</b> at ~7wk EGA (Admitted to hospital overnight 10days later for vaginal hemorrhage)	Reason for elective abortion not reported. Agree with investigator that delayed vaginal hemorrhage is a known complication of abortion.

Patient ID#	Age (years)	Dose (mg)	Exposure Timing	Pregnancy Outcome (M=maternal, F=fetal)	Reviewer's Comments
<b>Trial 156-08-271: Open-label Extension Study, Long-term Safety and Efficacy in ADPKD</b>					
(b) (6)	26	45/15	1 <sup>st</sup> trimester  (Preconception to 3wk EGA)	<b>Preterm Live birth (NSVD)</b> at 36wk EGA M: Chronic HTN Pre-eclampsia at 36wk F: Healthy infant, Weight 5lb 11oz, No birth defects	Maternal history of chronic HTN and chronic kidney disease are risk factors for pre-eclampsia and preterm birth.
	36	90/30	1 <sup>st</sup> trimester  (Preconception to 5wk EGA)	<b>Term Live birth (NSVD)</b> at 38wk EGA M: Chronic HTN F: Healthy infant, Weight (2800grams), Apgars 9/10, No birth defects	
	41	90/30	N/A  (Discontinued 3 months prior to pregnancy)	<b>Missed abortion</b> at ~8wk (LMP not provided)	Concomitant med: amlodipine, methyldopa.  Agree with investigator advanced maternal age is a risk factor for miscarriage.
		N/A	N/A  (No tolvaptan exposure in this 2 <sup>nd</sup> pregnancy)	<b>Live birth (NSVD)</b> at unknown EGA (LMP not reported) M: Chronic HTN Pre-eclampsia F: Low birth weight (2440grams), Apgars 8/9, No birth defects	Hospitalized for pre-eclampsia 1 month prior to the birth and treated with magnesium during delivery.  Advanced maternal age, chronic HTN, and chronic kidney disease are known risk factors for pre-eclampsia.
	36	45/15	Not reported  (Preconception to positive pregnancy test)	<b>Live birth</b> at unknown EGA (LMP not reported) M: Chronic HTN F: Healthy infant, No birth defects	
	35	90/30	Not reported  (Discontinued 1 month prior to positive pregnancy test)	<b>Ectopic pregnancy</b> at unknown EGA (LMP not provided)	Investigator stated this event was not likely related to drug exposure considering drug discontinuation prior to pregnancy.
	34	60/30	Not reported  (Preconception to positive pregnancy test)	<b>Stillbirth</b> at unknown EGA (LMP not reported) Vaginal Delivery	Stillbirth occurred 209 days after the last dose of tolvaptan. Autopsy not performed. Concomitant med: amlodipine.  Investigator assessed the stillbirth as not drug related. Sponsor agreed and cited the short period of drug exposure, maternal HTN, and maternal history of abortion.

Patient ID#	Age (years)	Dose (mg)	Exposure Timing	Pregnancy Outcome (M=maternal, F=fetal)	Reviewer's Comments
<b>Trial 156-10-003: Open-label Extension Study, Long term Safety and Efficacy in ADPKD</b>					
(b) (6)	40	90/30	1 <sup>st</sup> trimester  (Preconception to 5wk EGA)	<b>Term Live birth (NSVD)</b> at 38wk EGA M: Gestational HTN, Pre-eclampsia 38wk F: Low birth weight (2440grams), Apgars 8-9, No birth defects	Hospitalized for pre-eclampsia 2 days prior to delivery. Blood pressure normalized at discharge on postpartum day 5.  Advanced maternal age and chronic kidney disease are risk factors for pre-eclampsia.
	38	60/30	Not reported  (Preconception to positive pregnancy test)	<b>Live birth</b> at unknown EGA (LMP not reported) F: Neonatal Jaundice, Bilateral Renal Cysts	Baby had neonatal jaundice which resolved; relationship to tolvaptan could not be ruled out, since neonatal jaundice commonly occurs in newborns. Neonate also had bilateral renal cysts.
<b>Trial 156-13-210: Phase 3b, Double-blind, Placebo-controlled, Safety and Efficacy in ADPKD with CKD (Stage 2-4)</b>					
(b) (6)	37	60/30	1 <sup>st</sup> trimester  (Preconception to 4wk EGA)	<b>Spontaneous abortion</b> at 10wk EGA	Concomitant meds: omeprazole, cholecalciferol, losartan, promethazine. Maternal medical history: HTN, obesity, miscarriage, and advanced maternal age.  Patient had another pregnancy 4 months later off tolvaptan with a normal birth.
	36	60/30	Not reported	<b>Elective abortion</b> at unknown EGA (LMP unknown)	Reason for elective abortion not reported.

*Reviewer's Comment*

*Overall, the pregnancy exposures to tolvaptan from clinical trials in ADPKD as listed in Table 1 do not demonstrate a clear association between the use of the drug in pregnancy and a risk of adverse developmental outcomes. However, this limited number of pregnancy exposures is insufficient to determine or exclude a risk associated with tolvaptan use in pregnancy.*

*In summary, a total of 17 pregnancies occurred in clinical trial participants and the outcomes included: 7 live births, 5 elective abortions, 3 spontaneous abortions, 1 ectopic pregnancy, and 1 stillbirth. No birth defects were noted in the 7 live births. Maternal pre-eclampsia occurred in 3 of the 7 pregnancies that resulted in live birth. Pre-eclampsia is not unexpected in this population considering these patients had multiple risk factors such as advanced maternal age, hypertension, chronic kidney disease, etc. The reasons for the 5 elective abortions were not provided. In addition, information regarding any abnormal prenatal tests which could have influenced the decision making was not reported. All 3 of the patients who had a miscarriage were of advanced maternal age which is a known risk factor for this outcome. Finally, only limited information was available for review in the case of the 1 stillbirth (no autopsy done). However, the last day of drug exposure occurred remotely to the stillbirth (209 days later). Similarly, in the case of the 1 ectopic pregnancy, tolvaptan had been discontinued 1 month prior to the positive pregnancy test because the patient had reported an intent to try to get pregnant.*

### ***Post-marketing Experience***

The applicant performed a search of the tolvaptan multinational safety database from the time of initial approval on May 19, 2009 to May 18, 2017, including all worldwide indications, to determine the total reported adverse events (AE) for postmarketing cases. The incidence of serious AE's was reported by MedDRA System Organ Class (SOC) and Preferred Term (PT). A total of 18,886 postmarketing AE's were reported to the sponsor in the above timeframe. The search for "pregnancy, puerperium and perinatal conditions" yielded 8 total adverse events:

- 1 missed abortion, 3 spontaneous abortions, 3 ectopic pregnancies, and 1 stillbirth

### ***Reviewer's Comment***

*The reader should note that 6 of the 8 above reported postmarketing AE's occurred simultaneously with the applicant's clinical trials for the new ADPKD indication (see Table 1 which describes 1 missed abortion, 3 spontaneous abortions, 1 ectopic pregnancy, and 1 stillbirth). The other 2 postmarketing AE's were ectopic pregnancies that occurred with tolvaptan use unrelated to the clinical trials for ADPKD. Overall, the postmarketing experience with tolvaptan has been too limited to draw any meaningful safety conclusions about the risks of use in human pregnancy.*

### **Summary**

There is insufficient evidence to determine the risks of tolvaptan use in human pregnancy. In the 17 pregnancies that occurred in clinical trial participants with ADPKD, no specific pattern or increased frequency of major malformation was reported. The 8 total adverse events reported during postmarketing use of tolvaptan in pregnancy also did not indicate a clear safety concern, but a potential safety risk cannot be excluded from such a limited number of cases. Moreover, no clinical published literature is available for the effects of tolvaptan use in pregnancy on maternal and fetal outcomes.

Consequently, DPMH discussed the clinical significance of the animal reproductive findings with the Nonclinical Team and these reviewers agreed with the applicant that the "May Cause Fetal Harm" statement should remain in (b) (6) the tolvaptan labeling. The Nonclinical Team stated the findings in rat and especially rabbit fetuses appear to be severe and may be independent of the observed maternal toxicity.

### ***LACTATION***

#### **Nonclinical Experience**

Radioactive tolvaptan was found in rat milk at 1.5 to 15.8-fold higher levels than in blood. In a prenatal and postnatal study in rats, increased perinatal death and decreased body weight of the offspring during the lactation period and after weaning were observed at the maternally toxic dose of 1000mg/kg/day (17 times the human exposure at the 90/30mg dose based on AUC).

For further information see the previous Nonclinical Review by Xavier Joseph, DVM<sup>8</sup> and the current Nonclinical Review by Gowra Jagadeesh, PhD.

### Applicant's Review of Literature

The applicant searched BIOSIS Previews, Embase, and MEDLINE up to December 11, 2017 using keywords OPC-41061, tolvaptan, Samsca, and Jinarc regarding "lactation" and "breastfeeding". No reports for tolvaptan use during lactation were found.

### DPMH's Review of Literature

A search was performed in Briggs<sup>12</sup>, *Medications and Mother's Milk*<sup>14</sup>, LactMed<sup>15</sup>, Micromedex<sup>10</sup>, PubMed, and Embase using the terms "tolvaptan and lactation" and "tolvaptan and breastfeeding."

The only citation found was in Briggs<sup>12</sup>, which states there are no reports of tolvaptan use during human lactation and the effects of exposure on a breastfed infant are unknown. However, the author expressed concern for potential toxicity in the breastfed infant including dehydration and hypovolemia considering tolvaptan causes urinary water excretion.

### Summary

The lack of clinical data during lactation precludes a clear determination of the risk of tolvaptan to an infant during lactation. Specifically, there are no human data available on the presence of tolvaptan in milk, its effects on the breastfed infant, or its effect on milk production.

Tolvaptan is present in rat milk at up to a 15 times higher concentration in maternal milk than plasma. When a drug is present in animal milk, it is possible that the drug will be present in human milk, although the relative levels may vary. Breastfeeding should be discontinued during treatment with tolvaptan in lactating women due to the concern for potential serious adverse reactions in the breastfed infant, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion.

Overall, DPMH agrees with the applicant that Subsection 8.2 should advise women not to breastfeed during treatment with tolvaptan.

## ***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

### Nonclinical Experience

Tolvaptan was not carcinogenic in animal studies conducted in mice and rats. There was no evidence of genotoxicity. In a fertility study in rats, tolvaptan was administered orally at doses of 100, 300, and 1000 mg/kg/day. Altered estrous cycles due to prolongation of diestrus were observed in dams given 300 and 1000 mg/kg/day (9.7 and 17.3 times the human exposure at the 90/30mg dose based on AUC). Tolvaptan had no effect on copulation or fertility indices.

For more information, refer to the previous Pharmacology/Toxicology review by Xavier Joseph, DVM<sup>8</sup> and the current review by Gowra Jagadeesh, PhD.

---

<sup>14</sup>Hale, Thomas (2017) *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

<sup>15</sup><http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 12/27/17.

### Applicant’s Review of Literature

The applicant searched BIOSIS Previews, Embase, and MEDLINE up to December 11, 2017 using keywords OPC-41061, tolvaptan, Samsca, and Jinarc regarding “male fertility” and “female fertility”. No reports for the effect of tolvaptan use on fertility were found.

### DPMH’s Review of Literature

No reports were found in the published literature related to tolvaptan and fertility or interactions with hormonal contraceptives. A search was performed in PubMed, Embase, and Reprotox<sup>11</sup> using the terms, “tolvaptan and fertility,” “tolvaptan and contraception,” “tolvaptan and oral contraceptives,” and “tolvaptan and infertility.”

### Summary

DPMH recommends omitting Subsection 8.3 Females and Males of Reproductive Potential from tolvaptan labeling. As mentioned, there are no human data regarding the effects of tolvaptan on fertility or contraception. In addition, DPMH discussed the rat fertility study findings with the Nonclinical Team who concluded tolvaptan had no clinically relevant effect on fertility.

## **CONCLUSIONS**

DPMH concludes there is insufficient evidence to clearly determine the risk of tolvaptan use in pregnancy, lactation, and reproduction. Specifically, pregnant and lactating women were excluded from all tolvaptan clinical trials. Although no increased risk of adverse developmental outcomes was identified in the 17 pregnancies of clinical trial participants with ADPKD, these limited data are insufficient to exclude risk. In addition, post-marketing exposure to tolvaptan has been limited in this population. Consequently, published clinical literature is not available to guide pregnancy and lactation labeling recommendations.

Aforementioned, the Nonclinical Review team recommends keeping the labeling statement “May Cause Fetal Harm” in subsection 8.1 because the adverse reproductive effects observed in animals may have been independent of maternal toxicity. In addition, DPMH recommends against breastfeeding during treatment due to the presence of tolvaptan in rat milk and the potential risk for serious adverse reactions with exposure to the breastfed infant.

Therefore, the JYNARQUE (tolvaptan) labeling subsections for *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Subsection 8.1**
  - The “Pregnancy” subsection of labeling was formatted in the PLLR format to include: “Risk Summary” and “Data” sections.
- **Lactation, Subsection 8.2**
  - The “Lactation” subsection of labeling was formatted in the PLLR format to include: “Risk Summary” and “Data” sections.
- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of labeling was updated to correspond with changes made to subsection 8.1 and 8.2 of labeling.

## LABELING RECOMMENDATIONS

DPMH revised the Highlights and subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with DCRP on February 1, 2018. The recommendations below reflect input from the Pharmacology/Toxicology Review Team. DPMH refers to the final NDA action for final labeling.

### DPMH Proposed JYNARQUE (tolvaptan) Pregnancy and Lactation Labeling

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### -----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm (8.1)
- Lactation: Breastfeeding not recommended (8.2)

## FULL PRESCRIBING INFORMATION

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

(b) (4) available data with JYNARQUE use in pregnant women are insufficient to (b) (4) a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure (*see Data*). Advise a pregnant woman of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

##### Data

##### *Animal Data*

Oral administration of tolvaptan during the period of organogenesis in Sprague-Dawley rats produced no evidence of teratogenesis at doses up to 100 mg/kg/day. Lower body weights and delayed ossification were seen at 1000 mg/kg, which is approximately 17 times (b) (4) the exposure in humans at the 90/30 mg dose (AUC<sub>24h</sub> 6570 ng h/mL). The fetal effects are likely secondary to maternal toxicity (decreased food intake and low body weights). In a prenatal and postnatal study in rats, tolvaptan had no effect on physical development, reflex function, learning ability or reproductive performance at doses up to 1000 mg/kg/day.

In New Zealand White rabbits, placental transfer was demonstrated with  $C_{\max}$  values in the yolk sac fluid approximating 22.7% of the value in maternal rabbit serum. In embryo-fetal studies, teratogenicity (microphthalmia, embryo-fetal mortality, cleft palate, brachymelia and fused phalanx) was evident in rabbits at 1000 mg/kg (approximately 3-times the exposure at the 90/30 mg dose). Body weights and food consumption were lower in dams at all doses, equivalent to 0.6 to 3-times the human exposure at the 90/30 mg dose.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary (*see Data*). Because of the potential for serious adverse reactions in breastfed infants, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion, advise a woman not to breastfeed during treatment with JYNARQUE.

### Data

In lactating rats administration of radiolabeled tolvaptan, lacteal radioactivity concentrations reached the highest level at 8 hours after administration and then decreased gradually with time with a half-life of 27.3 hours. The level of activity in milk ranged from 1.5- to 15.8-fold higher than those in blood over the period of 72 hours post-dose. In a prenatal and postnatal study in rats, maternal toxicity was noted at 100 mg/kg/day or higher ( $\geq 4.4$  times the human exposure at the 90/30 mg dose). Increased perinatal death and decreased body weight of the offspring were observed during the lactation period and after weaning at approximately 17.3 times the human exposure at the 90/30 mg dose.

## 17 PATIENT COUNSELING INFORMATION

### Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

### Lactation

Advise women not to breastfeed during treatment with JYNARQUE [*see Use in Specific Populations (8.2)*].

## MEDICATION GUIDE

Tell your doctor about all of your medical <sup>(b) (4)</sup> including if you:

- **Are pregnancy or plan to become pregnant.** It is not known if JYNARQUE will harm your unborn baby. <sup>(b) (4)</sup>.
- **Are breastfeeding or plan to breastfeed.** It is not known if JYNARQUE passes into your breast milk. Do not breastfeed during <sup>(b) (4)</sup> treatment with JYNARQUE. Talk to your healthcare provider about the best way to feed your baby during this time.

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

/s/  
-----

KRISTIE W BAISDEN  
02/21/2018

TAMARA N JOHNSON  
02/21/2018

LYNNE P YAO  
02/21/2018

---

**LABELS AND LABELING REVIEW**

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

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

---

<b>Date of This Review:</b>	February 16, 2018
<b>Requesting Office or Division:</b>	Division of Cardiovascular and Renal Products (DCRP)
<b>Application Type and Number:</b>	NDA 204441
<b>Product Name and Strength:</b>	Tolvaptan Tablets, 15 mg, 30 mg, 45 mg, 60 mg, 90 mg
<b>Product Type:</b>	Single-Ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Otsuka Pharmaceutical CO LTD (Otsuka)
<b>Submission Date:</b>	October 24, 2017
<b>OSE RCM #:</b>	2017-2185
<b>DMEPA Safety Evaluator:</b>	Sarah Thomas, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD, BCPS

---

## 1. REASON FOR REVIEW

As part of the NDA review process, this review evaluates the proposed tolvaptan container labels and carton labeling, as well as the proposed Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that could lead to medication errors.

### 1.1 REGULATORY HISTORY

Samsca (tolvaptan) tablets, 15 mg and 30 mg, are currently marketed for the treatment of hyponatremia (NDA 022275). Samsca is dosed 15 mg orally once daily up to a maximum dose of 60 mg daily.

Otsuka now proposes tolvaptan tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg strengths, for the treatment of autosomal dominant polycystic kidney disease (ADPKD) under NDA 204441. The proposed dosing is a split-dose regimen that ranges from 15 mg as the first dose followed by 15 mg 8 hours later, up to a maximum split-dose regimen of 90 mg as the first dose followed by 30 mg 8 hours later.

## 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed tolvaptan packaging configuration is a 7-day dosage regimen blister cards of 14 tablets:

- combination of seven 45 mg tablets (1<sup>st</sup> dose) and seven 15 mg tablets (2<sup>nd</sup> dose)
- combination of seven 60 mg tablets (1<sup>st</sup> dose) and seven 30 mg tablets (2<sup>nd</sup> dose)
- combination of seven 90 mg tablets (1<sup>st</sup> dose) and seven 30 mg tablets (2<sup>nd</sup> dose)

Although the proposed packaging configurations meet the need of the recommended initial, titrated, and target doses, the proposed packaging configurations do not facilitate the recommended dose adjustments for patients also taking moderate and strong CYP 3A inhibitors (e.g., 15 mg/15 mg split-dose regimen, 30 mg/15 mg split-dose regimen, etc.). We communicated information requests to Otsuka on January 18, 2018 and January 26, 2018 requesting clarification on their intent for using the proposed packaging configurations to facilitate the full dosing range, including the dosage modifications. Otsuka responded on January 24, 2018<sup>a</sup> and January 31, 2018<sup>b</sup> that in the case of prescriptions with dose reductions, the specialty pharmacies enrolled in the REMS and dispensing tolvaptan will prepare the medication by punching out the appropriate doses from the blister cards. The tablets will then be dispensed to the patient in a pharmacy bottle with the dosing instructions and medication guide. The remaining tablets in the blister card will be subsequently returned to Otsuka. Otsuka anticipates only very few patients (approximately 30 to 40 patients in the US) will require dose reductions due to concomitant CYP 3A inhibitor use for longer than 60 days. Otsuka also states that the proposed closed pharmacy network will be limited to 3 Specialty Pharmacies, and that these pharmacies will be contracted and trained in the dispensing instructions and REMS requirements. The training will include information on dosing for specific patient types, including the dose adjustments for severe or moderate CYP 3A inhibitors. We find Otsuka's proposed plan and rationale acceptable.

We communicated Otsuka's proposed plan for dose adjustments with CYP 3A inhibitor use to DCRP and met to discuss the proposal on February 15, 2018. From this meeting, the Review Team discussed that:

- DCRP finds Otsuka's approach to estimate the number of patients who will concomitantly use moderate inhibitors reasonable, and agrees the data indicates that only a small proportion of the population will need dose reduction.
- DCRP plans to contraindicate the use of tolvaptan with strong CYP 3A inhibitors.
- DMEPA expressed the risk of concomitant administration of tolvaptan without dose reduction and moderate CYP 3A inhibitors, but the Review Team agreed this risk is similar to other drugs on the market with drug-drug interactions with other drugs.
- The Review Team finds the concomitant administration of tolvaptan and moderate CYP 3A inhibitors, especially under short-term use (e.g. 7-day course of antibiotics), may result in a 2-fold overdose that is unlikely to have a clinical impact. Thus, DCRP finds the risk of concomitant use of tolvaptan without dose reduction with the CYP 3A inhibitor acceptable.
- DCRP plans to revise the PI language in relation to dose reduction for concomitant moderate CYP 3A use to add an additional option for prescribers: either dose reduction

---

<sup>a</sup> See DARRTS, Product Correspondence Resubmission Information Request, dated January 25, 2018 available at <\\cdsesub1\evsprod\nda204441\0065\m1\us\cover-0065.pdf>

<sup>b</sup> See DARRTS, Product Correspondence Resubmission Information Request, dated February 1, 2018 available at <\\cdsesub1\evsprod\nda204441\0067\m1\us\cover-0067.pdf>

of tolvaptan or holding tolvaptan during the short-term use of a moderate CYP 3A inhibitor.

We agree with DCRP's and the Review Team's plan regarding moderate CYP 3A inhibitors. We also note that the PI and Medication Guide labeling provide a mitigation in the form of a warning for patients to alert their healthcare provider if they begin any new medications while on tolvaptan.

Our review of the materials identified some areas where the proposed PI, MG, container labels, and carton labeling need clarification and revision to optimize safe use. In addition, we note

[REDACTED] (b) (4). Therefore, we provide recommendations in Section 4 below.

#### 4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Tolvaptan container labels, carton labeling, PI, and MG can be improved to promote the safe use of the product as described in 4.1 and 4.2.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

###### A. Prescribing Information (PI)

1. We recommend adding the route of administration "oral" to the Dosage and Administration section of the Highlights and Section 2 of the full PI.
2. We recommend adding a space between the "8hr later" dosing instructions provided in the first table under the Dosage and Administration Section in the Highlights section of the PI (e.g., 8\_hr later).
3. We recommend adding the mg units to the split dose designations as well as adding "and" between 2 strengths (in place of "/") provided in the dose adjustment tables under the Dosage and Administration Section in the Highlights section of the PI and the dose adjustment tables under Section 2.4 of the full PI (e.g., revise 90/30 mg, 60/30 mg, 45/15 mg, 30/15 mg, and 15/15 mg to 90 mg and 30 mg, 60 mg and 30 mg, 45 mg and 15 mg, 30 mg and 15 mg, and 15 mg and 15 mg).
4. Clarify the following statement provided under Section 2.1 of the full PI: [REDACTED] (b) (4)
5. In Section 16 of the full PI, revise the presentation of the [REDACTED] (b) (4) packaging configurations to include the total number of tablets per [REDACTED] (b) (4) or carton and as well as the number of tablets per strength, as follows:
  - i. [REDACTED] (b) (4)



B. Medication Guide (MG)

1. Add the route of administration “oral” under the section titled “How should I take TRADENAME?”, as follows: “Take TRADENAME orally twice daily, (b) (4)



**4.2 RECOMMENDATIONS FOR OTSUKA PHARMACEUTICAL CO LTD**

We recommend the following be implemented prior to approval of this NDA:

A. General recommendations for the Container Labels and Carton Labeling

1. We recommend revising the strength presentation on the container labels and carton labeling to express the numerical strength and unit of measure per tablet as follows: e.g., “15 mg per tablet” and “45 mg per tablet.”<sup>c</sup>

B. Weekly Blister Card Carton Labeling and Monthly Supply of Blister Cards Carton Labeling (carton contains 4 blister cards each)

1. The established name lacks prominence commensurate with the proprietary name and is not at least half the size of the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Revise the statement, (b) (4) to the following: “Usual Dose: See prescribing information.”
3. We recommend adding the word “and” between the 2 strengths presented on the carton labeling (e.g., on the 45 mg/15 mg blister card, specify “45 mg per

---

<sup>c</sup> Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

tablet **and** 15 mg per tablet”), which will help indicate to the end-user that the blister card contains 2 different strength tablets.

C. Blister Card Container Labels

1.



D. Weekly Blister Card Carton Labeling

1. We recommend revising the net quantity statement on the principal display panel of the carton labeling to include the total number of tablets for each strength per blister card. For example, for the 45 mg and 15 mg blister card carton:

14 Tablets

Weekly Pack contains 1 blister card with 14 tablets (7 x 45 mg tablets and 7 x 15 mg tablets).

E. Monthly Supply of Blister Cards Carton Labeling (carton contains 4 blister cards each)

1. We recommend revising the net quantity statement on the principal display panel of the carton labeling to include the number of blister cards, total number of tablets per blister card, and total number of tablets for each strength per blister card. For example, for the 45 mg and 15 mg blister card carton:

56 Tablets

Monthly carton contains 4 child resistant Weekly Packs.

Each Weekly Pack contains 1 blister card with 14 tablets (7 x 45 mg tablets and 7 x 15 mg tablets).

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Tolvaptan tablets that Otsuka Pharmaceutical CO LTD submitted on October 24, 2017.

<b>Table 2. Relevant Product Information for Tolvaptan</b>				
<b>Initial Approval Date</b>	N/A			
<b>Active Ingredient</b>	Tolvaptan			
<b>Indication</b>	Selective vasopressin V <sub>2</sub> -receptor antagonist indicated to slow kidney function decline <span style="background-color: #cccccc;">(b) (4)</span> in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)			
<b>Route of Administration</b>	Oral			
<b>Dosage Form</b>	Tablets			
<b>Strength</b>	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg			
<b>Dose and Frequency</b>	<b>Dosing</b>	<b>Initial Dose</b>	<b>Titration Step (at least weekly intervals between titrations)</b>	<b>Target Dose</b>
	<b>Split Dose (mg)</b>	1st dose: 45 mg 2nd dose (8hr later): 15 mg	1st dose: 60 mg 2nd dose (8hr later): 30 mg	1st dose: 90 mg 2nd dose (8hr later): 30 mg
	<b>Total Daily Dose (mg)</b>	60 mg	90 mg	120 mg
	(b) (4)			
<ul style="list-style-type: none"> <li>• Dose adjustment is recommended for patients taking moderate CYP 3A inhibitors:</li> </ul>				

	Daily Split Dose	Reduced Split Dose
	90/30 mg	45/15 mg
	60/30 mg	30/15 mg
	45/15 mg	15/15 mg
<b>How Supplied</b>	<p>Tolvaptan tablets are supplied as:</p> <ul style="list-style-type: none"> <li>• <b>Weekly Pack</b> contains a 7-day dosage regimen child-resistant blister card of 14 tablets: <ul style="list-style-type: none"> <li>○ <b>NDC 59148-087-07:</b> combination of 15 mg and 45 mg strengths</li> <li>○ <b>NDC 59148-088-07:</b> combination of 30 mg and 60 mg strengths</li> <li>○ <b>NDC 59148-089-07:</b> combination of 30 mg and 90 mg strengths</li> </ul> </li> <li>• <b>Monthly Carton</b> contains 4 weekly packs, each containing a 7-day dosage regimen child-resistant blister card of 14 tablets: <ul style="list-style-type: none"> <li>○ <b>NDC 59148-087-28:</b> combination of 15 mg and 45 mg strengths</li> <li>○ <b>NDC 59148-088-28:</b> combination of 30 mg and 60 mg strengths</li> <li>○ <b>NDC 59148-089-28:</b> combination of 30 mg and 90 mg strengths</li> </ul> </li> </ul>	
<b>Storage</b>	Store at (b) (4) excursions permitted between 15 °C and 30 °C (59 °F to 86 °F) [see USP controlled Room Temperature].	
<b>Container Closure</b>	<p>(b) (4)</p> <ul style="list-style-type: none"> <li>• Child-resistant (b) (4) /Foil Blisters</li> </ul>	

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

On January 17, 2018, we searched DMEPA's previous reviews using the term "tolvaptan" to identify reviews previously performed by DMEPA and related to this labels and labeling review. Our search identified no previous reviews relevant to this labels and labeling review.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/  
-----

SARAH E THOMAS  
02/16/2018

CHI-MING TU  
02/16/2018

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: August 29, 2013

TO: Norman L. Stockbridge, M.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs

FROM: Xingfang Li, M.D., RAC  
Consumer Safety Officer  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
Michael F. Skelly, Ph.D.  
Pharmacologist  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Addendum to review of EIR Covering NDA 204-441,  
Tolvaptan tablets, sponsored by Otsuka Pharmaceutical  
Company

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the following study:

**Study Number:** 156-11-295  
**Study Title:** "An Open-label, Randomized, Crossover Trial to Assess Dose Strength Equivalence among 30 and 90 mg Strengths of Oral Tolvaptan Tablets and to Determine the Effect of Food (Standard Food and

Drug Administration High-fat Breakfast) on  
Tolvaptan Pharmacokinetics following the 90 mg  
Tablet in Healthy Subjects”

**Clinical Site:**

The inspection of the clinical portion was conducted by Amanda  
J. White (ORA) at Covance Clinical Research Unit, Inc., Dallas,  
TX. Following the inspection (June 6-7, 2013), Form FDA-483 was  
e failed

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers several lines of text.

Following DBGLPC's original evaluation of the Form FDA-483  
observations, and communications from the ORA investigator, the  
DBGLPC reviewers recommended that the clinical results from  
Study Number 156-11-295 are unacceptable for Agency review.

(b) (4)

A very large rectangular area of the document is redacted with a solid grey fill, covering the majority of the lower half of the page.

had an opportunity to respond. However, these DBGLPC reviewers  
do not foresee any suitable correction for this study.

Xingfang Li, M.D., RAC  
Division of Bioequivalence and GLP  
Compliance

Michael F. Skelly, Ph.D.  
Division of Bioequivalence and GLP  
Compliance

**Final Classifications:**

**NAI:**

[REDACTED] (b) (4)

**OAI: Covance Clinical Research Unit, Inc., Dallas, TX**

**FEI: 3007024261**

**Reason for change from ORA tentative classification:  
Significant objectionable conditions were not cited on Form  
FDA 483.**

Attachment: Form FDA 483

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernett

DBGLPC/Haidar/Bonapace/Choi/Skelly/Li

OMPT/CDER/OND/ODEI/DCRP/Stockbridge/Park

OMPT/CDER/OTS/OCP/DCPI/Mehta

OGROP/ORASW-FO/DAL-DO/DAL-IB/FTWOR-TX/Bias/White

OGROP/ORANE-FO/NYK-DO/NYK-DIB/Sacco/Schlossin

Draft: XFL 8/29/2013

Edit: MFS 8/29/2013

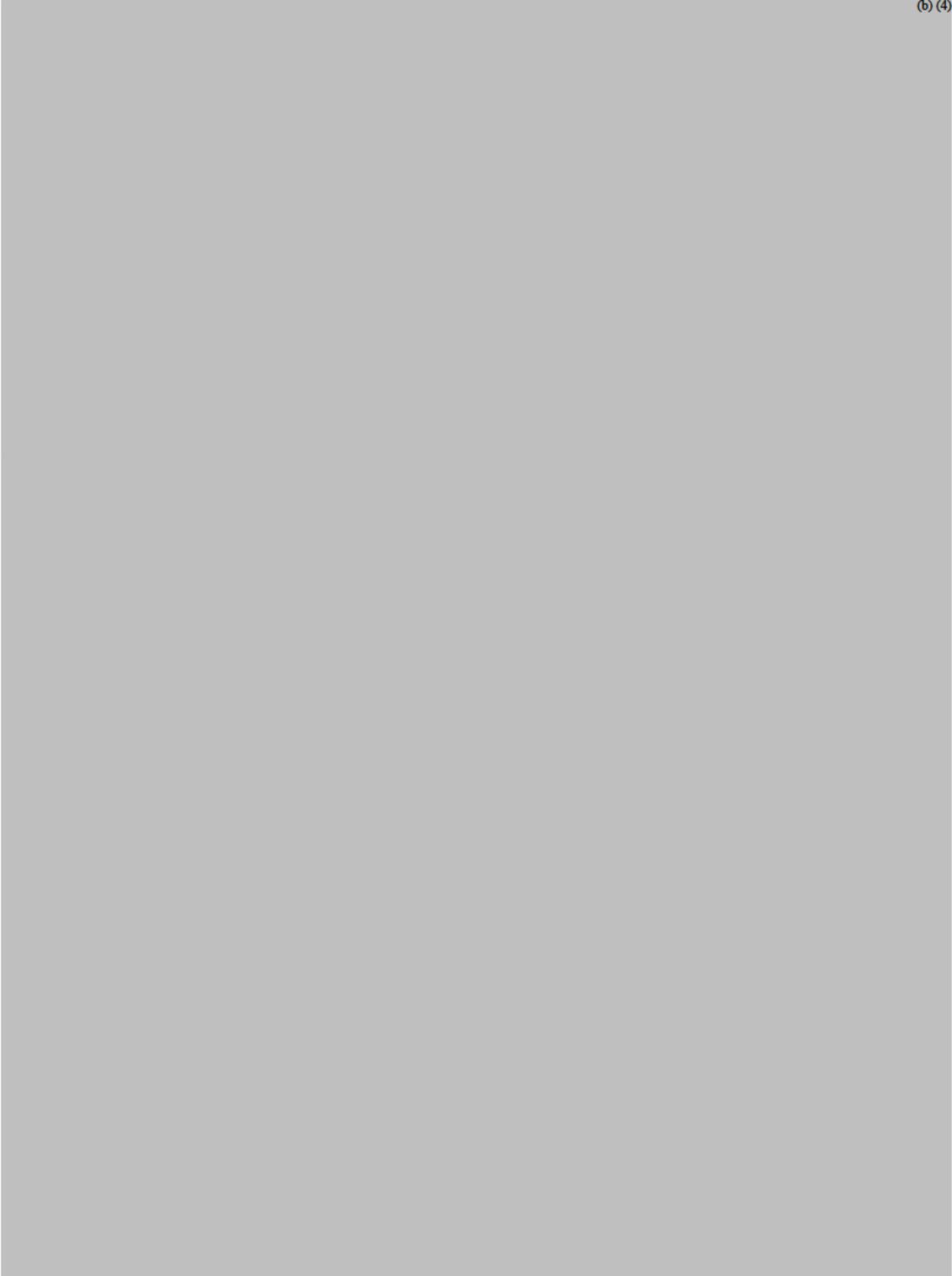
BE File # 6442; O:\BE\EIRCOVER\204441lots.tol.add.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good

Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: [REDACTED] (b) (4)

(b) (4)



(b) (4)



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

/s/  
-----

XINGFANG LI  
09/09/2013

SAM H HAIDAR  
09/10/2013

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: August 19, 2013

TO: Norman L. Stockbridge, M.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs

FROM: Xingfang Li, M.D., RAC  
Consumer Safety Officer  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
Michael F. Skelly, Ph.D.  
Pharmacologist  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 204-441, Tolvaptan  
tablets, sponsored by Otsuka Pharmaceutical Company

At the request of the Division of Cardiovascular and Renal Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the following study:

**Study Number:** 156-11-295  
**Study Title:** "An Open-label, Randomized, Crossover Trial to Assess Dose Strength Equivalence among 30 and 90 mg Strengths of Oral Tolvaptan Tablets and to Determine the Effect of Food (Standard Food and Drug Administration High-fat Breakfast) on

Tolvaptan Pharmacokinetics following the 90 mg Tablet in Healthy Subjects"

The audits included thorough examination of study records, facilities, and equipment, and interviews and discussions with the firms' managements and staff.

**Clinical Site:**

The inspection of the clinical portion was conducted by Amanda J. White (ORA) at Covance Clinical Research Unit, Inc., Dallas, TX. Following the inspection (June 6-7, 2013), Form FDA-483 was issued (Attachment 1). The firm's response was received by DAL-DO on July 23, 2013. To date (8/16/2013), the DBGLPC reviewers have not received the firm's response. The Form FDA-483 observations and our evaluations follow:

(b) (4)



(b) (4)

(b) (4)



(b) (4)

**Bioanalytical Site:**

The inspection of the bioanalytical portion was conducted during [REDACTED] (b) (4) by Joanne M. Schlossin, Consumer Safety Officer, NYK-DO, Michael F. Skelly, Ph.D., Pharmacologist, CDER, and Xingfang Li, M.D., Consumer Safety Officer, CDER at [REDACTED] (b) (4). At the conclusion of the inspection, no objectionable conditions were observed and no Form FDA-483 was issued.

**Conclusion:**

(b) (4)

(b) (4)

Xingfang Li, M.D., RAC  
Division of Bioequivalence and GLP  
Compliance

Michael F. Skelly, Ph.D.  
Division of Bioequivalence and GLP  
Compliance

**Final Classifications:**

**NAI:**

(b) (4)

**OAI: Covance Clinical Research Unit, Inc., Dallas, TX  
FEI: 3007024261**

**Reason for change from ORA tentative classification:  
Significant objectionable conditions were not cited on Form  
FDA 483.**

Attachment: Form FDA 483

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernet

DBGLPC/Haidar/Bonapace/Choi/Skelly/Li

OMPT/CDER/OND/ODEI/DCRP/Stockbridge/Park

OMPT/CDER/OTS/OCP/DCPI/Mehta

OGROP/ORA/SW-FO/DAL-DO/DAL-IB/FTWOR-TX/Bias/white

OGROP/ORA/NE-FO/NYK-DO/NYK-DIB/Sacco/Schlossin

Draft: XFL 8/16/2013

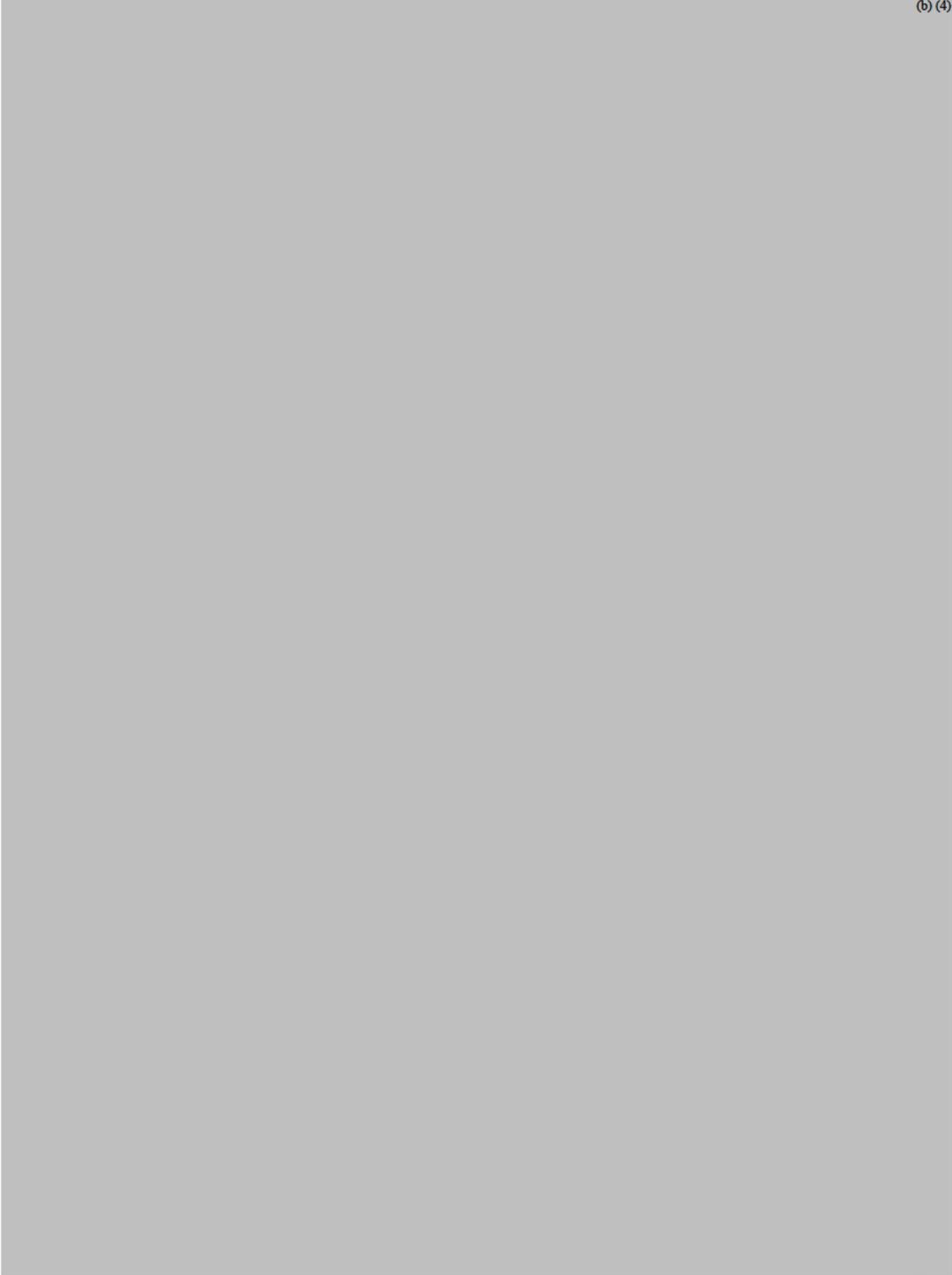
Edit: MFS 8/16/13, YMC 8/16/13, RCA 8/16/13; WHT 8/19/13

BE File # 6442; O:\BE\EIRCOVER\204441ots.tol.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: (b) (4)

(b) (4)



(b) (4)



---

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

---

/s/

---

MICHAEL F SKELLY

08/19/2013

We intend to amend this report when the Covance EIR and exhibits are available to us.

Young Moon: Please sign on behalf of Sam Haidar, who is on leave today.

Xingfang: I was unable to put your name as primary author, and as #1 in the signing order. My name should have been #2.

/Mike

YOUNG M CHOI

08/19/2013

WILLIAM H TAYLOR

08/20/2013

XINGFANG LI

08/20/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

CLINICAL INSPECTION SUMMARY

**DATE:** July 26, 2013

**TO:** Aliza Thompson, Medical Team Leader  
Nhi Beasley, Medical Officer  
Anna Parks, Regulatory Project Manager  
Division of Cardio-Renal Drug Products

**FROM:** Sharon K. Gershon, Pharm. D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA#:** 204441

**APPLICANT:** Otsuka Pharmaceuticals

**DRUG:** tolvapan

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority

**INDICATIONS:** Slowing the progression of kidney disease in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)

**CONSULTATION REQUEST DATE:** April 10, 2013

**INSPECTION SUMMARY GOAL DATE:** August 2, 2013

**ADVISORY COMMITTEE MEETING:** August 5, 2013

**DIVISION ACTION GOAL DATE:** August 31, 2013

**PDUFA DATE:** September 1, 2013

## **I. BACKGROUND**

Otsuka seeks approval to market tolvaptan for the treatment of patients with autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan is a vasopressin V2 receptor antagonist that was approved on May 19, 2009 for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). At the time of approval, tolvaptan was also being developed under IND 72,975 as a treatment for ADPKD.

ADPKD is an inherited disease characterized by progressive development of cysts that destroy normal kidney architecture. Cysts develop from abnormal (mutated) tubular epithelial cells scattered throughout the kidney. The number, distribution, and growth rate of cysts determines timing and severity of related (negative) clinical outcomes, including polyuria, hypertension (HTN), infections, nephrolithiasis, hematuria, renal pain, and progressive loss of renal function. Most of these (negative) clinical outcomes occur years to decades before declining renal function is detected.

The pivotal trial for this NDA was No. 156-04-251, entitled “A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease”.

After determining eligibility, subjects were randomized 2:1, tolvaptan: placebo, and began treatment. During the 3-week titration phase, tolvaptan or placebo tablets (as multiples of 15 mg or 30 mg) were titrated in weekly intervals from lowest to highest tolerated levels, given in split-dose regimens of 45 mg AM/15 mg PM, 60 mg AM/30 mg PM, or 90 mg AM/30 mg PM. As soon as a subject could not tolerate a dose, the titration phase was considered completed and the maintenance phase began at the dose level tolerated and was continued up to Month 36. Subjects were allowed to down-titrate at any time for reasons of safety or tolerability.

The **primary efficacy endpoint** was: rate of total kidney volume (both kidneys) change from baseline. To evaluate the primary efficacy endpoint, a magnetic resonance imaging (MRI) was performed at baseline (31 to 14 days prior to randomization), and at Months 12, 24 and 36/Early Termination visits.

The **secondary composite efficacy endpoint** was the key endpoint for regulatory decision-making. The endpoint was a clinically important complication of progressing ADPKD and included:

- Onset or progression of hypertension,
- Severe renal pain requiring medical intervention,
- Worsening albuminuria,
- Worsening renal function (25% decrease in 1/serum creatinine as a measure of renal function from steady-state post dose baseline value).

The trial screened 2122 subjects, and randomized 1445 subjects. A total of 961 subjects received tolvaptan and 483 subjects received placebo.

The most notable safety issue in the trial was the potential to cause liver injury capable of progression to liver failure.

**II. RESULTS (by Site):**

Four foreign and one domestic site were selected to inspect for NDA 204441. These sites were selected based on high enrollment along with a high risk ranking as determined by the GCP Site Selection Tool.

<b>Name of CI</b>	<b>Protocol # and # of Subjects</b>	<b>Inspection Date</b>	<b>Final Classification</b>
Peter A. Gross Blasewitzer Str. 43, Dresden Germany 01307	No. 156-04-251  Site 510  75 enrolled	June 24 – 28, 2013	Pending (Preliminary VAI)
Bernd-Detlef Schulze Kreuzburger.2 90471 Nurnberg Germany	No. 156-04-251 Site 511  46 enrolled	June 17-21, 2013	Pending (Preliminary VAI)
Daniel G. Bichet Hospital du Sacre-Coeur de Montreal Clinical Research Unit 5400 Boulevard Guin West Unite de recherche C-2085 Montreal Quebec CAN	No. 156-04-251  Site 181  33 enrolled	July 22 – 26, 2013	Pending (Preliminary NAI)
Ron T. Gansevoort Department of Medicine Division of Nephrology Groningen Hanzeplein 1 Groningen Netherlands	No. 156-04-251  Site 550  52 enrolled	June 17 – 21, 2013	Pending (Preliminary NAI)
Jennifer Tuazon (former PI Battle) 710 N. Fairbanks Ct. Olson Bldg, Room 4-500 Chicago, IL 60611	Protocol 156-04-251  Site 104  28 subjects	June 26 – July 10, 2013	Pending (Preliminary VAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**Note:** Observations noted below for all sites are based on the Form FDA 483 and communications with the field investigator. An addendum to this inspection summary will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

### 1. Peter Gross, Blasewitzer Str. 43, Dresden Germany 01307

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 95 subjects were screened, 75 subjects enrolled and 70 subjects completed the study. (b) (4)



The study records were in German, which required the use of a translator during the inspection. For the audit of NDA 204441, the FDA field investigator reviewed study records for 20 subjects that included verifying secondary efficacy endpoint data for onset or progressing hypertension and renal pain requiring intervention, adverse events, laboratory reports, adherence to the protocol, and discontinuations. The secondary endpoints of events of worsening albuminuria and renal function were based on categories of magnitude of change. The FDA field investigator did not verify if the clinical progression events had shifted to a higher or lower category because the units of the source data were different from the units in the data listings and those defining the categories specified in the protocol. For example, the data listings and the categories for worsening of GFR were in mg/dl whereas the source data at the site listed the values in umol/l.

- b. **General observations/commentary:** For the 20 subject records reviewed, renal pain scale was verifiable and no discrepancies were observed. All observed abnormalities in liver function tests were reported as adverse events. There was no evidence of underreporting of adverse events. However there were many instances of blood/urine safety labs that were collected out of window (range 1 day to 13 days, described below). No discrepancies were observed between study medication discontinuation dates and reasons for discontinuations.

For the 20 records reviewed, 17 subjects had multiple out- of- window visits, and thus MRI scans, ECG and blood pressure measurements, and blood or urine draws were done outside the protocol specified timeframes. For example, the protocol required that blood and urine safety labs be collected at Baseline, Weeks 1, 2 and 3, and at Months 4, 8, 12, 16, 20, 24, 28, 32 and 36. Subjects (b) (6) had their Month 28 and Month 32 blood and urine safety labs completed out of window by 13 and 7 days, respectively, whereas

Subject (b) (6) had the Month 20, Month 28 and Month 32 blood and urine labs performed 4, 10 and 13 days out-of window, respectively. Protocol deviation forms were not completed for these out-of-window visits. This observation was included as an observation on the Form FDA 483, and the field investigator cited examples of 17 subjects with out-of-window visits (range was 1 to 13 days, with one subject (b) (6) ] out of window by 43 days).

The protocol required that magnetic resonance imaging (MRI) be performed at baseline, Months 12, 24 and 26. The FDA field investigator reported that 9 of 20 subject records reviewed had MRIs conducted outside of the protocol specified timeframes (out- of- window range was 1 day to 99 days). For example, Subjects (b) (6) had their baseline MRIs performed 2 months late, Subject (b) (6) had the Month 12 MRI performed 99 days late, and Subject (b) (6) had the Month 12 and Month 24 MRI performed 2 days and 11 days late, respectively. No protocol deviation forms were completed for these out of window visits. This observation was included on the FDA 483, with nine examples provided.

The protocol required that electrocardiograms (ECG) be completed at baseline, Day 1, Week 3 and Month 36. The field investigator reported that 6 of 20 subject records reviewed revealed that ECGs were done outside the protocol required timeframe (out- of- window range was 1 day to 23 days). No protocol deviation forms were completed. Six examples were cited on the FDA 483 under failure to follow the protocol.

The protocol required that pharmacokinetic (PK) and pharmacodynamics (PD) samples be collected at baseline, Week 3, Month 12, Month 24 and Month 38. Seven of 20 subjects had PK and PD samples not completed during the protocol required timeframes (out of window range was 1 day to 11 days). Protocol deviation forms were not completed. Seven examples were cited on the FDA 483 under failure to follow the protocol.

The protocol required that blood pressure measurements be repeated at least twice. The average of all valid measurements was to be recorded on the case report form at each scheduled visit. The FDA field investigator reported that for 20 of 20 subject records reviewed, this procedure was not followed during most visits. For six subjects (Subjects (b) (6) ) baseline through Month 12 visits included only one blood pressure recording. For five subjects (Subjects (b) (6) ) baseline through Month 8 visits included only one blood pressure recording. For three subjects (Subjects (b) (6) ) baseline through Month 4 visits included only one blood pressure recording. For six subjects (Subjects (b) (6) ) baseline through Week 4 visits included only one blood pressure recording. No protocol deviation forms were completed. Twenty examples were cited on the FDA 483.

The FDA field investigator observed four documented discrepancies in blood pressure measurements between source documents and case report forms. For example, for Subject (b) (6) at the Month 36 visit, the source document documented the blood pressure measurement as 111/66 and 107/63, whereas the CRF documented a measurement of 126/71. For Subject (b) (6) the Week 1 source document documents the blood pressure as 128/68, whereas the CRF documented 128/86. This observation was reported on the FDA 483 under failure to prepare accurate case histories.

Dr. Peter Gross submitted a response letter dated July 13, 2013 to the FDA 483 inspectional observations, and promised immediate corrective action to prevent the recurrence of the above issues.

- c. **Assessment of data integrity:** The FDA field investigator verified that all adverse events were accurately reported, and confirmed two of the composite secondary efficacy endpoints (renal pain and hypertension) as verifiable. The review division may wish to consider whether the out-of-window visits are likely to impact the efficacy and safety analysis at this site. Despite the large number of out of window visits, which caused some procedures to be done outside protocol required timeframes, the study appears to have been conducted adequately. OSI recommends that the data be accepted in support of the claimed indication.

## 2. Bernd-Detlef Schulze, Kreuzburger.2, 90471 Nurnberg Germany

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 55 subjects were screened, 46 subjects enrolled and 41 subjects completed the study. The FDA field investigator reviewed 26 subject records for reporting adverse events, site's ability to follow the protocol (visit schedule, performing all measurements and procedures), and primary and secondary efficacy endpoints. The field investigator corroborated source data to the data listings for the above parameters. Study records were written in German, which required the use of a translator.
- b. **General observations/commentary:** The FDA field investigator reported that the secondary efficacy endpoint data for onset/progression of hypertension and renal pain events were verifiable; there were no discrepancies between source records and data listings. The secondary efficacy endpoint data listings for albuminuria and renal function (as measured by GFR) submitted by the sponsor to the NDA and provided to the field were not able to be compared to the source documents due to inability to make unit conversions while on inspection. For example, the creatinine data (GFR) in the data listings was listed as mg/dl whereas the source data at the site listed the value in umol/l. The FDA field investigator did not verify if the

clinical progression events had shifted to a higher or lower category because of these different units. .

At the end of the inspection, the field investigator issued a Form FDA 483, citing two observations:

1) An investigation was not conducted according to the investigational plan.

Specifically, the protocol required that blood pressure measurements be repeated at least twice, and that the average be recorded in the CRF. For the 26 subject records reviewed, the FDA field investigator identified five instances for four subjects in which only one blood pressure measurement was performed. Protocol deviation forms were not created for these instances. This issue was identified during monitoring at the site, and retraining was provided. Because this finding was an isolated finding, OSI does not consider this finding as significant.

Another finding identified under this regulatory violation was that the site did not maintain a daily temperature log in the drug storage area. Temperature recordings were done every few days instead of each day. Since study drug was maintained at controlled room temperature, it is not expected that wide temperature fluctuations occurred. Therefore, OSI does not consider this finding as significant.

2) Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. For this observation, the FDA field investigator identified 10 instances where the site used white-out correction fluid or stickers to make corrections in the source records. This finding was identified during monitoring at the site, and the site was retrained on the use of Good Clinical Practices. This finding is unlikely to affect data integrity.

Dr. Schulze submitted a response letter to the FDA 483 observations on June 28, 2013. His responses are acceptable.

- c. Assessment of data integrity:** Minor regulatory regulations were observed during the inspection at this site, and are unlikely to significantly impact data integrity. OSI recommends that the data are acceptable in support of the claimed indication.

**3. Daniel G. Bichet, Hospital du Sacre-Coeur de Montreal, Clinical Research Unit  
5400 Boulevard Gouin West, Unite de recherche C-2085, Montreal Quebec CAN**

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 44 subjects were screened, 33 subjects enrolled and 31 subjects completed the study, with early 2 early terminations. The reasons for discontinuations were: Subject (b) (6) experienced adverse events, primarily loss of appetite and epigastric fullness. The subject completed all study visits through the Month 20 visit and also the Early Termination Visit. Subject (b) (6) withdrew informed consent.

The FDA field investigator comprehensively reviewed 10 subject case history records from the beginning, middle and end of the enrollment period. He reviewed reporting of all adverse events, including serious AEs. He reviewed the primary efficacy endpoint data, and the secondary composite efficacy endpoints.

- b. General observations/commentary:** The FDA field investigator reported that for the 10 subject records reviewed, there was no evidence of under-reporting of adverse events. Likewise all SAEs were reported to the Sponsor and the Ethics Committee, as required. The primary efficacy endpoint (rate of renal volume change to both kidneys) was not verifiable because the CI was blinded to this data, and the renal volumes as measured by MRI at required Study Visits was not made available to the CI. The only renal volume measurement available to the CI was the Screening/Baseline renal volume measurement.

The secondary composite efficacy endpoints were verifiable for each subject case history reviewed. No discrepancies were noted. The only significant deficiency noted during the inspection was the CI's failure to quantify the number of cysts present in each kidney, as required by inclusion criterion #2 and measured by the Screening/Baseline visit MRI. The radiology facility used by the CI described the cysts as numerous or many, but did not provide the actual number as required by the protocol. This deviation was identified by the study monitor after all subjects had been enrolled, and as corrective action, the CI reviewed the screening/baseline MRI for each subject and determined the number of cysts present in each kidney. This was documented by the CI in a Note to File for each subject. This observation was discussed with the CI at the close of the inspection. No FDA-483 was issued.

- c. Assessment of data integrity:** No discrepancies were found. The study was conducted well at this site, and OSI recommends the data be accepted in support of the claimed indication.

**4. Ron T. Gansevoort, Department of Medicine, Division of Nephrology  
Groningen Hanzeplein 1, Groningen Netherlands**

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 66 subjects were screened, 52 subjects enrolled and 43 subjects completed the study between September 18, 2007 and November 27, 2008. There were nine early terminations. This was the first FDA inspection of this clinical investigator.

The study records were maintained in Dutch which required the use of a translator. The FDA field investigator reviewed informed consent documents for all 66 subjects screened to verify the site used the approved Ethics Committee (EC) version, and reviewed 10 forms to verify that IC was properly obtained prior to study participation. No discrepancies were found.

Ten subject records were completely reviewed for clinic notes, MRI assessment dates, composite secondary efficacy endpoints of serum creatinine, albuminuria, PKD outcomes, patient assessed pain scale and medications for progressing hypertension and renal pain. The source documents (medical and clinical notes) were reviewed to identify comments relating to subject pain and the use of medications. Adverse events were also reviewed.

- b. General observations/commentary:** For all ten subject records reviewed, both the serum creatinine and albuminuria data on the CRFs were verified against the data listings, and no discrepancies were found. Of the ten subject records reviewed, Subjects [REDACTED] <sup>(b) (6)</sup> were terminated early from the study (three of the nine noted in the first paragraph above). The FDA field investigator reviewed clinic notes to ensure that phone follow-up calls occurred. Reasons for termination were reported as: felt immediately better once medication was stopped, increased urinary output, thirsty and no complaints.

There were no discrepancies between the data at the site and the data listings. Study files and source documents were generally complete and well organized. Study procedures were performed as required and within the required timeframes. Adverse events (AEs) were well documented; there was no under-reporting of AEs. The FDA field investigator observed that monitoring occurred approximately once a month until the study closed. The FDA field investigator confirmed that required laboratory reports for the ten subjects reviewed were present in the study file and signed by the clinical investigator. Out of range findings were documented as clinically significant or not clinically significant in the clinic notes and on the lab reports. There were no objectionable observations related to test article accountability procedures. No FDA 483 was issued.

- c. Assessment of data integrity:** No discrepancies were found. The study was

conducted well at this site, and OSI recommends the data acceptable in support of the claimed indication.

#### 5. Jennifer Tuazon, 710 N. Fairbanks Ct., Olson Bldg, Room 4-500, Chicago, IL 60611

- a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 71 subjects were screened, 28 subjects enrolled and 21 subjects completed the study. There were 8 early terminations. This was the first inspection of Dr. Tuazon who had taken over this study from the original CI, Dr. Daniel Batlle.

The FDA field investigator corroborated the data listings to source documents at the site for 15 subjects with respect to adverse events, protocol procedures, and secondary efficacy measurements.

- b. General observations/commentary:** In general the data listings were consistent with the data in the subject source documents. The FDA field investigator observed that the site did not understand the procedure for taking blood pressure measurements for the first number of subjects enrolled, and would sometimes document both measurements as the same. The clinical investigator at the time was Dr. Batlle. Another observation was that the pre-enrollment radiology reports for 8 of 15 subjects described the cysts as numerous or many, but did not provide the actual number as required by the protocol. The CI went back and reviewed the scan closest to study entry to verify that the subjects met eligibility criteria. During the conduct of the study under Dr. Batlle, the original clinical investigator, the FDA field investigator observed that the CRO performing monitoring had many concerns about study conduct and oversight. Although the CRO conducted additional site staff training many CRFs were not completed, and the study coordinator seemed overwhelmed and unclear about the protocol. Concerns resulted in a sponsor audit of this site, and the IRB subsequently suspending approval for additional study enrollment. The FDA field investigator reported that a new trial management group was brought on board starting in May 2009, and that this new group worked hard to clear up all data queries, and adhere to the protocol schedule for the remainder of the study.

Review of data revealed that the data was consistent between line listings and source records for data reviewed. There was no underreporting of adverse events. Protocol deviations were appropriately reported. Proper procedures were followed regarding GCP. All subjects were appropriately consented. A one observational Form FDA 483 was issued for an investigation not conducted in accordance with the investigational plan. For three subjects, blood pressure measurements were not taken as specified in the protocol at Screening, Baseline, and Day 1 or during titration of study drug. For example, for Subject (b) (6), blood pressure measurements were not taken at the

Day 1 or Week 3 visits, and for Subject (b) (6), blood pressure measurements were not done at the Baseline, Day 1 or Week 1 visits. In addition, pregnancy tests were not performed for some subjects.

- c. **Assessment of data integrity:** The observation concerning the lack of specificity in the pre-enrollment radiology reports occurring at this site was also noted at Dr. Bichet's site in Canada. Because the scans were re-read and subjects met eligibility criteria, this is not considered to have impact on data integrity. In general, the study was conducted adequately, and OSI recommends the data be accepted in support of the claimed indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites (four foreign, one domestic) were inspected in support of NDA 204441. No regulatory violations were found during the inspections at two sites (Dr Gansevoort, Netherlands and Dr. Daniel Bichet, Canada), and no Form FDA- 483 was issued. The inspections of Dr. Peter Gross (Germany) and Dr. Schulze (Germany) as well as the inspection of Dr. Tuazon (Chicago), were classified as VAI. For these inspections the regulatory violations were minor and/or isolated and unlikely to impact data integrity.

Although regulatory violations were noted as described above, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data generated by the sites inspected for this study may be considered reliable based on available information.

**Note:** The EIRs for all sites were not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{ See appended electronic signature page }

Sharon K. Gershon, Pharm.D.  
Reviewer  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

{ See appended electronic signature page }

Kassa Ayalew, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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

/s/  
-----

SHARON K GERSHON  
07/26/2013

SUSAN LEIBENHAUT  
07/26/2013

KASSA AYALEW  
07/26/2013

## Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 28 June 2013

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE)

TO: Norman Stockbridge, M.D., Director, Division of CardioRenal Products (DCRP), Office of New Drugs (OND)  
Stephen Grant, M.D., Team Leader, DRCP  
Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCRP  
Aliza Thompson, M.D., Medical Reviewer, DRCP  
Nhi Bach Beasley, Pharm.D., Safety Reviewer, DRCP

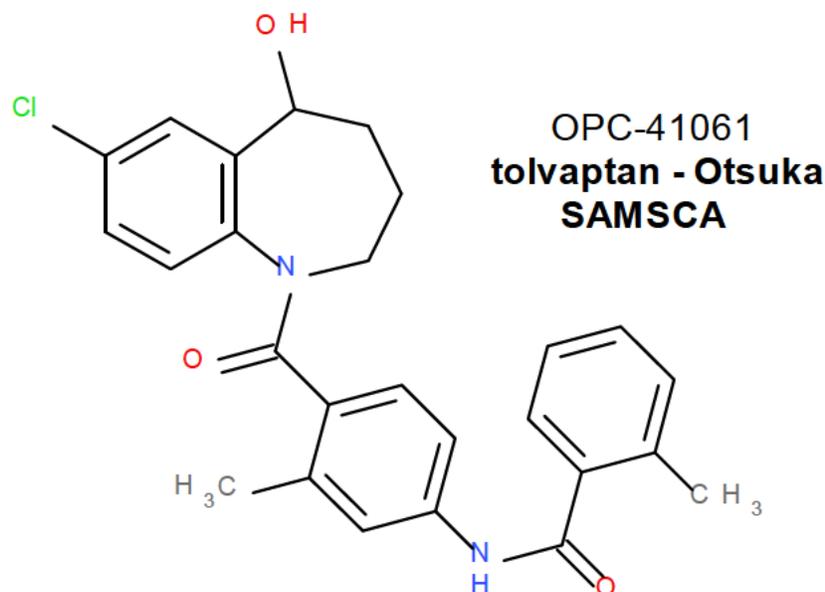
VIA: Gerald Dal Pan, M.D., Director, Office of Surveillance and Epidemiology  
Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic safety of **tolvaptan** (NDA 204441), proposed for slowing progression of autosomal dominant polycystic kidney disease (ADPKD). Tolvaptan, as (SAMSCA® Otsuka), was approved 19 May 2009 for treatment of retention of fluid in patients with heart failure, cirrhotic ascites, and the syndrome of inappropriate antidiuretic hormone (SIADH) in patients with symptomatic hyponatremia, or were resistant to fluid intake restriction, or for clinically significant hyper- or eu-volemic hyponatremia (serum sodium <125 mEq/L).

### Documents reviewed:

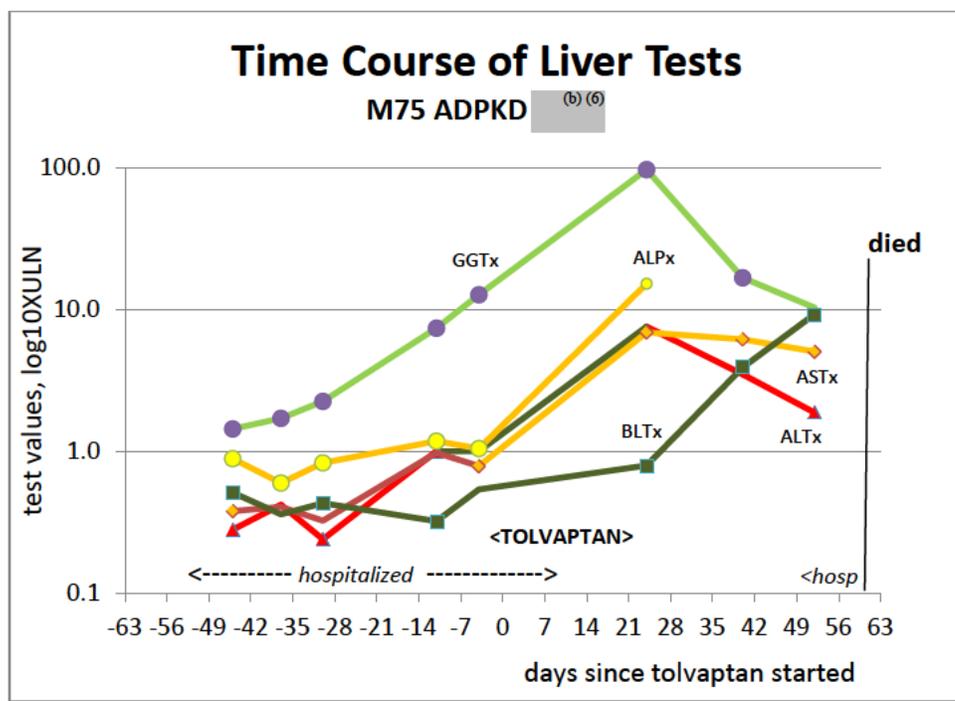
- 1) Consultation request 2 April 2013 from Dr. Aliza Thompson via Ms. Lori Wachter (DCRP) and Ms. Cheryle Milburn (OSE), requesting response by 1 July 2013, OSE tracking #2013-1420;
  - 2) Otsuka proposal for Risk Mitigation Plan dated 13 November 2012, including report from consulting hepatologist Paul B. Watkins dated 28 October 2012 (“A review of the liver safety database for tolvaptan in the treatment of Autosomal Dominant Polycystic Kidney Disease”);
  - 3) Previous consultation request 29 November 2012, alerting us that the sponsor (Otsuka) had identified a potentially serious signal for liver injury in ADPKD studies, with possible impact on labels for approved indications, prior to our receipt of data for the new PKD work, with partial consultation responses dated 3 and 13 February 2013;
  - 4) Memorandum on Tolvaptan (Samsca) and hepatotoxicity, TSI # 1332, NDA 22275, dated 13 December 2012 from D. Mary Ross Southworth to file;
  - 5) Otsuka letter to Healthcare Providers, 22 January 2013, **IMPORTANT DRUG WARNING** of significant liver injury associated with the use of SAMSCA (tolvaptan);
  - 6) Approved labeling for tolvaptan (SAMSCA, Otsuka) for treating euvolemic or hypervolemic hyponatremia, last updated 3 May 2013.
-

Tolvaptan, initially designated OPC-41061 by the Otsuka development team (Yamamura et al., 1998), was designed as a new orally effective non-peptide agent for blocking renal collecting ductular arginine-vasopressin (AVP) V2-receptors to inhibit reabsorption of free water from glomerular filtrate, for treatment of water-retaining states such as hepatic cirrhosis, congestive heart failure, nephrotic syndrome, and inappropriate anti-diuretic hormone secretion. Earlier potent peptide vasopressin antagonists had not been found to be clinically useful because of low oral bioavailability and anti-diuretic effect in humans. Otsuka chemists had reported in 1991-2 the synthesis of OPC-21268 and OPC-31260 as non-peptide AVP antagonists of interest, active at cyclic adenosine monophosphate-dependent V1 and 2 receptors. Stable expression of cloned human AVP receptors in HeLa cells allowed development of a more potent non-peptide human AVP-V2-receptor antagonist leading to OPC-41061. Testing in male Sprague-Dawley rats using oral doses of 1 or 10 mg/kg showed very significant aquaretic effects after single and multiple doses for up to 28 days. The encouraging results of effectiveness and apparent safety had already led to initiation of human studies (IND 050533, 17 May 1996) for investigation of effects of OPC-41061 on states of hyponatremia, and for treatment of hyponatremia (IND 054200, 23 September 1997). Using generic name tolvaptan under IND 072975 submitted 28 July 2005 it was studied in patients with hyponatremia in liver cirrhosis, congestive heart failure, and syndrome of inappropriate antidiuretic hormone (SIADH).



New Drug Application 022275 for tolvaptan (SAMSCA®, Otsuka) was approved 19 May 2009 for treating clinically significant hyper- and eu-volemic hyponatremia. Since that approval for marketing and clinical use, only one report of liver test abnormalities associated with tolvaptan has been published (Cabello Ortiz, et al. 2011), occurring in a 75-year-old man with SIADH who showed sharp rises in serum ALT, AST, and GGT activities 24 days after starting tolvaptan at 15 mg/day then increasing to 30 mg/day. Stopping drug led to reversal of the abnormalities after 11 and 23 days, thought possibly drug-related, although liver metastases confirmed by biopsy were found later. No symptoms or functional abnormality of bilirubin concentration or prothrombin time were reported, but the authors considered the injury clearly related to tolvaptan.

*Comment: Because the report of that case raised several questions, beyond my somewhat limited ability to translate from the Spanish text and understand all the details, I asked my colleagues and friends Maribel Lucena and Raúl Andrade, of the University of Málaga in southern Spain, for their comments about the case. (They have for several years been very active in our annual conferences on drug-induced liver injury (DILI) old French woman started in 1999 and have continued since. They are both nationally and internationally well recognized hepatologists with special expertise in DILI.). They reviewed the paper published by the three pharmacists (Cabello, Marin, Alcalá) and an internist (Carrillo) in Jaén, Andalusia, contacted them and obtained more information:*



*During a previous hospitalization for stroke 20 months before in (b) (6) the patient had shown slight elevations of serum ALT, AST, ALP and especially of GGT activity that were not explained but resolved. He was readmitted (b) (6) for hyponatremia due to a paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH) secretion, during which he had recurrent urinary tract infections treated with unstated antibiotics. He was started on tolvaptan on (b) (6). Recheck of his liver tests two weeks later (b) (6) showed marked elevations of ALT (7.6xULN, AST 6.9xULN, ALP 15.2xULN, and GGT up to 96.9xULN but normal total bilirubin. Tolvaptan was stopped. Two weeks later (b) (6) serum enzymes were falling but bilirubin rose to 3.9 mg/dL. He was rehospitalized (b) (6) in deteriorating condition, bilirubin 9.2, and died in hospital 10 day later. Liver metastases were found and confirmed by biopsy. Tolvaptan administration appeared to worsen a cholestatic liver problem present before, but did not appear to be the main cause of the liver problems that seem more related to liver metastases. Drs. Lucena and Andrade were displeased at how this case was reported in the literature, as well as with others from (b) (6) and elsewhere. They are forming a group to write a paper stating what minimal information should be collected and reported for making diagnoses of probable drug-induced injury.*

Study of tolvaptan for slowing the rate of progression of autosomal dominant polycystic kidney disease (ADPKD) was started under IND 072975. Clinical trials since resulted in pre-submission of NDA 204441 on 15 November 2012, but not with all the data. This genetically transmitted disease is said to affect about 600,000 persons in the United States, is the fourth most common cause of end-stage renal disease, after diabetes, hypertension, and glomerulonephritis (Helal et al., 2012). The development program for use of tolvaptan for slowing progression of ADPKD was granted fast-track designation 20 January 2006, and orphan drug designation 6 April 2012, according to a review submitted by Otsuka on 13 November 2012 (despite having prevalence of greater than that usually specified for orphan drug status as the upper limit [200,000 in USA]).

It is somewhat unclear exactly when the sponsoring company became aware of the problems of possible tolvaptan-induced liver injury in ADPKD patients, but the issue was discussed with FDA in July 2012 when the accumulated long-term data from pivotal clinical trial 156-04-251 in 1444 adult subjects with ADPKD were being evaluated in preparation for submission of NDA 204441. Otsuka was concerned enough that they convened a special consulting committee of academic hepatologists (Drs. Paul Watkins, James Lewis, Neil Kaplowitz, and David Alpers) to review the clinical data and render an opinion as to whether they believed tolvaptan to be the probable cause of several cases of serious (but not fatal) liver injury and dysfunction. Results of those studies showed a notable increase in the frequency of moderate to severe elevations of serum ALT and AST activities in patients treated with tolvaptan, compared to those receiving placebo. The report of the expert hepatology consultants, submitted by Paul Watkins on 28 October 2012, indicated that the consultants had carefully reviewed the data, and they concluded that long-term treatment with tolvaptan carried a risk of liver failure in about 1 per 3000 treated patients. They opined that the risk of liver injury would probably be lowered with more frequent monitoring of serum liver tests but would not likely be eliminated. Further, they agreed that a hepatotoxicity risk from the approved SAMSCA tolvaptan product could not be discerned among patients treated for serum hyponatremia due to hepatic cirrhosis, congestive heart failure, or SIADH, perhaps because of the lower doses used in those patients, but also suggesting a mechanistic link between ADPKD and susceptibility to tolvaptan-induced liver injury.

Following receipt of the consultants' report, Otsuka submitted updated labeling for SAMSCA on 16 November 2012, not even mentioning hepatotoxicity, but almost simultaneously submitting a proposal (13 November) for negotiating with DCRP a risk mitigation plan, and followed that by an urgent letter to all healthcare providers sent 22 January 2013 as an **IMPORTANT DRUG WARNING** of the potential risk of liver injury with use of SAMSCA® (tolvaptan) that it has the potential to cause irreversible and even fatal liver injury, as derived from the data in the ADPKD trials. They also noted that SAMSCA is not approved for treatment of ADPKD. This led to a proposed new brand name (b) (4), for the same drug, but at higher dose for much longer time in the proposed indication for slowing the rates of renal cyst enlargement and of renal function loss. It also led to labeling revision in April 2012, promulgated 2 May 2013, for the approved product SAMSCA that limits its use to 30 days at up to 60 mg/day, removes the indication for use in patients with cirrhosis, and mentions tolvaptan-induced liver toxicity. This confusing and apparently internally inconsistent behavior of the sponsor had led DCRP to request a review of the old data, dating back to 1996-2004 on clinical trials of its use for treatment of hyponatremia due to various disorders. DCRP refused to accept the proposed new trade name pending further review of the clinical data.

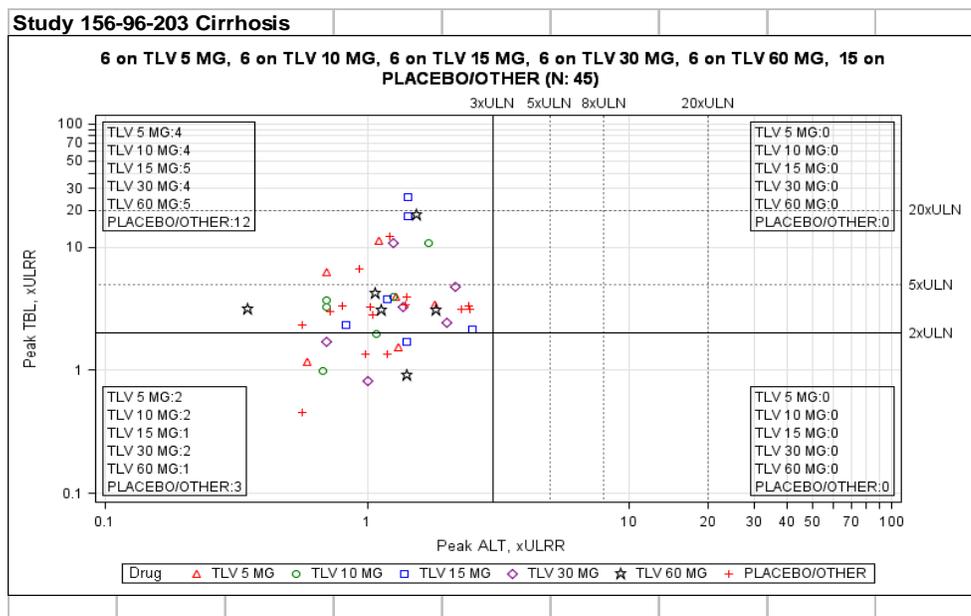
### Results of Past Studies for Treatment of Hyponatremia

The earliest trials were those for cirrhosis (156-96-203), where 156- refers to tolvaptan, 96- to the year when the study was started, and 203 to the protocol number. In referring to individual study subjects randomized to treatment with tolvaptan or other, they are identified within each study by numbers such as 03236- (b) (6), in which the first two digits are the year of the study, and the next three of the five the protocol number (03 236), the next set of three the site where the study was done ( (b) (6) ), and the last four the individual subject number.

<u>Cirrhosis</u>	<u>Heart Failure</u>	<u>Hyponatremia</u>
156- (b) (6)	156- (b) (6)	156 (b) (6)
	156- (b) (6)	156 (b) (6)
	156- (b) (6)	156 (b) (6)

These studies included about 45 patients with cirrhosis, 4685 with heart failure, and 610 with huponatremia (5340 in all). After attempting to get those data into format suitable for eDISH analyses for over two months, the data were forwarded to Dr. Guo on Wednesday 30 Jan 2013. Dr. Guo very promptly prepared a first-cut, preliminary version of those data, sorted by dose of tolvaptan or alternative drug given, and I began looking at the more serious cases that showed elevations of both serum alanine aminotransferase (ALT) activity and serum total bilirubin (BLT) concentration (at the same time or with BLT following ALT).

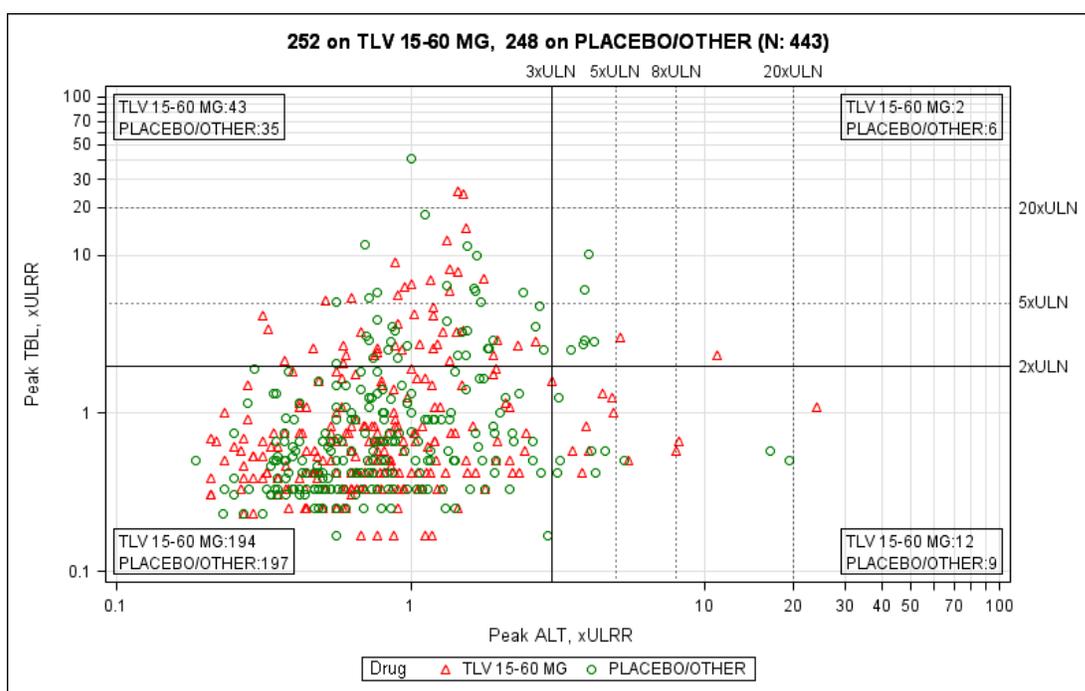
For the 45 patients with cirrhosis, no narratives were provided for any of them, nor were any needed, because none of them showed any increased serum activity of ALT during the course of treatment with tolvaptan (see graph, attached). Elevated bilirubin levels observed appeared to be consequences of damage from what had caused the cirrhosis, not acute tolvatpntan-induced injury.



Inspection of the data on January 31 using eDISH showed that there had been *NO* serious cases among the 45 cirrhotic patients in the very old (1996) and cautious dose-ranging studies, but an incidence of about 1.4% of serious liver dysfunction in both the other groups (heart failure and hyponatremia) that did not appear to be related, either to whether or not the patient had received placebo or tolvaptan, or to the dose of tolvaptan given, but were more likely related to the very severe underlying cardiac or other diseases in these very sick patients (see below)

For the hyponatremia studies we chose to focus attention on the subjects who had shown peak levels of ALT and BLT at some time, but not necessarily at the same time, in their courses of observation on or off drug.

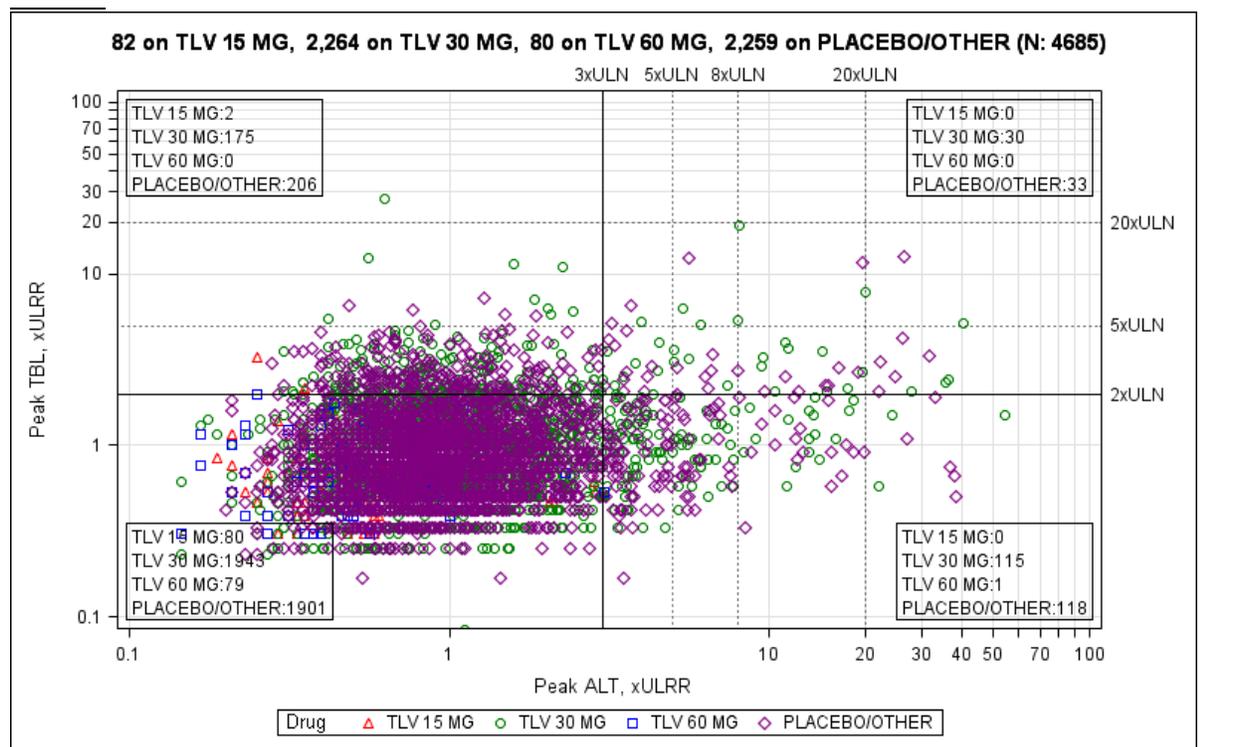
TOLVAPTAN Hyponatremia Studies 156-02-235, 156-03-238, 156-03-244: 500 patients



In the hyponatremia studies there were data provided for 443 patients in Studies 02-235 and 03-238, in which there were 8 patients showing both ALT and BLT elevations, 2 on tolvaptan and 6 on placebo. In the follow-up Study 03-244 of 110 patients, another 3 on tolvaptan showed both ALT and BLT elevations during the course of their observations, bringing to 11 the total of patients of special interest, 5 on tolvaptan and 6 on placebo. For them, 10 narratives were submitted (none for patient (b)(6), an 80-year-old man studied in the (b)(6) who showed peak ALT of 383 U/L, 10.9 times the upper limit of the normal range (xULN) with no rise in his ALP activity and only modest peak BLT of 2.8 mg/dL, 2.33 xULN. Further, his ALT and BLT were elevated even before tolvaptan was given for only 2 days, so it was very unlikely the cause of the abnormalities. In the other 10 cases an alternative clinical cause could be found in the clinical narrative in all but one ( (b)(6), an almost obese Hispanic man of 49 with only modest elevation of ALT that occurred over a week after he was off placebo. In summary, no cases of probable tolvaptan-induced serious liver injury were found among the studies of the 610 patients in the hyponatremia studies.

By far the largest clinical experience submitted was for treatment of fluid retention in patients with congestive heart failure, with data from one study (156-03-236) including 4685 patients, many of them quite sick with various manifestations of circulatory problems that often impacted adversely of hepatic function.

TOLVAPTAN Heart Failure Studies 156-01-232, 156-03-236. (4685 patients)

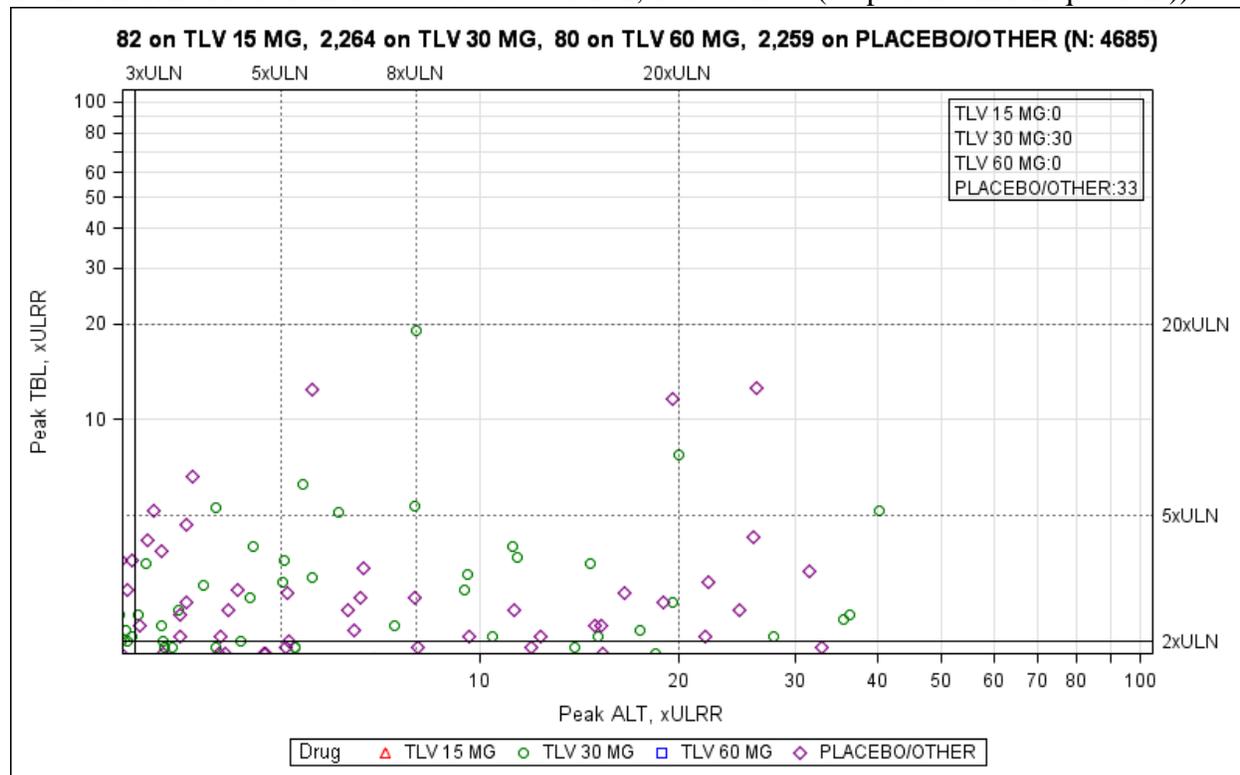


In this study (03-236) there were many very sick patients, with some dying of their cardiac insufficiency, which caused secondary back-up of blood into the liver or reduced flow of blood from the liver. The consequences were depletion of oxygen in the hepatic sinusoidal blood, most marked in the centrilobular zones, where metabolically active hepatocytes had used most of the oxygen and had become so depleted that their necrosis led to leakage of enzymes from the cytoplasm into the plasma, to elevations of serum ALT and especially AST, as well as increased bilirubin concentrations. Even more striking rises in serum AST and ALT occurred in those patients who also had cardiogenic shock or at least severe hypotension, with decreased hepatic arterial flow of oxygenated blood into the liver, sometimes leading to enormous and rapid rises in serum aminotransferase enzyme activities. These were often rapidly reversible if treatment of the cardiac problems improved the circulation and supply of oxygen to the hepatocytes.

It is evident from a glance that there was no imbalance in the incidence of marked abnormal liver tests, and from Tables II and III in the attached Excel listing. However, confident assessment of causality could not be made for more than two-thirds because of insufficient diagnostic information or no narratives at all. The eDISH displays show no imbalance in the incidence of either ALT increases only or both ALT and TBL, in the studies on patients with heart failure.

Because of the very large number of patients in study 156-03-326, we chose to focus on those who showed the more serious evidence of secondary liver test abnormalities, those in the right upper (or “NE”) quadrant of the eDISH display. They included 1 patient (b)(6) and 29 more from study 156-03-236 who had been treated with tolvaptan, and 33 patients from the latter study who had been randomized to placebo. Those 63 patients, plus the 11 (5 tolvaptan, 6 placebo) from the hyponatremia studies mentioned above, have their data tabulated in Tables I, II, and III, attached after references. Let us focus on the 63 (30 tolvaptan, 33 placebo) from the heart failure studies who were more severely affected, as displayed below:

TOLVAPTAN Heart Failure Studies 156-01-232, 156-03-236. (63 patients in NE quadrant))



A major deficiency of this submission of old data was the lack of narrative information from so many of the 63 cases (see attached EXCEL table submitted as a supplement to this review). Only 12 of 30 of the heart failure cases randomized to tolvaptan and 6 of 33 who were randomized to placebo had narratives, and many of them were of such poor quality that they provided little sound information that could be used in differential diagnosis of what might have caused the abnormalities in liver tests found. Although the eDISH program did provide time-course graphics for all of the 63 patients who showed both ALT and BLT elevations, much uncertainty remained and the retrospective attempt to determine probable causes for the liver test abnormalities was not convincingly effective. It is likely that the long time passage for cases treated all over the world made the sponsor’s narrative writers left with nothing but case reports to use in attempting to write the stories of the cases. It seems unlikely that the sponsor will be able to do much better in this retrospective attempt at re-diagnosis, even with greater efforts and expenditures. We are left with much uncertainty as to the real causes of the abnormalities found in most of these cases.

In the EXCEL tables there were no cases listed from the 1996 cirrhosis Study 203 because none showed ALT elevations. Table I, shows the 11 cases of hyponatremia subjects, all studied in the United States in 2002-2003; Table II, the 30 cases with heart failure who had been treated with tolvaptan 30 mg daily for sometimes long periods of time, over a year in four, over two years in one, and more than 6 months in another 11 cases; and Table III, the 33 cases who were assigned to placebo or other control regimens for over a year in 6, more than 6 months in another 10 patients, of the 33. In total, of the 74 such cases, 35 on tolvaptan, and 39 on placebo, approximately equal numbers of patients on each, there was no imbalance in the incidence, but no adequate assessment of likely causality could not be done using the data provided. For many but not all of those patients, narrative summaries of the clinical course and other information were provided by the sponsor, and time-course graphs of ALT, AST, ALP, and BLT for all submitted data for those patients were available via eDISH.

The sponsor prepared graphic displays, using their own versions of our eDISH program (see the Watkins' report [28 October 2012] in the sponsor's Risk Mitigation Proposal of 13 November 2012.), but only for the initial ALT-BLT x-y plots (both with log<sub>10</sub>-transformations to keep values in somewhat more comparable ranges, since ALT tends to vary far more than BLT), with a point showing one pair of values for each subject. Although Watkins did show selected time courses of ALT, AST, and BLT, the sponsors did not submit any graphic displays of the time-courses of all the data (ALT, AST, ALP, and BLT) for a given subject over the entire period of observation in the study.

*Comment: The sponsor showed only the group ALT-BLT plots, and no time- courses for individuals, perhaps because they mistakenly considered points in the right upper quadrant (or "NE" in the parlance of Ted Guo and the eDISH program) as diagnostic of "Hy's Law." That is a totally incorrect interpretation. Hy Zimmerman's adage was "**drug-induced** hepatocellular jaundice is a serious lesion, with substantial likelihood of mortality," and not just a pair of abnormal serum chemistry values. The observation has been repeatedly confirmed in decades since, both at FDA and in academic reports. However, the clinical adjudication of probable causality is a medical process of careful differential diagnosis to establish the most likely cause of the abnormal findings, a process of reasoning and information gathering and weighting familiar to and practiced by clinicians, but not by statisticians, pharmacologist, toxicologists, or other preclinical scientists., A time course of changes is a clue to possible causal relationships, for if jaundice results (follows or is coincident with) from loss of liver cell functional capacity to remove bilirubin from blood plasma as it circulates through the liver, then causal relationship becomes more likely. Bilirubin elevations that precede the ALT rise are far more likely to have another cause such as inherited Gilbert syndrome (reduced ability to conjugate bilirubin with glucuronide), biliary tract disease, or some cholestatic problem. Because there is no accurate or dependable pathognomonic biomarker for diagnosing drug-induced liver injury, it is necessary to consider all of the many possible causes for the observed abnormal findings, many of which do have truly accurate diagnostic biomarkers, and eliminate them to show that DILI cannot be excluded confidently, or find some other very likely cause that eliminates or makes DILI very unlikely. Diagnosis of the probable cause requires much more information than just a pair of abnormal liver tests. Most valuable is a well written medical narrative, discharge summary, or death summary composed by a physician, but not by a research assistant.*

Issues on which DCRP wanted feedback in the initial consultation of 29 November 2012 were:

- **Based on the time-course of serum transaminase elevations observed, is it likely that periodic monitoring of liver enzymes would minimize the risk of developing significant liver injury?**

*Monitoring of serum enzyme activities in labeling assumes that it will be done and the results both interpreted and acted upon appropriately. Reality has shown repeatedly that this is not done consistently or for long. If it isn't done, it won't minimize risk of detecting more serious liver injury and subsequent dysfunction. Therefore, experience has shown it isn't likely to work.*

- **What do we know about dose-response as it relates to DILI in general? Duration of therapy? Because of the low exposure to tolvaptan for hyponatremia (both in the clinical trials and postmarketing) it is not surprising that we have not seen cases, but the sponsor asserts that this may be because the dose and duration of therapy for hyponatremia is lower and shorter, and therefore this risk may not apply to this population. Is this consistent with our experience with other drugs?**

*After drugs have been evaluated during development to detect and eliminate compounds likely to cause predictable dose-related hepatotoxicity, the form of idiosyncratic DILI seen in humans both before and after marketing tends to be rare, dependent more on individual characteristics of the people being treated (therefore "idiosyncratic"), and less clearly on the dose. This is due to the increased susceptibility of a few people to show liver injury at doses well tolerated by most people, for reasons not yet known. This susceptibility is actually dose-related but often at a far lower range of dosing. We cannot at present identify those individuals likely to show initial susceptibility to liver injury or who cannot adapt to repeated exposure; only observation will tell us. Genetic biomarkers of susceptibility are only in their infancy, and are still far too general for individual prediction.*

*There have been at least two rather clear situations in which duration of dosing showed very definite effects: fialuridine and bromfenac. Both drugs seemed to be tolerated for short times but then showed very severe, even irreversible and fatal liver failure on prolonged exposure.*

- **Is there any reason to think that patients with ADPKD would be at increased risk for hepatotoxicity with tolvaptan?**

*Not from the polycystic renal disease itself, but from the need for very long or life-time drug treatment administered in hope of slowing the inexorable progression of this genetic disorder. Treatment could conceivably be started in childhood when the diagnosis might be made by finding hypertension or hematuria in a child, confirmed by testing for genetic markers PKD1 or PKD2. There could possibly be a duration-related factor of importance, in addition to perhaps a requirement for higher doses. This is something that will need to be considered and explored, in comparing the data for the short-term use of SAMSCA for correction of hyponatremia, and the very long-term need for (b) (4) in hope of slowing progression of ADPKD to renal failure.*

Now to consider the cases in ADPKD studies that caused concern at Otsuka and resulted in their raising questions to DCRP at the pre-NDA meeting on 19 July 2012, and to deciding on the basis of full risk assessment of the ADPKD data if they would submit with the NDA a Risk Evaluation and Mitigation Strategy (REMS). After reviewing the data, Otsuka decided the a REMS would be appropriate for tolvaptan in treating ADPKD, to focus education about the risk of possible hepatotoxicity and strategies to reduce the risk of liver injury. A Risk Mitigation Plan Proposal was submitted 13 November 2012, involving measures beyond labeling, to include:

- 1) A Medication Guide to be provided to patients before starting tolvaptan, educating them on the need for liver function testing prior to starting therapy, regular monthly testing for the first 18 months, and the need to self-monitor for signs or symptoms, prompt reporting, and interruption of treatment followed by immediate retesting.
- 2) A Communication Plan for healthcare providers likely to prescribe tolvaptan for ADPKD treatment, conveying to them the risk of potential hepatotoxicity especially within the first 18 months, and periodically thereafter, and to re-educate patients on the same points listed above, plus a Dear Healthcare Provider Letter within 60 days of approval and every 3 years. Copies of the letters were to be sent to appropriate professional and patients organization, and posted at a Tolvaptan ADPKD REMS website, with full prescribing information and the Medication Guide.
- 3) Additional voluntary safety measures to be developed by Otsuka, as necessary (but not specified), to ensure effective education of both patients and prescribers.
- 4) Otsuka proposed to submit REMS assessments to FDA at 18 months, 3 and 7 years after initial approval.

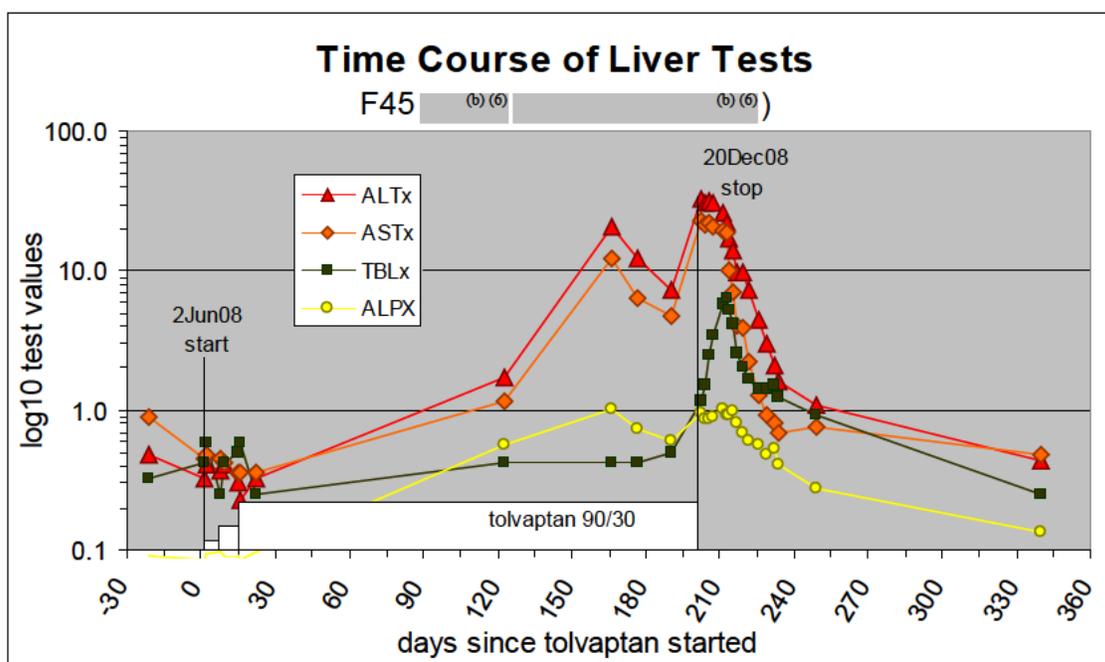
In reaching this conclusion to accept a REMS, the sponsor reviewed the findings in 1444 adult patients studied in the placebo-controlled pivotal trial 156-04-251, with an open-label follow-up study 156-08-271, plus an additional ten clinical pharmacology studies in Japan, Korea and USA in both patients and healthy subjects, and another placebo-controlled trial 156-09-290 and five open-label studies in patients. Patients treated with tolvaptan showed statistically significantly slower increase in kidney volume of 2.80%/year, compared to 5.51%/year in patients on placebo.

Reduced incidence rates of a combined (declining renal function (serum creatinine concentration, renal pain, progressive hypertension, and albuminuria) biomarker showed 0.439/year in patients on tolvaptan, compared to 0.500/year on placebo, driven mainly by renal function and renal pain. Renal function, calculated by Cockcroft-Gault or Modification of Diet in Renal Disease formulae also favored tolvaptan – 2.61 vs -3.80 for placebo, as 100/serum creatinine, mg/dL.

Of 961 patients treated with tolvaptan for an average of 2.4 years, and 483 treated on placebo for an average of 2.7 years, the tolvaptan-treated patients showed considerably higher incidence of thirst, polyuria, nocturia, and pollakiuria (frequency) than those on placebo, and slightly more dry mouth, fatigue, diarrhea, dizziness, and glaucoma. Incidence was higher also for elevations in serum ALT and AST, uric acid, sodium, and cholesterol. Elevations of ALT or AST above 10 times upper limit of normal (xULN) were seen only in tolvaptan-treated patients, and there were two who also showed total bilirubin elevations. A set of 46 patients treated with tolvaptan who showed elevation liver tests was selected for individual case review and adjudication for the most likely cause by the panel of four hepatologists (Watkins' report 28 October 2012).

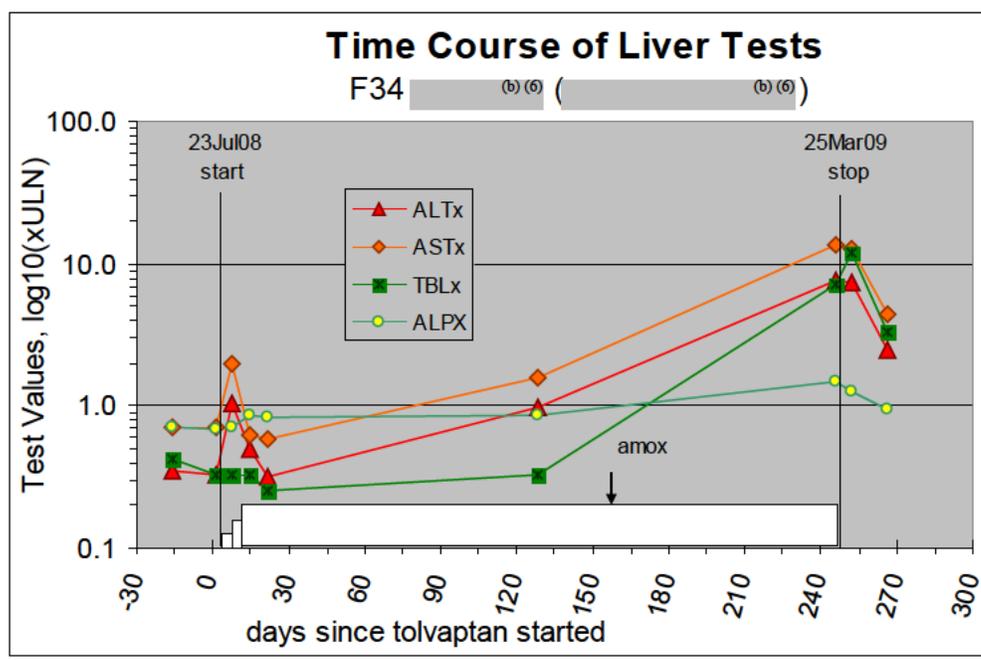
The Otsuka report of 13 November 2012, “Risk Mitigation Plan Proposal,” reviewed briefly the history of developing tolvaptan for a new indication of slowing progression of ADPKD in adult patients. Before submitting the new NDA 204441 for the ADPKD indication, the sponsor proposed a full risk assessment of the data obtained in study of adults with that disorder since submission of IND 072975 in 2005. Let us review in a little more detail the index cases of apparently serious liver injury occurring in patients under treatment with tolvaptan.

The first of the cases ( (b) (6) ) appeared in (b) (6) in (b) (6) ( at site (b) (6) (b) (6) ) in a 45-year-old woman (date of birth (b) (6) ), after she had been on tolvaptan since (b) (6), starting at 45/15, increasing to 60/30, and to 90/30 mg/day at weekly intervals. She complained of nausea and stomach discomfort on (b) (6) (Day 166), and marked elevations of ALT and AST were found, repeat testing of serum enzyme activities on (b) (6) showed them to have declined somewhat but her nausea persisted and became worse on (b) (6) (Day 202) at which time her serum bilirubin began to rise (without visible jaundice) and the ALT and AST were even higher. She was hospitalized for imaging studies and investigation, but no other cause was found, the tolvaptan was stopped. Her bilirubin continued to rise, with jaundice, despite declining serum enzyme activities, and IV prednisolone was initiated on (b) (6) (Day 213). Symptoms subsided, test values declined, oral prednisolone was substituted on (b) (6), and she was discharged 17 days later (Day 237).



*Comment: This episode of liver injury, with nausea and jaundice, prolonged hospitalization, treatment with steroids, was thought by the investigator to be caused by tolvaptan. The experts also agreed that the findings were probably (>50-75% likely) due to tolvaptan. The slight ALT and AST rises in early (b) (6) (Day 123) were not rechecked for almost six weeks. The rate of enzyme release began to slow immediately upon stopping the drug, but the bilirubin continued to rise for 11 more days, and she was clinically ill. The injury was almost entirely hepatocellular, with almost no increase in alkaline phosphatase.*

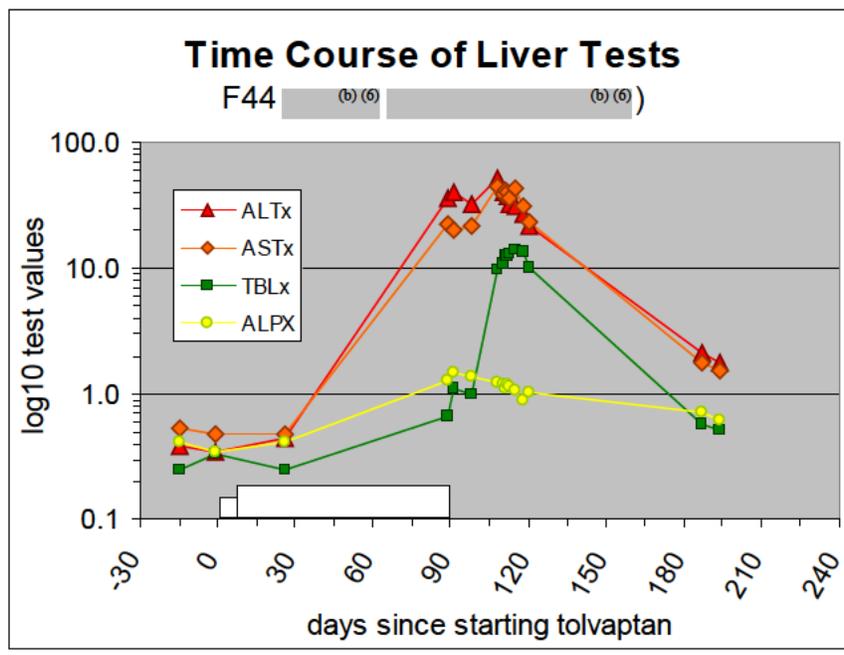
The second case appeared in (b) (6) a few months later, in (b) (6), in a 34-year old woman ( (b) (6); date of birth (b) (6) site 302. (b) (6) treated since (b) (6) with tolvaptan starting at 45/15 and increasing to 60/30 and to 90/30 mg/day at weekly intervals. She had a history of urinary tract infections, nephrolithiasis, and hypertension. She was not closely followed, appeared (b) (6) (Day 246) with obvious jaundice, nausea and vomiting, and was found to have marked elevations of AST and ALT. The tolvaptan was stopped that day. She gave a history of a toothache at the end of (b) (6) (Day 158), for which she was given a single dose of 8 g amoxicillin-clavulanate. She was seen again on (b) (6), after which she refused to return, said she felt better, and her liver test abnormalities were declining. The investigator spoke with her by telephone on (b) (6), but she did not return and was removed from the study.



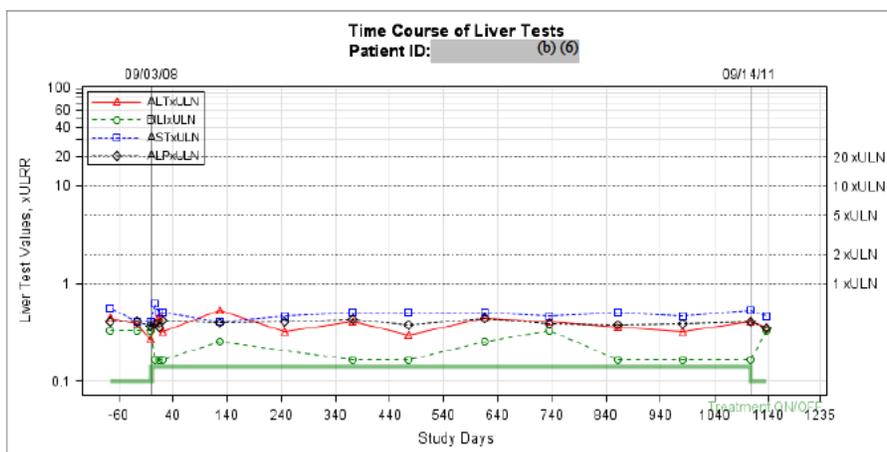
*Comment: The investigator judged that the liver injury was relatively mild but tolvaptan-related, and the sponsor was said to have agreed. The expert hepatology panel also decided that the liver injury was probably tolvaptan-induced. In retrospect, there was a very slight bump upward of the AST activity after the first dose increase, but the second dose increase was tolerated with no recurrent rise. It is unclear why the AST was somewhat higher at peak than ALT, but both enzyme elevations subsided quickly after stopping tolvaptan.*

The third case occurred in (b) (6) in January 2012 in a 44-year-old woman (b) (6), date of birth (b) (6), site 268 (b) (6) who had participated for three years (2005-8) in study 04-251 but had been randomized to placebo. She had reported no problems except for a bout of tonsillitis and a knee sprain not attributable to study drug. She entered open-label study 08-271 on (b) (6), started tolvaptan 45/15 on (b) (6), increasing to 60/30 and 90/30 on (b) (6). Her history included hematuria, proteinuria, kidney pain urinary infections, hypertension, smoking, and ectopic pregnancy. On (b) (6) Day 89) she showed elevated serum ALT and AST, with no symptoms or notable bilirubin

elevation, but tolvaptan was stopped the next day. Despite this, she developed hot flushes, pain in the right upper quadrant, dark urine on (b) (6) (Day 98), and 10 days later was obviously jaundiced. Liver test abnormalities then subsided slowly over months. Tests in hospital for viral hepatitis A, B, C, and E showed no acute infection, liver biopsy only cytolytic inflammation, and no alternative explanation was found, leaving only tolvaptan induced. The investigator assessed the liver injury as moderately severe, probably related to tolvaptan; the sponsor as “possibly” so.



This patient’s earlier three-year participation in study 04-251 on placebo, during which she showed no liver test abnormalities, as may be noted in the eDISH time-course plot shown below:

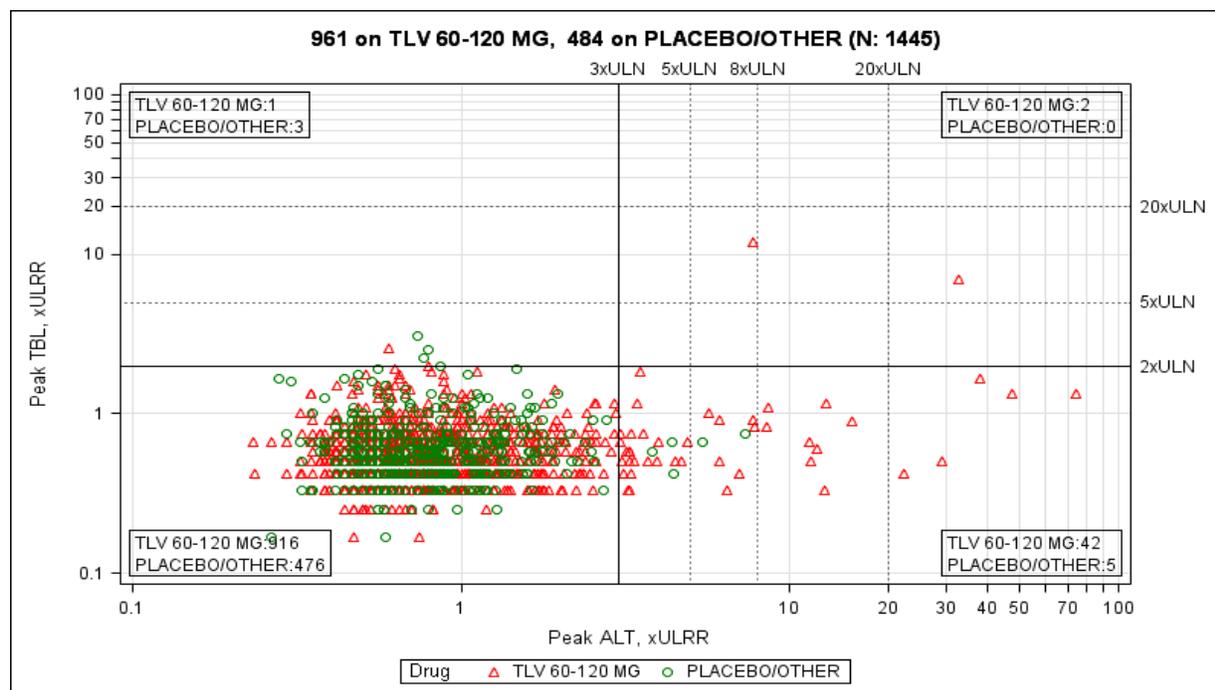


*Comment: The expert hepatology panel consensus was that the findings were highly likely (>75-95% likely) tolvaptan-induced. We are all looking at the same information, and we concur in this third case. They also reviewed several of the other cases chosen for them to review, cases in which there were very notable increases in serum ALT and AST activities, but without jaundice or significant rise in serum bilirubin concentration, of which several appeared to be*

tolvaptan-induced, with no alternative causal explanation. They found significant preponderance of cases attributable to tolvaptan versus placebo in those patients with ADPKD.

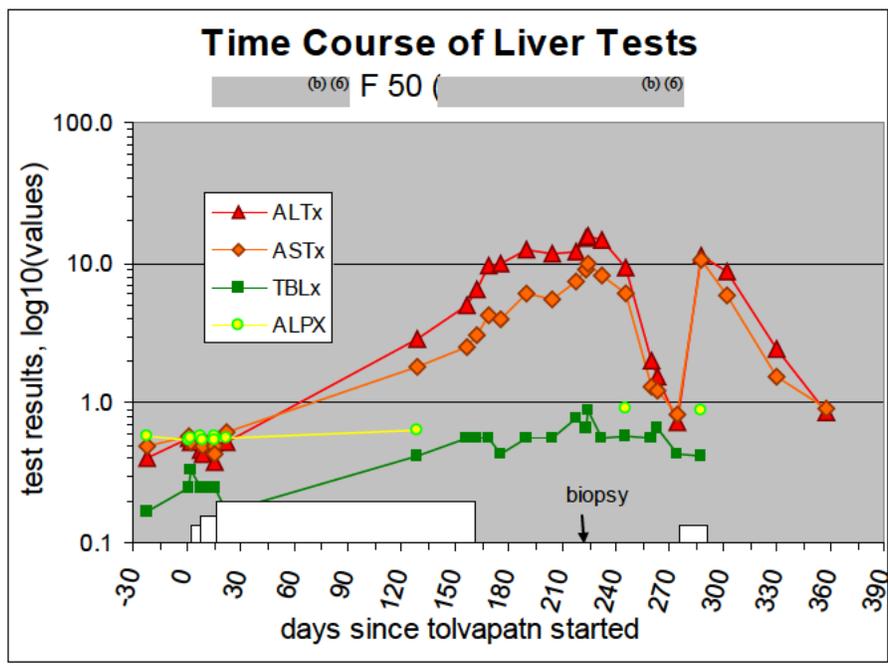
However, in their review of the earlier experience in non-ADPKD patients with heart failure, hyponatremia, and cirrhosis they selected 28 cases of serum ALT increases  $>5xULN$  AND  $BLT >3xULN$  they found none clearly attributable to tolvaptan. They concluded, as have we, that patients with ADPKD may have greater susceptibility to tolvaptan-induced liver injury than patients with heart failure, cirrhosis, and hyponatremia, with no clear explanation as yet, and that the problem is idiosyncratic rather than simply dose-related. Extrapolation of the results based on extensive previous experience with DILI in general suggests that roughly 10% of patients who show drug-induced hepatocellular jaundice may progress to liver failure and risk of death or need for transplantation.

The point that patients with ADPKD may be different in their risk of liver injury from tolvaptan than were previously treated patients with water retention from cirrhosis or heart failure or with hyponatremia from other causes may be seen by glancing at the current pivotal trial data for the controlled study 156-04-251 in which almost a thousand patients with ADPKD were treated with tolvaptan, compared to about half that number on placebo.



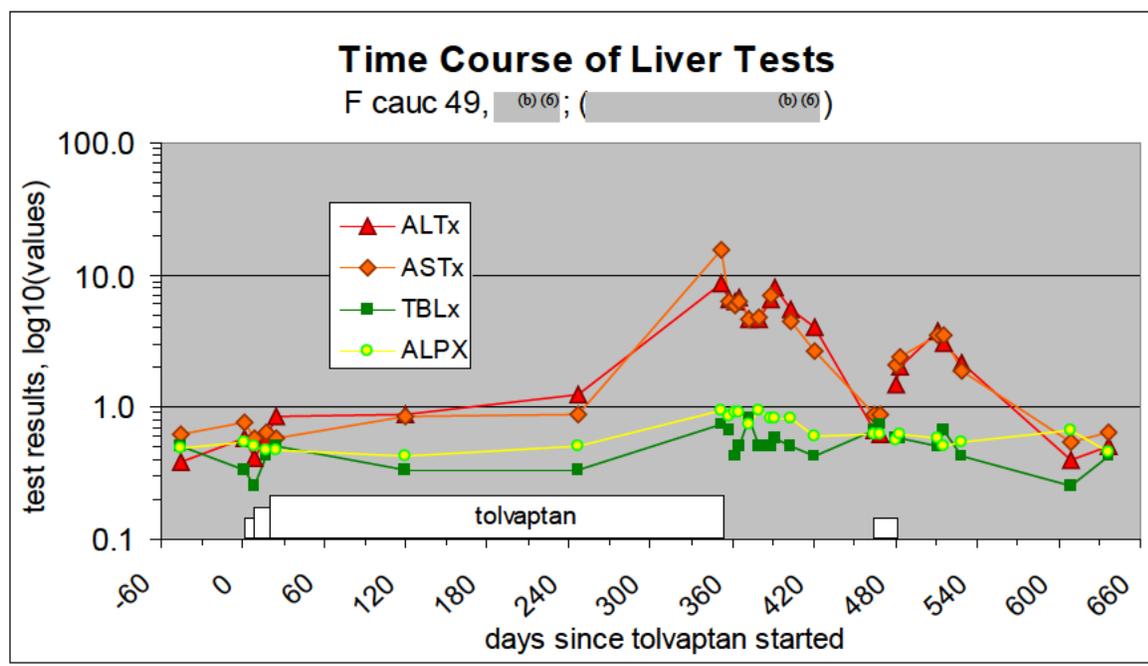
At a glance it may be seen that there was a marked preponderance of tolvaptan-treated patients (red triangles) who showed significant serum ALT elevations of  $>8$  and  $>20xULN$  (seen in the right lower quadrant of the plot) compared to none on placebo, and two more who also showed serum total bilirubin elevations (right upper quadrant), described above as 04251-731-2738 and 04251-302-4053, both patients meeting criteria for “Hy’s Law” cases because of probable cause by tolvaptan. Of the 961 patients randomized to tolvaptan there were two Hy’s Law cases, plus another 42 with ALT elevations  $>3xULN$  without bilirubin increase, an incidence of of 4.6% (unadjudicated), compared to 5 of 484 (1.0%) among those on placebo. In addition to the two

Hy's Law cases, it may be noted from the eDISH plot that there were 5 patients who showed ALT peak values >20xULN, and 8 more > 8xULN, compared to none among placebo patients. Of particular interest are two patients who showed serum aminotransferase elevations of considerable magnitude but little or no rise in bilirubin concentration before the tolwavpatan was stopped, after which the enzyme elevations subsided, only to recur when tolwavpatan was restarted (a positive rechallenge).



*Comment: A (b) (6) woman 50, diagnosed with ADPKD at age 44, was started on 45/15 daily of tolwavpatan on (b) (6), increased a week later to 60/30, and a week later to 90/30 (120 mg daily). Modest elevations of aminotransferases were noted (b) (6) (Day 129) but greater increases on Days 257 and 162 led to interruption of treatment on (b) (6) and closer follow-up. Aminotransferase elevations, even somewhat greater, persisted for about 12 weeks until (b) (6) (Day 246) with only slight rise in total bilirubin within the normal range, before finally subsiding and normalizing over 4 weeks in (b) (6) (Day 274). Liver biopsy on (b) (6) (Day 223) showed centrilobular inflammation and focal necrosis, portal-central bridging and slight portal fibrosis, diagnosed as drug-induced liver injury. After subsidence of the liver test abnormalities, restart of tolwavpatan at the low dose of 45/15 daily on (b) (6) (Day 274) led to almost immediate recurrence of aminotransferase elevations and drug was permanently stopped on (b) (6) (Day 288). Follow-up of the patient showed no development of jaundice or symptoms over the next 10 weeks and her elevated aminotransferases subsided to normal. There was no increase in serum alkaline phosphatase activity to indicate cholestasis or biliary disease, and the reaction appeared almost purely hepatocellular.*

Another case followed shortly thereafter, at site 104 in Chicago IL:



*Comment: This patient, a 49-year-old woman in (b) (6), was diagnosed with ADPKD at age 16, and was started on tolvaptan in Study 251 on (b) (6), at 45/15 for a week, then 60.30 for another week, and then on 90/30 (120 mg daily, the larger dose in the morning and lower dose in the evening). A very slight rise in ALT was recorded after 8 months (Day 246) but when a much greater rise occurred four months later (Day 352, (b) (6)), tolvaptan administration was interrupted. Both ALT and AST activities subsided and normalized over the next 15 weeks and tolvaptan was restarted (b) (6) (Day 464) at the lower daily dose of 45/15. The prompt rise in aminotransferases led to permanent discontinuation of tolvaptan in less than two weeks on (b) (6).*

*It cannot be known whether continued administration of tolvaptan might have caused rise in serum bilirubin concentration or other evidence of whole liver dysfunction in either case, if the drug had been continued longer, but cases such as these pose substantial concerns about the possibility. Nothing in these patients' histories suggested any reason for special susceptibility to tolvaptan-induced liver injury, which must be considered idiosyncratic.*

It has been noted that there appears to be a marked contrast between the review findings for patients with water retention from heart failure, cirrhosis, or hyponatremia from various causes, with respect to their lack of susceptibility to tolvaptan-induced liver injury, compared to that seen in patients with ADPKD. The sponsor was not quick to realize this, and it took from the first real Hy's Law case in (b) (6) in (b) (6), the second in (b) (6) in (b) (6), and then the third in (b) (6) in (b) (6) for the problem to be recognized, or at least acted upon by convening the panel of four expert hepatologists who reviewed cases last summer and early fall (b) (6) and issued the Watkins' report (b) (6). It also slowed submission of the recently received NDA 204441, discussed back in July 2012, until 1 March 2013.

The new consultation request was sent 2 April 2013 as a supplementary set of questions following those posed in November (see above, page 9). Those questions, for which DCRP would like comments, were:

**1. Otsuka has provided an eDISH plot and narratives of 60 subjects for the pivotal trial 156-04-251. Do you agree that they have provided narratives for all subjects who may have had tolvaptan-induced liver injury? Are all narratives adequate? Please provide feedback about adequacy of the information provided as quickly as possible, as reviews for this NDA must be completed by the end of June.**

*Comment: It is not possible to be certain that Otsuka has submitted narratives and clinical data for all subjects who may have had tolvaptan-induced liver injury, because we are dependent on their detection systems and reporting. What they have submitted is of fairly good quality and allows reasonable assessment of the problem. Although not every case submitted has been reviewed again in detail here, we have examined the more serious cases, plotted, reviewed, and discussed findings in the consultation response above, sufficient to appreciate the seriousness of the problem. In order to allow time for thoughtful discussion of the problems and consideration of issues raised in this response, we aim to submit it by the end of May (31<sup>st</sup>). In view of the high visibility of the liver injury issue, it seems unlikely that Otsuka would be negligent in reporting cases, especially serious ones. Whether or not their systems for detecting cases of liver injury or dysfunction were fully adequate is another matter, but it was not the aim of any of the studies to detect meticulously and investigate cases of possibly tolvaptan-induced serious hepatotoxicity. In view of the time elapsed, and the worldwide scope of the studies, we shall probably have to take the information we have received as nearly all we can expect.*

**2. If the information is adequate please provide an estimate with 95% confidence intervals for the expected incidence of tolvaptan-induced liver injury in patients with ADPKD if tolvaptan is approved for treatment of ADPKD.**

*Comment: Although such an estimate and exact confidence intervals would be nice to have, it is not so easy to provide. The important consideration is that the severity of liver injury is not a simple binary problem, but a range of severity progressing from just serum enzyme elevations that may be transient and reversible, to more severe cases with enough hepatocellular injury to cause some dysfunction of the whole liver, with reduced ability to clear the plasma of bilirubin, conjugate it and excrete it into bile, or to synthesize proteins such as albumin (not very sensitive) or prothrombin so that the international normalized ratio (INR) is raised. Beyond that level of injury even more severe hepatocellular dysfunction causes clinical illness, jaundice, diasability, hospitalization; even more severe injury results in acute liver failure, with life-threatening risks of secondary renal failure (hepatorenal syndrome), encephalopathy, bleeding, and consideration of need to transplant the liver to avoid death. The less severe levels of drug-induced injury are far more frequently seen, but are often reversible because of the great capacity of opst people's livers to adapt and change themselves so that the drug is tolerated and can be continued. We are caught between the two horns of stopping the drug too soon and unnecessarily, and continuing it too long to the point of progressive irreversibility. This cannot be reduced to a single number with confidence intervals.*

**3. Please identify all other drugs with similar or higher rates of drug-induced liver injury (DILI) that are marketed in the USA. Please describe previous FDA regulatory action (e.g., approval, non-approval, withdrawal) on other drugs with similar rates (or lower) rates of DILI.**

*Comment: To answer this request would require a book, or at least a chapter. We have learned that DILI comes in many guises, is not just one narrowly defined disorder, and varies both in its severity and in the types of responses that individual patients show. Fortunately it is usually quite rare, at least in its more serious degrees of severity. It cannot be treated as a simple binary diagnosis: present or not. The incidence of the less serious forms, just elevations of serum aminotransferase activity without symptoms of evidence of whole organ dysfunction (such as jaundice or prolonged prothrombin time (elevated INR), is far greater than that for the more serious degrees of liver injury that are extensive enough to reduce the ability of the whole liver to carry out its true functions such as clearing plasma of bilirubin and synthesizing critical proteins need for controlling bleeding. Once again: serum enzyme tests are not measures of liver function, should not be termed thoughtlessly as “LFTs”, and their degree of elevation is NOT a valid measure of the severity of the injury. The severity of the injury is measurable only by how much impaired are the true functions of the liver. That is why we use the combined peak values of both ALT and BLT as a screening test to identify patients who deserve more detailed study and investigation to determine the time course and probable cause of the abnormal findings. Use of eDISH has been badly misinterpreted by statisticians and toxicologists in the pharmaceutical industry to diagnose “Hy’s Law,” because they make no attempt to determine the probable or likely cause of the findings, the very first point emphasized by Dr. Hyman Zimmerman when he stated that “**drug-induced hepatocellular jaundice is a serious lesion**” with substantial (10 to 50%) mortality.*

*FDA (CDER) has not approved a drug since 1997 that subsequently had to be taken off the market because of induced hepatotoxicity, following the disastrous approvals in January 1997 of troglitazone, and in July 1997 of bromfenac, both of which drugs promptly began to kill patients with acute liver failure. Bromfenac was withdrawn in June 1998, but it took until March 2000 to overcome the political and financial arguments of the troglitazone sponsor, until less dangerous –glitazones (rosi- and pio-) were available. In the summer of 1998 we began to plan a program of educating FDA reviewers (mostly CDER, some CBER, a few CDRH) about hazards of drug-induced liver injury, extended in 2001 to include industry and academia, and continuing annually (DILI Conference XIII was just held 20-21 March 2013; the entire meeting, the slides shown, comments made about them, and full texts of discussions that followed were available on the internet last week (go to [www.aasld.org](http://www.aasld.org), point to heading Training/Education, drop down and select Drug-Induced Liver Injury 2013 Program), or via the FDA public web site, but not Inside FDA, (enter “drug liver toxicity” into the search box). Programs back to April 1999 are posted there, along with detailed slides and texts from recent years since 2009 (text only at FDA website because of 508 rules).*

*Because of this increased awareness of the problem of dangerous hepatotoxicity of drugs, we developed the eDISH (evaluation of **d**rug-**i**nduced **s**erious **h**epatotoxicity) to identify cases of special interest for further diagnostic investigation for selected patients in large clinical trials, using the time courses for all liver test results available for a given patient, and clinical narratives preferably prepared by the treating or investigating physician). The first major use of the system resulted in the rejection in 2004 for approval of ximelagatran (EXANTA, AstraZeneca)*

despite its approval in Europe and vigorous protests by the sponsor, who finally conceded in 2007 to study patients who had shown liver injury versus those who had not, and discovered that patients with a genetic marker in the HLA system, DRB1\*0701, had increased susceptibility to sustain hepatotoxicity from the drug, as reported by Kindmark et al. in 2008 and Andersson et al. in 2009.. The FDA also refuse (b) (4)

allowing publication of work by Singer et al. showing that patients with HLA haplotype DRB1\*1501 were particularly susceptible to lirinacoxib-induced liver injury.

On the other hand, isoniazid, useful for preventing tuberculosis, has been known for many years, since the work of Mitchell et al. in 1975 revealed the high incidence of elevations of serum aminotransferase activities in patients on prophylactic treatment against tuberculosis. Some 15-20% of patients starting isoniazid (only) may show significant elevations in activities of aminotransferases, often asymptomatic, but nearly all of them (>99%) show adaptation by the liver to the drug, and therefore become tolerant to its continuation or resumption. It was then shown that it is not necessary to stop the drug permanently in all those who show only initial serum enzyme increases, although those rare cases, 1 or 2 per 1000, who failed to adapt are at serious risk for progressive injury and fatal liver failure if the drug is not stopped. The classic observation by Nolan et al. in 1999 was that routine laboratory monitoring over-diagnosed the problem, and that clinical monitoring and vigilant follow-up based on education of both patients and physicians was far more effective in preventing serious hepatotoxicity from isoniazid while still allowing its beneficial effects in those who could adapt to it.

It is overly simplistic just to list drugs that are still on the market with similar or higher rates of at least some liver injury. Tacrine and heparins induce very high rates of minor serum transaminase elevations, but not progressive, severe liver dysfunction leading liver failure and death or need for transplantation. The ratio of severe injury and life-threatening dysfunction to minor "transaminitis" from various drugs is not constant, and a single figure is not valid for each drug. This discussion certainly does not cover all drugs, but is illustrative of the problem faced. As far as experience to date with use of tolvaptan is concerned, we have not yet found any case of explosively rapid progression to irreversible liver damage and fatality as seen with troglitazone ---- BUT experience with tolvaptan is very limited. It did not appear to cause serious liver injury in patients treated with SAMSCA under the previously approved indications, but even that was rather limited exposure in terms of numbers, shorter exposure times, at a lower dose, so it is not statistically proved that patients with ADPKD are different. More information will be needed, and caution is advised.

**4. A single dosing regimen was tested in the pivotal trial 156-04-251. In your experience, are small changes (<0.5 log) in dosing likely to have significant effect of the incidence of DILI?**

*Comment: The choice of a single dose of 90/30 (120 mg daily) for all patients did not appear to be well established by the pharmacologic data prior to that, and appears to have been driven by marketing considerations that "one dose fits all." It is far more likely that the hepatotoxicity seen in some patients with ADPKD is idiosyncratic, depending on particular sensitivity of some individuals, than simply a dose effect. Change of <0.5 log<sub>10</sub> (about three-fold) are less likely to be important than individual susceptibility, although the evidence for that is so far flimsy. It was of interest that the very prompt rise in serum enzyme activities upon rechallenge in the two cases*

discussed above (both from Study 04-251: the Japanese woman 50, 727-2401, and the woman 49 from Chicago, 104-0605) occurred at half the dose that had caused the more delayed initial rise in serum enzyme activities.

**5. Otsuka asserts, in the Watkins Tolvaptan Safety Report, that there were 3 cases of DILI among 860 ADPKD subjects exposed long term, and no cases in the 589 non-ADPKD subjects. If the true incidence is 3/860, then no cases will be observed in 589 subjects about 13% of the time. Please comment on the apparent difference in rate of incidence in the two clinical programs. In your experience, is DILI likely to vary among patients based on indication, or is it more likely that the rate of DILI is independent of indication?**

*Comment: This statistical comparison is not at all compelling, as is pointed out. However, the whole clinical trial program for ten years from 1999 until approval, and the several thousands of patients treated since approval, did not disclose a problem with liver injury from the SAMSCA version of tolvaptan. This suggests, but certainly does not prove, that patients with ADPKD may be different in some way. We know that they differ in a least one respect, a genetic inheritance of PKD1 or PKD2 genes that lead to renal tubular cyst development and slow growth. It is not known whether this might also confer some increased risk of hepatocellular injury (apart from the also associated development of liver cysts). The liver injury observed was not that of a slow cyst-growth obstructive type, but of rapid, although delayed and seldom immediate, injury to the hepatocytes in affected individuals. The sponsor should be tasked to investigate whether PKD1 or PKD2 are associated with an increased chance of hepatocellular injury in patients with the disease being treated ADPKD.*

*All this states the problem, but does not address what should be done about it. The sponsor has submitted a Risk Mitigation Plan (proposal of 13 November 2012), even before submission of the NDA 204441 itself. A Medication Guide to supplement appropriate labeling is proposed, to educate patients on the risk of liver injury, the importance of monthly blood testing for evidence of early liver injury for at least 18 months, the need to self-monitor daily for early symptoms of liver dysfunction, and to report them promptly to their physicians so that investigation can be done to determine the probable cause, interrupting drug use until the questions are resolved. These are reasonable provisions to implement. Review of the sponsor's proposal by the Risk Evaluation Mitigation Strategy team of OSE, has emphasized the educational aspects of the proposal, but considers monthly blood testing unnecessary, based on the long history of failed laboratory monitoring plans.*

*Comment: Both the sponsor and the OSE Division of Risk Management (DRISK) are right, but neither goes far enough. We have learned that sensitive serum enzyme tests, such as high alanine aminotransferase activities, may occur before symptoms, but are not specific or diagnostic. Conversely, in some patients symptoms may develop within 28- or 30-day monitoring intervals, demanding immediate recheck of the serum tests within a few days. Use of routine laboratory monitoring often has not worked because it simply is not done well, results are not known or used, and both physicians and their patients and physicians grow weary of normal test results, especially if they do not understand why the monitoring is being done. Even with the drug troglitazone, despite reported deaths from its use, monitoring was not done well by many physicians (Graham et al., 2001, 2003).*

*It is recognized that there is no other known treatment for ADPKD, but the studies done to date have been inadequate to answer many questions. No experience has been sought for use in children, in whom the genetic defect might be recognized, especially if some treatment was to become available. The optimal dose, for what time, in which patients, needs to be determined better. Whether some patients may have different susceptibility to liver injury is a critical point that still needs to be established. The role of PKD1 or PKD2 mutations has not been clarified. Because there is no biomarker to predict or diagnose DILI, only careful clinical observation can serve to protect patients from potentially severe harm from liver failure. That hasn't been seen so far, but the exposure has not yet been adequate in number or time to be reassuring. How to make the treatment safely available to those who need it, without being overly cautious and excluding those with trivial, transient, reversible serum enzyme rises, but not missing the few who may progress to severe injury, dysfunction, and liver failure, is the difficult path to find.*

**Recommendations:**

1. Accept the sponsor's proposal for monthly monitoring of serum ALT, with vigorous attempts to educate both patients, or their parents, and physicians as to the reasons and need for it, to have the patients also informed of the results, and insist that their doctors know them.
2. Accept also the plans for education emphasized by the REMS group of OSE, but not their proposal to eliminate monthly laboratory testing.
3. Do pre-treatment baseline evaluation of liver tests (ALT, AST, ALP, BLT and BLD) at least twice before starting tolvaptan for treatment of ADPKD, and repeat the whole set immediately in case of elevated serum enzyme activities or suspicious symptoms, interrupting tolvaptan administration until the probable cause of the problem is found.
4. Establish a registry to keep careful track of a cohort of the first 5000 patients who are treated, to be supported by the sponsor but maintained by an independent agency such as the National Institutes of Health, with semi-annual reporting for two years and annually for three more years.
5. Carry out studies to investigate the role of PKD1 mutations and PKD2 on both the rate of response to tolvaptan, as measured by imaging measurements of renal volumes with parallel testing of renal functions, and hepatic effects. Additional genome-wide testing for increased susceptibility to liver injury, as done earlier for ximelagatran and lumiracoxib, should also be undertaken by the sponsor.

John R. Senior, M.D.,

Associate Director for Science, Office of  
Pharmacovigilance and Epidemiology, Office of  
Surveillance and Epidemiology, Center for Drug  
Evaluation and Research, Food and Drug Administration

cc: Mary Ross Southworth, DCRP

Nhi Bach Beasley, DCRP

Aliza Thomson, DCRP;

Stephen Grant, DCRP

Norman Stockbridge, DCRP

Gerald Dal Pan, OSE

Solomon Iyasu, OPE

**REFERENCES**

- Alfirevic A, Gonzolex-Galarza F, Bell C, Martinsson K, Platt V, Bretland G, Evely J, Lichtenfels M, Cederbrant K, French N, Naisbitt D, Park BK, Jones AR, Pirmohamed M. In silico analysis of HLA associations with drug-induced liver injury: use of a HLA-genotyped DNA archive from healthy volunteers. *Genome Med.* 2012 Jun 25;4(6):51(1-14). PMID 22732016
- Andersson U, Lindberg J, Wang S, Balasubramian R, Marchusson-Stahl M, Hunnula M, Zeng C, Juhasz PJ, Kolmert J, Backstrom J, Nord L, Nilsson K, Martin S, Glinghammar B, Cederbrant K, Schuppe-Kostinen I. A systems biology approach to understanding elevated serum alanine transaminase levels in a clinical trial with ximelagatran. *Biomarkers* 2009 Dec;14(8):572-86. PMID 19780643
- Cabello Muriel A, Marin Pozo JF, Alcalá Sanz A, Carrillo Ortiz D. Alteración hepática tras tratamiento con tolvaptán. [*Hepatic change after treatment with tolvaptan*] *Farm Hosp. [Farmacia Hospitalaria]* 2011 Mar-Apr;35(2):94-6. (Spanish) PMID 20864371
- Chapman AB, Torres VE, Perrone RD, Steinman TI, Bae KT, Miller PJ, Miskulin DC, Oskoui FR, Masoumi A, Hogan MC, Winklhofer FT, Braun WE, Thompson PA, Meyers CM, Kelleher C, Schrier RW. The HALT polycystic kidney disease trials: design and implementation. *Clin J Am Soc Nephrol.* 2010 Jan;5(1):102-9. PMID 20089507
- Cornec-Le Gall E, Audrézet MP, Chen JM, Hourmant M, Morin MO, Perrichot R, Charasse C, Whebe B, Renaudineau E, Jousset P, Guillodo MP, Grall-Jezequel A, Saliou P, Le Meur Y. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol.* 2013 May;24(6):1006-13. PMID 23431072
- Gaglio P, Marfo K, Chiodo J. Hyponatremia in cirrhosis and end-stage liver disease: treatment with the vasopressin V<sub>2</sub>-receptor antagonist tolvaptan. *Dig Dis Sci.* 2012 Nov;57(11):2774-85. PMID 22732834
- Grantham JJ, Chapman AB, Torres VE. Volume progression in polycystic kidney disease: the major factor determining clinical outcomes. *Clin J Am Soc Nephrol.* 2006 Jan;1(1):148-57. PMID 17699202
- Grantham JJ. Autosomal dominant polycystic kidney disease. *N Engl J Med.* 2008 Oct 2; 359(14):1477-85. PMID 18832245
- Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King Jr BF, Wetzel LH, Baumgartner DA, Kenney PJ, Harris PC, Klahr S, Bennett WM, Hirschman GN, Meyers CM, Zhang X, Zhu F, Miller JP. Volume progression in polycystic kidney disease. *N Engl J Med.* 2006 May 18;354(20):2122-30. PMID 16707749
- Helal I, Reed B, Schrier RW. Emergent early markers of renal progression in autosomal-dominant polycystic kidney disease patients: implications for prevention and treatment. *Am J Nephrol.* 2012;36(2):162-7. PMID 22846584

Harris PC, Hopp K. The mutation, a key determinant of phenotype in ADPKD. [Ed] *Am J Soc Nephrol*. 2013 May;24(6):868-70. PMID 23687354

Kindmark A, Jawaid A, Harbon CG, Barratt BJ, Bengtsson OF, Andersson TB, Carlsson, Cederbrant KE, Gibson NJ, Armstrong M, Lagerström-Fermer ME, Dellsén A, Brown EM, Thornton M, Dukes C, Jenkins SC, Firth MA, Harrod GO, Pinel TH, Billing-Clason BM, Cardon LR, March RE. Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs of immunopathology suggests an underlying immune pathogenesis. *Pharmacogenomics J*. 2008 Jun; 8(3):186-95. PMID 17505501

Kistler AD, Poster D, Krauer F, Weishaupt D, Raina S, Senn O, Binet I, Spanaus K, Wuthrich RP Serra AL. Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. *Kidney Int*. 2009 Jan;75(2):235-41. PMID 18971924

Miyazaki T, Fujiki H, Yamamura Y. Tolvaptan, an orally active non-peptide arginine vasopressin V2 receptor antagonist, reduces ascites in rats with chronic liver injury. *Hepatol Res*. 2013 Jan 18; [Epub ahead of print] PMID 23413814

Mochizuki T, Tsuchiya K, Nitta K. Autosomal dominant polycystic kidney disease: recent advances in pathogenesis and potential therapies. *Clin Exp Nephrol*. 2012 Nov 29; [Epub ahead of print] PMID 23192769

Singer JB, Lewitzky S, Leroy E, Yang F, Zhao X, Klickstein L, Wright TM, Meyer J, Paulding CA. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat Gen*. 2010 Aug;42(8):711-4. PMID 20639878

Spital A; Kher A; Sexton DJ; Jouret F, Krzesinski J-M. Comments on Torres et al. 2012. *N Engl J Med* 2013 Mar 28;368(13):1257-9. PMID 23534568-72.

Stephens C, Lucena MI, Andrade RJ. Genetic variations in drug-induced liver injury (DILI): resolving the puzzle. *Front Genet*. 2012;3:253-4. PMID 23162573

Thong KM, Ong AC. The natural history of autosomal dominant polycystic kidney disease: 30-year experience from a single centre. *QJM*. 2013 Apr 15 [Epub ahead of print] PMID 23587574

Torres VE, Harris PC, Pirson Y.. Autosomal dominant polycystic kidney disease. *Lancet* 2009 Apr 14;369(9569):1287-301. PMID 17434405

Torres VE, Harris PC. Autosomal dominant polycystic kidney disease: the last 3 years. *Kidney Int*. 2009 Jul;76(2):149-68/ PMID 19455193

Torres VE, Meijer E, Bae KT, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang JJ, Czerwiec FS. Rationale and design of the TEMPO (tolvaptan efficacy and safety in management of autosomal dominant polycystic kidney disease and its outcomes) 3-4 study. *Am J Kidney Dis*. 2011 May;57(5):692-9. PMID 21333426

Torres VE, Chapman AB, Perrone RD, Bae KT, Abebe KZ, Bost JE, Miskulin DC, Steinman TI, Braun WE, Winklhofer FT, Hogan MC, Oskoui FR, Kelleher C, Masoumi A, Glockner J, Halin NJ, Martin DR, Remer E, Patel N, Pedrosa I, Wetzel LH, Thompson PA, Miller PJ, Meyers CM, Schrier RW, for the HALT PKD Study Group. Analysis of baseline parameters in the HALT polycystic kidney disease trials. *Kidney Int.* 2012 Mar;81(6):577-85. PMID 22205355

Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS, for the TEMPO 3-4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med.* 2012 Dec 20;367(25):2407-18. PMID 23121377

Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, Yamashita T, Yamada Y, Tsujimae K, Aoyama M, Kotosai K, Ogawa H, Kondo K, Tominaga M, Tsujimoto G, Mori T. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple dosing in rats. *J Pharmacol Ther.* 1998 Dec;287(3):860-7. PMID 9864265

Yamamura Y, Ogawa H, Chihara T, Kondo K, Onogawa T, Kakamura S, Mori T, Tominaga M, Yabuuchi Y. OPC-21268, an orally effective, nonpeptide vasopressin V1 receptor antagonist. *Science* 1991 Apr 26;252(5005):572-4. PMID 1850553

Yamamura Y, Ogawa H, Yamashita H, Chihara T, Miyamoto H, Nakamura S, Onogawa T, Yamashita T, Hosokawa T, Mori T, Tominaga M, Yabuuchi Y. Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V<sub>2</sub> receptor antagonist. *B J Pharmacol.* 1992 Apr;105(4):787-91 PMID 1387020

Attach Excel Table I, II, III (Tables\_SAMSCA\_NEs.xcl)

Tolvaptan (SAMSCA, Otsuka drug 176): studies of cirrhosis, heart failure, hyponatremia –  
(selected cases with {peak ALT>3xULN & peak total bilirubin>2xULN } (eDISH RU or NE quadrant)

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

/s/  
-----

JOHN R SENIOR  
06/29/2013

# OSI/DGCPC CONSULT: Request for Clinical Inspections

**Date:** April 10, 2013

**To:** Ann Meeker-O'Connell, Acting Division Director, DGPCPC  
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB\*  
Susan Thompson, M.D., Acting Branch Chief, GCPAB  
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB  
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB  
CDER OSI PM Track  
Sharon Gershon, Pharm.D.  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** Aliza Thompson, M.D., Medical Team Leader/ Division of Cardiovascular  
and Renal Products (DCRP)  
Stephen Grant, M.D., Deputy Division Director

**From:** Anna Park, R.Ph., RAC Regulatory Project Manager, DCRP

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 204441

IND#: 072975

Applicant/ Applicant contact information (to include phone/email): Otsuka Pharmaceutical  
Development & Commercialization, Inc. 1 University Square Drive, Suite 500 Room 5125  
Princeton, NJ 08540

Drug Proprietary Name: TBD

Generic Drug Name: tolvaptan

NME or Original BLA (Yes/No/Not Applicable): No

Review Priority (Standard or Priority or Not Applicable): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No/Not Applicable): No

Proposed New Indication(s): **slowing kidney disease in adults at risk of rapidly progressing  
autosomal dominant polycystic kidney disease**

PDUFA: September 1, 2013

Action Goal Date: August 31, 2013

Inspection Summary Goal Date: July 3, 2013

OSI/DGCPC Consult

version: 01/16/2013

**II. Protocol/Site Identification**

All of the sites listed below participated in Protocol 156-04-251, titled “A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease.”

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Number of Subjects</b>	<b>Indication/Primary endpoint and other endpoints for verification</b>
Site 510 Gross, Peter Fetscherstrasse 74 Dresden, NA 1307 GM Western Europe phone:49-351-45-82645 fax:49-351-45-85333 email:Peter.Gross@uniklinikum-dresden.de	75	The first secondary endpoint is the time to multiple Investigator-reported ADPKD clinical progression events. This is the key endpoint for regulatory decision-making and the data supporting this endpoint should be verified.
Site 511 Schulze, Bernd-Detlef Breslauerstr. 201/Kreuzburger.2 Nuernberg, NA 90471 GM Western Europe phone:49-911-39-85130 fax:49-911-80-01037 email:b.schulze@klinikum-nuernberg.de	46	See above
Site 181 Bichet, Daniel 5400 Boulevard Gouin West, Unite de recherche C-2085 Montreal, Quebec H4J 1C5 CA Canada phone:1-514-338-2486 fax:1-514-338-2694 email:daniel.bichet@umontreal.ca	33	See above
Site 104 Tuazon, Jennifer 710 N . Fairbanks Ct., Olson Building, Rm. 4-500 Chicago, IL 60611 US United States phone:312-926-4880 fax:312-926-4885 email:j-tuazon@northwestern.edu	28	See above

Site # (Name,Address, Phone number, email, fax#)	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
Site 550 Gansevoort, Ron Hanzeplein 1 Groningen, NA 9713 GZ NL Western Europe phone:31 503 619023 fax:31 503 619310 email:r.t.gansevoort@int.umcg.nl	53	See above

### **III. Site Selection/Rationale**

No single site is driving the efficacy findings and so removal of a single site from efficacy analyses (based on inspection findings) is unlikely to alter the regulatory outcome. Clinical investigator sites are being inspected to assess the quality, integrity, and acceptability of the data submitted in support of the application and the adequacy of the protection of the rights and welfare of human research subjects. The sites were selected based on a high risk ranking as determined by the GCP Site Selection Tool.

#### **Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: Problems were identified at the site during the course of the trial by the CRO monitor

#### **International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: Site 510 given OAI field classification when inspected for another NDA (subsequently downgraded to VAI); other sites were also high enrollers with high risk rankings

**Five or More Inspection Sites:**

We have requested these sites for inspection (international and/or domestic) for the reasons cited above.

*(Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.)*

**IV. Tables of Specific Data to be Verified (if applicable)**

- The first secondary endpoint is the time to multiple Investigator- reported ADPKD clinical progression events, ie, progressing hypertension [blood pressure measurement, need for treatment], severe renal pain [requiring medical intervention], worsening albuminuria [by category], worsening renal function [25% change in reciprocal serum creatinine as a measure of glomerular filtration rate from steady-state post-dose Baseline] for subjects taking tolvaptan. This is the key endpoint for regulatory decision-making and the data supporting this endpoint should be verified.
- Drug-induced liver toxicity was observed in this trial and the accuracy of reporting of liver-related findings (e.g., adverse events, abnormalities in liver tests identified via local laboratory, subject follow up and work up) should be verified.
- Dates of study medication discontinuation and reasons for study medication discontinuation should be verified. Similarly, dates of study termination and reasons for premature termination should be verified.

Should you require any additional information, please contact Anna Park at (301)796-1129 or Aliza Thompson at (301)796-1957.

**Concurrence: (as needed)**

Stephen Grant, M.D., Deputy Division Director

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

/s/  
-----

ANNA J PARK  
04/11/2013

STEPHEN M GRANT  
04/11/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

---

DATE: March 13, 2013

TO: Director, Investigations Branch  
New York District Office  
158-15 Liberty Avenue  
Jamaica, NY 11433

Dallas District Office  
4040 N. Central Expressway  
Dallas, TX 75204

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER User Fee NDA, Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 204-441  
DRUG: Tolvaptan  
SPONSOR: Otsuka Pharmaceutical, Inc.  
Princeton, NJ

This memo requests that you arrange for inspections of clinical and analytical portions of the following bioequivalence study. Once an ORA investigator is identified, please contact the DBGLPC point of contact (POC) listed at the end of this memo for background materials. A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC POC upon receipt of this assignment to arrange scheduling of the analytical inspection. **Please complete the inspections by June 30, 2013.**

**Do not notify the sites of the application number, the study to be inspected, drug name, or the study investigator prior to the start of the inspection.** The information will be provided to the site(s) at the inspection opening meeting. **Please note that the inspection will be conducted under Bioresearch Monitoring**

**Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).**

**Study Number:** 156-11-295

**Study Title:** "An Open-label, Randomized, Crossover Trial to Assess Dose Strength Equivalence Among 30 and 90 mg Strengths of Oral Tolvaptan Tablets and to Determine the Effect of Food (Standard Food and Drug Administration High-fat Breakfast) on Tolvaptan Pharmacokinetics Following the 90-mg Tablet in Healthy Subjects"

**Clinical Site:** Covance Clinical Research Unit, Inc.  
1341 West Mockingbird Lane, Suite 400E  
Dallas, TX 75247

**Investigator:** William Lewis, MD (from Aug 17, 2011)  
T. Alex King, MD (from Aug 4 to August 17, 2011)

**At the completion of the inspection, please complete and send the sections A & B below to Dr. Sam Haidar and the DBGLPC POC.**

#### **SECTION A**

**RESERVE SAMPLES:** The above study is a bioequivalence study subject to 21 CFR 320.38 and 320.63 and the site conducting the studies is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the sponsor for subject dosing.

Please note that the Final Rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.**
- Please obtain a written assurance from the**

investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.

- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis at the following address:

Benjamin Westenberger, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Customhouse Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101  
TEL: (314) 539-2135

#### SECTION B

Please confirm the informed consent and records for 100% of subjects enrolled at the site. The study records in the NDA submission should be compared to the original documents at the site. Include a description of your findings in the EIR.

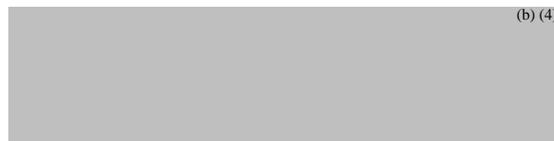
Please verify and scrutinize:

- Presence of 100% of signed and dated informed consent forms:\_\_\_\_\_
- Accurate transcription of data from source documents to case report forms:\_\_\_\_\_
- Adherence to inclusion and exclusion criteria per protocol: \_\_\_\_\_
- Any evidence of under-reporting of AEs: \_\_\_\_\_
- Data accuracy compared to NDA submission: \_\_\_\_\_
- Correspondence files for any sponsor- or monitor-requested changes to study data or reports:\_\_\_\_\_

- Number of subjects screened at the site: \_\_\_\_\_
  - Number of subjects enrolled at the site: \_\_\_\_\_
  - Number of subjects completing the study: \_\_\_\_\_
  - Number of subject records reviewed during the inspection: \_\_\_\_\_
  - List of source data and reports audited: \_\_\_\_\_
  - Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol: \_\_\_\_\_
  - Confirm that SOPs were followed during study conduct: \_\_\_\_\_
  - Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, case report forms for dosing, whether the randomization schedule was followed for dosing of subjects, etc.)
  - Other Comments:
- 
- 

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**Analytical Site:**



**Investigator:**



**Methodology:** LC/MS/MS

**Please confirm the following during the inspection:**

- All pertinent items related to the analytical method used for the measurement of tolvaptan (OPC-41061) concentrations in human plasma
- Accuracy of data provided in the NDA submission compared to the original documents at the site
- Evaluation of the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis compared with those obtained during method validation
- Verification that subject samples were analyzed within the validated stability period

- Use of freshly made calibrators and/or quality control samples (QCs) for stability evaluations during method validation
- Preparation of QCs and calibration standards in matrix with same anticoagulant as the study samples
- At least one demonstration of precision and accuracy from QCs and calibrators prepared from separate stock solutions
- Correspondence files between the analytical site and the sponsor for their content
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.

**Additional instructions to ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. We request the DBGLPC POC be contacted for inspection-related questions or clarifications and any data anomalies noted during review of study report.

**Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward the written response as soon as you receive it to Dr. Sam H. Haidar (Fax: 1-301-847-8748 or Email: [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)) and DBGLPC POC.**

DBGLPC POC: Seongeun Julia Cho, Ph.D.  
Email: [seongeun.cho@fda.hhs.gov](mailto:seongeun.cho@fda.hhs.gov)  
TEL: (301)796-5032  
FAX: (301)847-8748

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Cho/Skelly/Dejernett/CF

NYK-DO/Laurence Daurio (DIB)/Linda Sacco (BIMO)/Thomas Hansen (BIMO)

DAL-DO/ Susan M. Turcovski (DIB)/ Joel Martinez (BIMO)/Alanna Mussawwir-Bias (BIMO)

OND/OCP/Martina Sahre/Anna J Park

Draft: JC 3/13/13

Edit: MFS 3/13/13

OSI file BE6442; O:\BE\assigns\bio204441.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

FACTS: (b) (4)

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

/s/  
-----

SEONGEUN CHO  
03/14/2013

SAM H HAIDAR  
03/14/2013

<b>OSI Consult Request for Biopharmaceutical Inspections</b>	
Date	3/12/13
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, PhD Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	Office of Clinical Pharmacology, DCP1
Project Manager	Anna Park, R.Ph.
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	204-441
Drug Product	Tolvaptan
Sponsor Name	Otsuka Pharmaceutical Company, Ltd.
Sponsor Address	Craig Ostroff, PharmD, R.Ph. Senior Director, Regulatory Affairs Otsuka Pharmaceutical Development & Commercialization, Inc. 1 University Square, Suite 500, Room 5125 Princeton, NJ 08540 USA Office Phone: 609.524.6886, Mobile: 609.235.6535, Fax: 240.514.3986 email: craig.ostroff@otsuka-us.com
US Agent (if applicable)	
US Agent Address	
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date	9/1/2013
Action Goal Date	
OSI Review Requested By	Martina Sahre, Ph.D.

<b>Inspection Request Detail</b> (All fields should be fill out completely)				
<b>Study #1</b>				
Study Number	156-11-295			
Study Title				
Study Type	<input checked="" type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Others (specify)
<input checked="" type="checkbox"/> Inspection Request - <b>Clinical</b> Site		<input checked="" type="checkbox"/> Inspection Request - <b>Analytical</b> Site		
Facility #1 Name: Covance Clinical Research Unit, Inc. Address: 1341 West Mockingbird Lane, Suite 400E		Facility #1 Name: (b) (4)		

Dallas, TX 75247 (Tel) 214-920-9053 (from CV for Dr. Lewis) (Fax)	(Tel) (Fax)
Clinical Investigator: William Lewis (from 17 Aug 2011) T. Alex King (04 Aug to 17 Aug 2011) (email)	Principal Analytical Investigator: <span style="background-color: gray; color: gray;">(b) (4)</span> (email)
Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input checked="" type="checkbox"/> Study Report: 5.3.1.2.3	<input checked="" type="checkbox"/> Validation Report: (5.3.1.2.3) <input checked="" type="checkbox"/> Bioanalytical Report: (5.3.1.2.3) Both as attachments in study report

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.**

## ***I. Appendix***

<b>Specific Items To be Addressed During the Inspection</b>
<p>This study forms the pivotal BE study. The test products used in the pivotal efficacy study were 15 and 30 mg tablets, given multiple times to achieve doses of 45, 60 and 90 mg. Sponsor is proposing newer strengths of 45 mg, 60 mg and 90 mg. Study 156-11-295 provides the bridging information for the highest to-be-marketed strength.</p>

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

/s/  
-----

ANNA J PARK  
03/13/2013