REMS Data

An evidence-based answer to a common clinical question about JYNARQUE® (tolvaptan)

Are there any data on drug-induced liver injury from the Risk Evaluation and Mitigation Strategy (REMS) program?

INDICATION:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE REMS Program**

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Please see **IMPORTANT SAFETY INFORMATION** on pages 4–5.

JYNARQUE®
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

Post-marketing liver safety was investigated in a retrospective analysis of the ongoing JYNARQUE® (tolvaptan) REMS Program

Study Overview

- Retrospective interim analysis of adult patients with ADPKD who were JYNARQUE-naive and started JYNARQUE in the post-marketing setting
- REMS incidence rates were compared with those from JYNARQUE trials by calculating an incidence rate ratio (trials were: TEMPO 3:4, TEMPO 3:4 extension [TEMPO 4:4], REPRISE, and long-term extension, which enrolled subjects from REPRISE, TEMPO 4:4, and previous JYNARQUE trials)
- Caution should be applied in interpreting these data due to the limited duration of exposure to drug in the REMS population compared with the clinical trial population. In the clinical trials, the window of increased susceptibility to DILI was in the first 18 months of treatment. In this analysis, only 27% of patients were exposed to tolvaptan for longer than 18 months. The duration of treatment for some individuals with <12 months of exposure (ie, due to aquaretic side effects) may have been short, potentially biasing the analysis by the inclusion of patients unlikely to have experienced liver-related adverse events

Analysis Period

- **May 14, 2018** Start of REMS
- **2019**
- **2020**
- **February 23, 2021** Analysis cutoff date

How a severe drug-induced liver injury (DILI) was classified*

- A possible case was defined as a patient who met at least one of three criteria†, regardless of reported causality
- Possible cases were analyzed further to determine severity, timing, and outcomes and to identify the following events
  - Events confirmed as serious and potentially fatal liver injury
  - Hy's Law: ALT or AST ≥3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal in the absence of cholestasis and without any other reason to explain the elevations
  - Confirmed severe DILI by FDA criteria: irreversible liver failure that is fatal or requires transplantation

*The 3 criteria are development of any liver injury events leading to liver transplantation, or resulting in a fatal outcome or considered to be life-threatening, or development of any liver injury events meeting any of the laboratory criteria presented below:
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
- ALT or AST >5 × ULN for more than 2 weeks, or
- ALT or AST >3 × ULN and (total bilirubin >2 × ULN or international normalized ratio >1.5) (bilirubin measurement can be within 30 days of the ALT elevation), or
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

FDA=US Food and Drug Administration

Please see **IMPORTANT SAFETY INFORMATION** on pages 4–5.

Retrospective interim analysis from the REMS Program demonstrated a lower rate of possible severe DILI compared with the JYNARQUE® (tolvaptan) clinical trial population

Number of REMS Patients

6711	60 (0.9%)	48 (0.7%)	4 (0.06%)*	0
Patients initiated JYNARQUE in the post-marketing setting	Patients reported with possible severe DILI	Patients with possible severe DILI discontinued JYNARQUE	Patients confirmed with serious and potentially fatal DILI, including 1 Hy's Law	Patients with fatalities or liver transplantation due to DILI

Indirect comparison of DILI incidence in clinical trials vs REMS†

	Clinical Trials	REMS
Incidence Proportion	5.5% 151/2743 patients	0.9% 60/6711 patients
Incidence Rate Per 100 Patient-Years	1.57 154 events/9786 PYs	0.93 60 events/6486 PYs

IRR: 0.587; 95% CI, 0.436–0.792; *P*=0.000411

Results support that the REMS Program is facilitating management of risk in the real world due to close monitoring and limiting harm to patients

SELECT IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

CI=confidence interval; IRR=incidence rate ratio; PY=patient year.
*In all 4 patients, liver enzymes normalized after JYNARQUE discontinuation.

†The comparison of incidence in the REMS and clinical trials (TEMPO 3:4, REPRISE, and their extension trials) was post hoc and indirect, using 2 separate datasets.

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INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

INDICATION

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IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS LIVER INJURY

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CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
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Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

IMPORTANT SAFETY INFORMATION (CONT'D)

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING**.

Exploring the benefit of the REMS Program

Due to the risk of serious liver injury, JYNARQUE is available only through the REMS program. The JYNARQUE REMS Program makes monitoring patients and mitigating the risk of liver injury a top priority.

The program includes monitoring of liver function at specified times in patients prescribed JYNARQUE.

The REMS population in a retrospective interim analysis demonstrates a lower rate of possible severe drug-induced liver injury compared with the JYNARQUE clinical trial population

- Cases of possible severe DILI: **0.9%** (n=60 of 6711) in **REMS vs 5.5%** (n=151 of 2743) **in the clinical trial** population
- The incidence of possible severe DILI was lower in the REMS Program than in clinical trials: **incidence rate ratio 0.587; *P*=0.000411**
- Caution should be applied in interpreting these data due to the limited duration of exposure to drug in the REMS population compared with the clinical trial population.

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Reference: 1. Estilo A, Tracy L, Matthews C, et al. Evaluating the impact of a Risk Evaluation and Mitigation Strategy with tolvaptan to monitor liver safety in patients with autosomal dominant polycystic kidney disease. Published online March 11, 2022. *Clin Kidney J*. doi:10.1093/ckj/sfac076s

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Otsuka
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July 2022 10US22EBP0104