An evidence-based answer (EBA) to a

# common clinical question about JYNARQUE® (tolvaptan)

## REMS DATA

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 6–7.

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# 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[1]
- 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)[1,2]

**REMS patients N=8764[2]**

### Analysis Period[2]

May 14, 2018 Start of REMS — 2019 — 2020 — 2021 — February 23, 2022 Analysis cutoff date

## How a severe drug-induced liver injury (DILI) was classified[1,*]

- 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[1]:
- 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 6–7.

# 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[2]

| 8764 | 69 (0.8%) | 4 (0.06%)* | 0 |
|---|---|---|---|
| Patients initiated JYNARQUE in the post-marketing setting | Patients reported with possible severe DILI | Patients confirmed with serious and potentially fatal DILI, including 1 patient who met Hy's Law criteria[1] | Patients with fatalities or liver transplantation due to DILI |

## Indirect comparison of DILI incidence in clinical trials vs REMS[2]

| | Clinical Trials | REMS |
|---|---|---|
| **Incidence Proportion** | 5.5% (151/2743 patients) | 0.8% (69/8764 patients) |
| **Incidence Rate Per 100 Patient-Years** | 1.57 (154 events†/9786 PYs) | 0.64 (69 events/10,737 PYs) |

IRR: 0.408; 95% CI, 0.307–0.542; $P \leq 0.0001$

- Risk of possible severe DILI does not appear to increase following treatment exposure beyond 12 months with continued liver enzyme monitoring . Conclusions about the timing of possible severe DILI are limited by the fact that approximately half of REMS patients had JYNARQUE exposure no longer than 12 months

**Results support that the REMS Program is facilitating management of liver injury 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

*In all 4 patients, liver enzymes normalized after JYNARQUE discontinuation.[2]

†The number of events (n=154) in the clinical trial program differed from the number of patients with possible severe DILI (n=151) because some patients experienced >1 event.[2]

CI=confidence interval; IRR=incidence rate ratio; PY=patient-year.

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# Questions patients may ask about the JYNARQUE® (tolvaptan) REMS Program

Review some commonly asked questions and answers about liver monitoring and the REMS Program to help guide your conversations with patients.

## Why does my patient have to enroll in the REMS Program?

Due to the risks of liver injury, JYNARQUE is available only through a REMS Program. Both the healthcare team and the patient will be enrolled in the REMS Program, a special safety program that will allow you to monitor the patient's bloodwork to help reduce the risk of liver injury.

## How often does my patient have to get lab work done?

To help reduce your patient's risk of liver injury while taking JYNARQUE, it is required that they have a blood test before they start, and then 2 weeks and 4 weeks after they start. For the first 18 months of treatment with JYNARQUE, they will need to have a blood test every month.

Following that period, they will only need to have a blood test every 3 months to be able to continue on JYNARQUE.

## Lab work is expensive, and my patient doesn't live near a lab. What are their options?

If you have questions about helping your patients navigate the JYNARQUE REMS Program, connect with your Otsuka Health Science Advisor in person or over the phone.

Terms and conditions apply. See https://www.jynarquehcp.com/rems-program for more information.

**SELECT IMPORTANT SAFETY INFORMATION:**

**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.



Please see **IMPORTANT SAFETY INFORMATION** on pages 6–7.

# Questions patients may ask about the JYNARQUE® (tolvaptan) REMS Program (cont'd)

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

Advise your patients to immediately stop taking JYNARQUE and contact their healthcare team right away if they experience any of the following symptoms:

- feeling tired
- loss of appetite
- nausea
- right upper stomach (abdomen) pain or tenderness
- vomiting
- fever
- rash
- itching
- yellowing of the skin and white part of the eye (jaundice)
- dark urine

## Can my patient connect with other patients who are also taking JYNARQUE and enrolled in the REMS Program?

There are several ways for your patients to connect with other patients taking JYNARQUE. They can speak with a Peer Mentor to hear their experiences with the REMS Program and discuss everyday life with ADPKD, side effects, treatment with JYNARQUE, and more.

Another way they can connect is by joining an online ADPKD community and signing up for an ADPKD Peer Conversations webinar to learn more.

Visit **adpkdpeermentorprogram.com** to learn more.

Scan the QR code to sign your patients up.

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# INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

## INDICATION

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

## IMPORTANT SAFETY INFORMATION

### WARNING: RISK OF SERIOUS LIVER INJURY

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- **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**

**CONTRAINDICATIONS:**

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# 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 demonstrated a lower rate of possible severe drug-induced liver injury compared with the JYNARQUE clinical trial population[2]

- Cases of possible severe DILI: **0.8%** (n=69 of 8764) 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 0.408; *P*≤0.0001**

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

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**References: 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. *Clin Kidney J.* 2022;15(8):1553-1561. **2.** Lioudis M, Nunna S, George V, Kumar R, Fernandes AW. Post-marketing liver safety data from 4 years of the tolvaptan Risk Evaluation and Mitigation Strategy (REMS) in the treatment of autosomal dominant polycystic kidney disease. Poster presented at: NKF Spring Clinical Meetings; April 11-15, 2023; Austin, TX. Poster 350.

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Otsuka
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