Understanding and managing aquaretic adverse events (AEs) while your patients are on JYNARQUE® (tolvaptan)

A look at why it happens, what to expect, and how to help manage it

Featuring insights from peers who have counseled patients on managing aquaresis

> **It's helpful for patients preparing for JYNARQUE therapy to understand that the aquaretic side effects are related to JYNARQUE's mechanism of action.** If we're going to derive benefit from the treatment, then we're going to need to have increased urine output.

Dr Christopher Kwoh
Houston area nephrologist

Dr Kwoh is a paid consultant of Otsuka America Pharmaceutical, Inc.

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 Tolvaptan for ADPKD Shared System REMS**

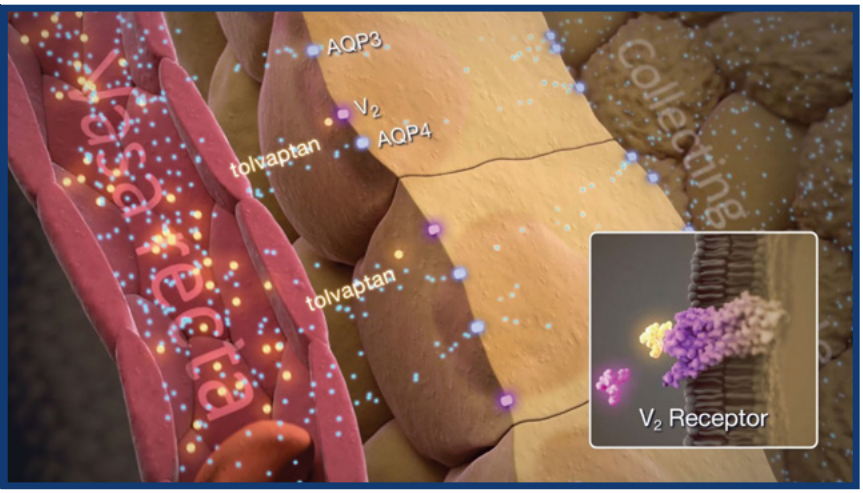
Please see **IMPORTANT SAFETY INFORMATION** on pages 10 and 11.

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

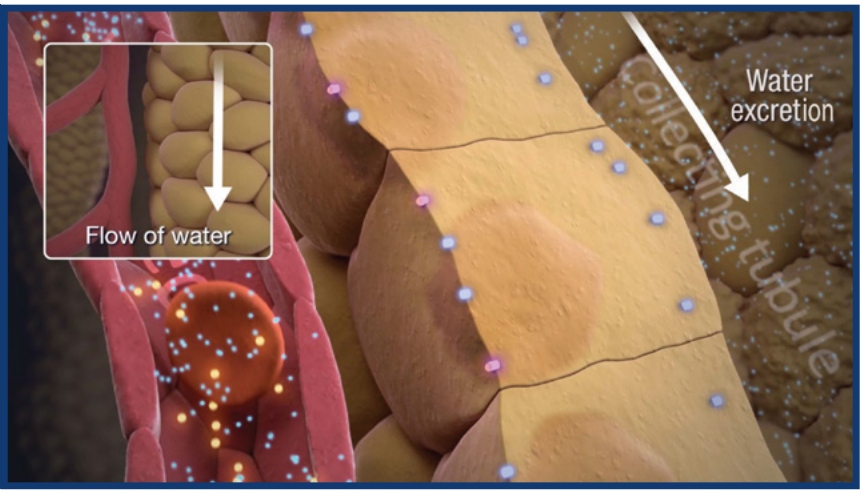
The onset of aquaretic AEs is related to the mechanism of action of JYNARQUE® (tolvaptan)

JYNARQUE is a vasopressin receptor antagonist. Vasopressin is a hormone that maintains the volume of water in the fluid space surrounding the cells. People with ADPKD have too much vasopressin, causing kidney cysts to grow[1-4]

- JYNARQUE works by selectively inhibiting the binding of vasopressin at the V_2-receptor in the kidney



- By antagonizing the activity of vasopressin in renal tubule cells, tolvaptan induces aquaresis (ie, increased free water clearance and decreased urine osmolality) and increased serum sodium concentrations



"I make sure patients understand that **aquaretic AEs are related to how JYNARQUE acts in the kidneys.**"

Dr Gerard J Tepedino
PRINE Health Medical Group, PLLC, Manhasset, NY

Dr Tepedino is a paid consultant of Otsuka America Pharmaceutical, Inc.

Changes in urine osmolality (Uosm) reflect activity of JYNARQUE® (tolvaptan) in the kidney

- If a patient on JYNARQUE experiences a decrease in Uosm (sustained Uosm <300 mOsm/kg), it suggests that JYNARQUE is inhibiting the binding of vasopressin at the V_2-receptor in the kidney[5]
- A decrease in Uosm to <300 mOsm/kg results from an increase in free water clearance and resultant excretion of more dilute urine

JYNARQUE has been studied in the 2 largest clinical trials of patients with ADPKD[6-8]

TEMPO 3:4 Trial — **A 36-month trial in patients with CKD Stages 1, 2, and 3[7,9]**

The primary endpoint was the annual rate of change in the total kidney volume.

REPRISE Trial — **A 12-month trial of patients with CKD late Stage 2 to early Stage 4[8,10]**

The primary endpoint was the treatment difference in the change of eGFR from pretreatment baseline to posttreatment follow-up, annualized by dividing by each participant's treatment duration.

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes.

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

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The safety profile of JYNARQUE® (tolvaptan)

Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria, and polydipsia. Instruct patients to drink water when thirsty

TEMPO 3:4—Treatment-emergent adverse reactions in ≥3% of JYNARQUE-treated patients with risk difference ≥1.5%, randomized period		
Adverse reaction	**Percentage of patients reporting reaction**	
	JYNARQUE (n=961)	**Placebo (n=483)**
Increased urination*	**69.5**	**28.0**
Thirst†	**63.7**	**23.4**
Dry mouth	**16.0**	**12.4**
Fatigue	**13.6**	**9.7**
Diarrhea	**13.3**	**11.0**
Dizziness	**11.3**	**8.7**
Dyspepsia	**7.9**	**3.3**
Decreased appetite	**7.2**	**1.0**
Abdominal distension	**4.9**	**3.3**
Dry skin	**4.9**	**1.7**
Rash	**4.2**	**1.9**
Hyperuricemia	**3.9**	**1.9**
Palpitations	**3.5**	**1.2**

- The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 patients discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described
- In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] vs 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug

ALT=alanine aminotransferase; ULN=upper limit of normal.

*Increased urination includes micturition urgency, nocturia, pollakiuria, and polyuria.

†Thirst includes polydipsia and thirst.

Frequency of discontinuations due to AEs[11]

Discontinuations due to an adverse event were 15% (n=148) for patients taking JYNARQUE® (tolvaptan) vs 5% (n=24) taking placebo

Post hoc analysis of discontinuations due to **aquaretic AEs** in TEMPO 3:4

78% of patients treated with JYNARQUE **reported an aquaretic AE** (750 of 961 in total)

- **10%** (72) of patients **discontinued** because of an aquaretic AE
- **76%** (573) **continued treatment**

Aquaretic AEs were most pronounced shortly after initiation of JYNARQUE, with tolerability appearing to **stabilize by the month 4 visit**

The median time to discontinuation due to an aquaretic AE was **96 days** (overall range: 2–877 days)

ADPKD patients at earlier stages of disease progression may be more sensitive to aquaretic symptoms, which might influence JYNARQUE dosing and titration decisions in the future

In the TEMPO 3:4 trial, the majority of patients who experienced an aquaretic AE were able to continue treatment with JYNARQUE.

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.

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NON-PIVOTAL DATA

Long-term safety and tolerability of JYNARQUE® (tolvaptan) in patients with ADPKD was investigated in a prospective, open-label safety study[12]

Study design

Subjects who completed REPRISE, the TEMPO 4:4 open-label extension, or a prior JYNARQUE trial (TEMPO 3:4 or the phase 2 NOCTURNE trial) could enroll in this phase 3, prospective, multinational, open-label safety study.

Subjects from TEMPO 4:4 continued on the same dose of JYNARQUE in this extension. Subjects from REPRISE or prior JYNARQUE trials were initiated on JYNARQUE at a split dose of 45/15 mg/day with upward titration every 3-4 days to 60/30 or 90/30 mg/day according to tolerability. For all subjects, downward titration was permitted at the investigator's discretion.

1800 subjects were included in the analysis. The median JYNARQUE exposure during the extension was 651 days, and cumulative exposure was up to 11 years (n=28; 520 patients were on JYNARQUE ≥7.5 years). Assessments included monthly liver enzyme testing during the first 18 months of tolvaptan exposure and every 3 months thereafter. Additionally, subjects were asked about adverse events at each monitoring visit.

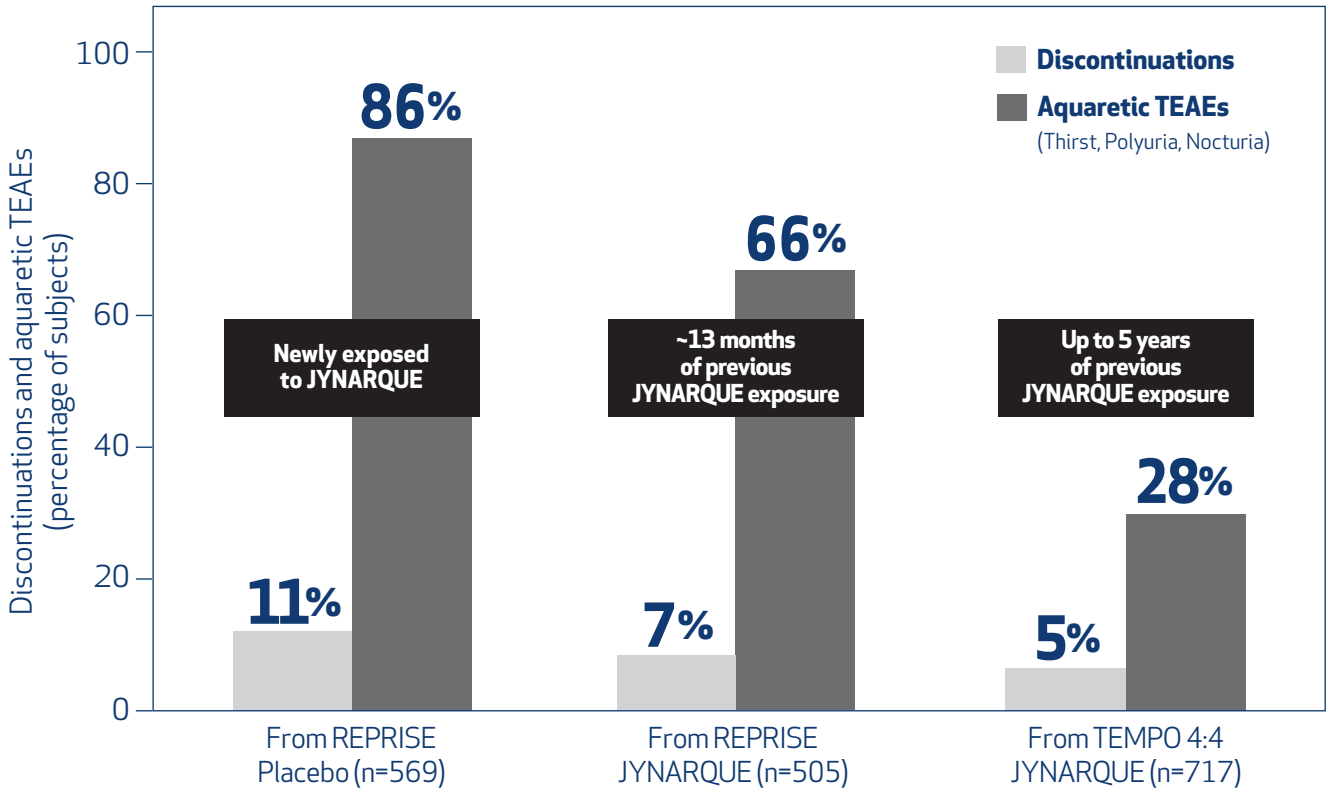
The results from long-term safety analysis were consistent with the known safety profile of JYNARQUE and support the current LFT monitoring protocols included within the Tolvaptan for ADPKD Shared System REMS. No new safety signals were detected.

LFT=liver function tests.

> What is encouraging is that discontinuations due to aquaretic side effects were more common in newer patients in the REPRISE and TEMPO 4:4 trials, **but discontinuations and aquaretic side effects decreased with longer exposure to JYNARQUE.**

Dr Christopher Kwoh

Aquaretic treatment-emergent adverse events (TEAEs) decreased with longer exposure to JYNARQUE® (tolvaptan)



SELECT IMPORTANT SAFETY INFORMATION:

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.

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Tips for starting your patient on JYNARQUE® (tolvaptan)

Working closely with your patients and setting expectations can help motivate them to stay on track throughout treatment

As part of patient counseling, review the JYNARQUE Medication Guide with every patient.

These peer-reviewed tips can help patients manage aquaretic AEs:

Reducing sodium and protein intake may help reduce urine volume[13-15]

Take a water bottle everywhere you go to stay hydrated, and try to stay away from drinks with high sugar content[13]

Plan ahead to find the restrooms near where you'll be

Take the first JYNARQUE dose upon waking up and the second dose exactly 8 hours later, and you may be able to reduce the need to wake up to urinate[13]

If the patient understands that aquaretic AEs mean the medication is working, it can help in the onboarding process when starting treatment.

Connect your patients with a Peer Mentor over the phone or video to help them get answers to questions, share thoughts, and get personal support

Topics discussed may include:

- ❑ Treatment with JYNARQUE® (tolvaptan)
- ❑ Side effects of JYNARQUE
- ❑ Treatment and the workplace
- ❑ Communication with family and friends

Scan the code or visit
jynarque.com/adpkd-peer-mentor-program
to sign up your patient

> **I was able to schedule a Peer Mentor call, and it was helpful.** It was interesting to hear someone else's story to understand the challenges and expectations I may have for my treatment.

Erika
Real patient living with ADPKD

This patient was compensated for their time. The patient image reflects their health status at the time the photo was taken.

SELECT IMPORTANT SAFETY INFORMATION:

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.

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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**.

Understanding and managing aquaretic AEs while your patients are on JYNARQUE® (tolvaptan)

HELP YOUR PATIENTS UNDERSTAND:

- The relationship between aquaretic AEs and the mechanism of action for JYNARQUE
- What to expect while on treatment with JYNARQUE in relation to aquaretic AEs
- Tips for starting JYNARQUE

> **The aquaretic effect may become more tolerable over time.** This tells us that we need to be more proactive in terms of coaching our patients on how to manage the aquaretic side effects—**and, based on my experience, for many patients, aquaretic effects can be managed.**

Dr Christopher Kwoh

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References: 1. Chapin HC, Caplan MJ. *J Cell Biol*. 2010;191(4):701–710. **2.** Boertien WE, Mejier E, Li J, et al. *Am J Kidney Dis*. 2013;61(3):420–429. **3.** Patel V, Chowdhury R, Igarashi P. *Curr Opin Nephrol Hypertens*. 2009;18(2):99-106. **4.** Yamaguchi T, Pelling JC, Ramaswamy NT, et al. *Kidney Int*. 2000;57(4):1460–1471. **5.** Higashihara E, Torres VE, Chapman AB, et al; for the TEMP042 and 156-05-002 Study Investigators. *Clin J Am Soc Nephrol*. 2011;6(10):2499-2507. **6.** Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **7.** Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med*. 2012;367(25):2407-2418. **8.** Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. **9.** Torres VE, Meijer E, Bae KT, et al. *Am J Kidney Dis*. 2011;57(5): 692-699. **10.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **11.** Devuyst O, Chapman AB, Shoaf SE, Czerwiec FS, Blais JD. *Kidney Int Rep*. 2017;2(6):1132-1140. **12.** Torres VE, Chapman AB, Devuyst O, et al. *Clin J Am Soc Nephrol*. 2020;31;16(1):48-58. **13.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **14.** Kramers BJ, van Gastel MDA, Boertien WE, Meijer E, Gansevoort RT. *Am J Kidney Dis*. 2019;73(3):354-362. **15.** Côté G, Asselin-Thompstone L, Mac-Way F, et al. *Int Urol Nephrol*. 2020;52(2):343-349.

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