An evidence-based answer to a

common clinical question about JYNARQUE® (tolvaptan)

How do I know JYNARQUE is "working" in my patients?

Is it physiologically active?

Is it slowing disease progression?

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**

Please see **IMPORTANT SAFETY INFORMATION** on pages 8–9.

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

JYNARQUE® (tolvaptan) has demonstrated effectiveness in slowing kidney function decline in the 2 largest clinical trials of over 2800 patients with ADPKD across CKD stages 1–4[1-3]

TEMPO 3:4 Trial[1]

A 36-month trial of patients with CKD stages 1, 2, and 3

The primary endpoint was the annual rate of change in the total kidney volume. The third endpoint was the rate of kidney function decline (slope of eGFR) during treatment.

REPRISE Trial[2]

A 12-month trial of patients with CKD late stage 2 to early stage 4

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.

Because JYNARQUE is a long-term treatment, reductions in eGFR decline may take time to be clinically evident

Please see pages 6–7 for additional information on pivotal trials.

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

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate.

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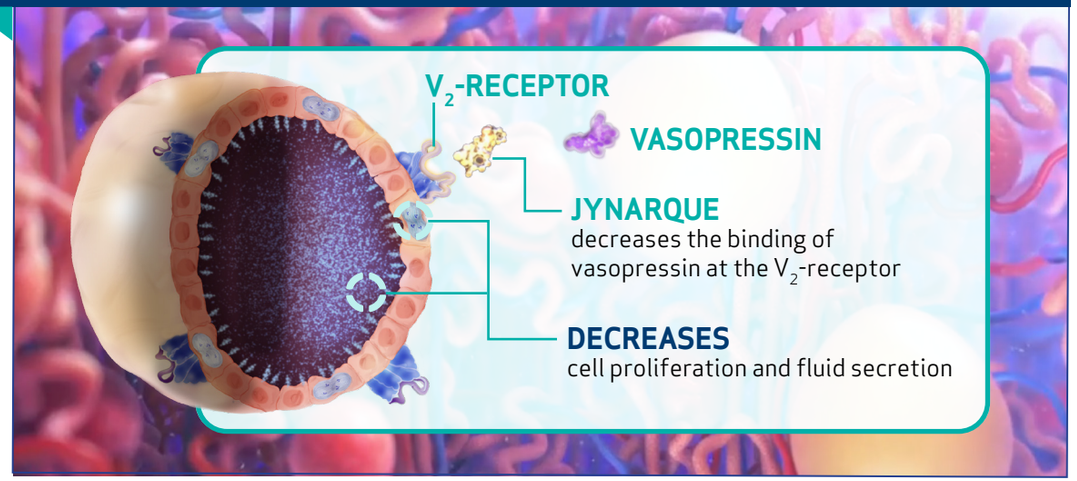
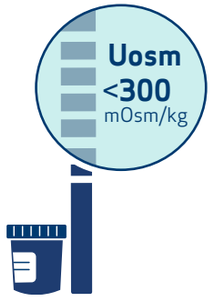
JYNARQUE® (tolvaptan) is a selective vasopressin V_2-antagonist

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



Changes in urine osmolality reflect activity of JYNARQUE in the kidney



- In the early dose-finding studies of tolvaptan for ADPKD, Uosm was chosen as the biomarker of V_2-receptor inhibition[4,5]
  - Efficacy was defined by the capacity to suppress the action of vasopressin on the kidney, defined by the capacity to achieve a sustained Uosm of <300 mOsm/kg[4,5]
- If a patient on JYNARQUE experiences a decrease in urine osmolality (sustained Uosm <300 mOsm/kg), it suggests that JYNARQUE is inhibiting the binding of vasopressin at the V_2-receptor in the kidney[4]
- A decrease in Uosm to <300 mOsm/kg results from an increase in free water clearance and resultant excretion of more dilute urine

In a post hoc analysis of data from TEMPO 3:4, patients with a greater suppression in Uosm experienced a significant reduction in the occurrence of clinical progression events (worsening renal function and kidney pain)[6]

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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There are a number of ways to assess the impact of JYNARQUE® (tolvaptan) on disease progression

Total kidney volume

- Physicians can obtain MRI or CT scan to measure TKV every 3–5 years to assess whether the rate of TKV growth compares with that anticipated from the initial imaging class assigned to the patient[7]
- If a patient's rate of TKV growth slows markedly, they may shift to a lower Mayo imaging classification (eg, from 1E to 1D)[8]

POST HOC EXPLORATORY ANALYSIS[8]
Shifting to a lower Mayo imaging classification

In a post hoc exploratory analysis of data from patients in the JYNARQUE arm (n=741) of TEMPO 3:4 with data available at 36 months[5]:

15%	79%	6%
SHIFTED TO A LOWER MAYO CLASSIFICATION*	STAYED THE SAME*	SHIFTED TO A HIGHER MAYO CLASSIFICATION*
vs 5% in the placebo arm (N=416)	vs 82% in the placebo arm (N=416)	vs 12% in the placebo arm (N=416)

Patients treated with JYNARQUE were[8]

3x

AS LIKELY TO SHIFT TO A LOWER MAYO CLASS

than those treated with placebo (15% vs 5%)[8]

*Compared with Mayo classification at baseline.

eGFR decline

Monitoring the rate of eGFR decline during JYNARQUE treatment can be used for reassurance that the rate of decline is less than anticipated according to the Mayo imaging class.[7]

Mayo imaging classification[9]

Mayo imaging class	1A	1B	1C	1D	1E
Estimated slope of change in eGFR	−0.23	−1.33	−2.63	−3.48	−4.78
Risk for eGFR decline	Low risk	Intermediate risk	High risk	High risk	High risk

eGFR units=mL/min/1.73 m^2/yr.

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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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In TEMPO 3:4, JYNARQUE® (tolvaptan) decreased the relative rate of ADPKD-related composite events by 13.5%*

The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of [1]:

COMPONENT 1	COMPONENT 2	COMPONENT 3	COMPONENT 4
Worsening kidney function	**Medically significant kidney pain**	**Worsening hypertension**	**Worsening albuminuria**
	Pain requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic, or surgical interventions[8]		

36% reduction
in the risk of worsening kidney pain events
(HR 0.64; 95% CI, 0.47 to 0.89)

The results were driven by effects on worsening kidney function and kidney pain events. In contrast, tolvaptan had no effect on progression of either hypertension or albuminuria.

*44 versus 50 events per 100 person-years of follow-up. HR, 0.87; 95% CI, 0.78 to 0.97; *P*=0.0095.

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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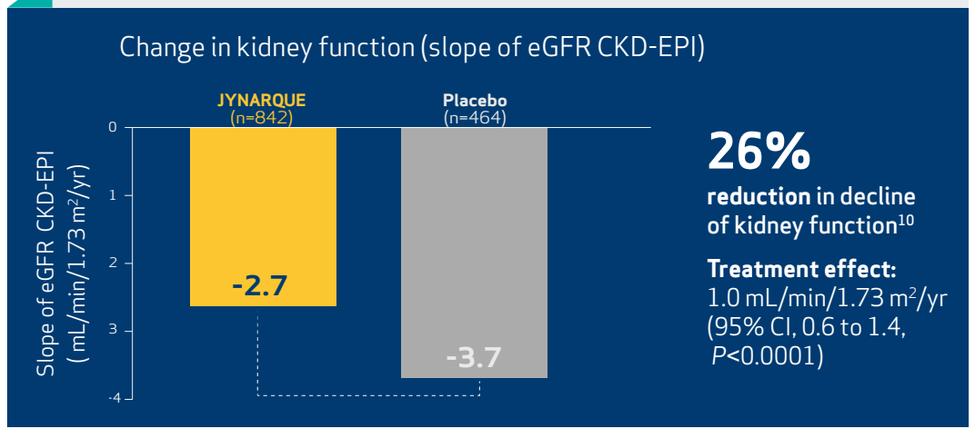
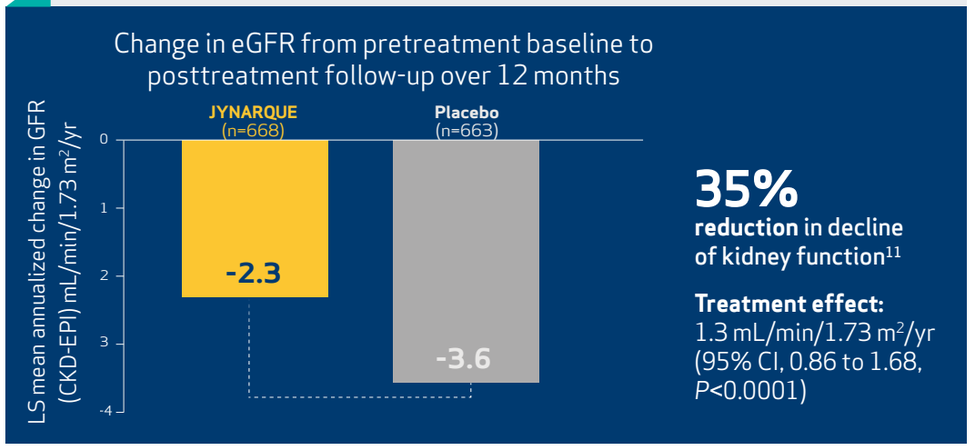
The TEMPO 3:4 and REPRISE trials showed JYNARQUE® (tolvaptan) effectiveness in slowing kidney function decline in ADPKD over a broad range of CKD stages[1,2]

TEMPO 3:4 Trial[1]
A 36-month trial of patients with CKD Stages 1, 2, and 3



TEMPO 3:4 met its prespecified primary endpoint of 3-year change in TKV ($P<0.0001$). The difference in TKV between treatment groups mostly developed within the first year, at the earliest assessment, with little further difference seen in years 2 and 3. In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received JYNARQUE and the difference between the groups in TKV was not maintained. Tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment.

REPRISE Trial[2]
A 12-month trial of patients with CKD late Stage 2 to early Stage 4



CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; CI=confidence interval; LS=least squares.

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Clinical Safety Profile of JYNARQUE® (tolvaptan)

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

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

- 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, polyuria.
†Thirst includes polydipsia and thirst.

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INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

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IMPORTANT SAFETY INFORMATION (CONT'D)

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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.**

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

Assessing the impact of JYNARQUE in clinical practice

If a patient on JYNARQUE experiences a decrease in urine osmolality (sustained Uosm <300 mOsm/kg), it suggests that JYNARQUE is inhibiting the binding of vasopressin at the V_2-receptor in the kidney.[4]

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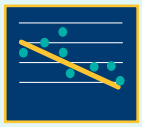

Monitoring the rate of eGFR decline during JYNARQUE treatment can be used for reassurance that the rate of decline is less than anticipated according to the Mayo imaging class.[7]

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References: 1. Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med*. 2012;367(25):2407-2418. **2.** Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. **3.** Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **4.** Higashihara E, Torres VE, Chapman AB, et al; for the TEMPO$_{4}$ [2] and 156-05-002 Study Investigators. *Clin J Am Soc Nephrol*. 2011;6(10):2499-2507. **5.** Shoaf SE, Chapman AB, Torres VE, Ouyang J, Czerwiec FS. *J Clin Pharmacol*. 2017;57(7):906-917. **6.** Devuyst O, Chapman AB, Gansevoort RT, et al. *J Am Soc Nephrol*. 2017;28(5):1592-1602. **7.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **8.** Data on file. JYN-114. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **9.** Irazabal MV, Blais JD, Perrone RD, et al. *Kidney Int Rep*. 2016;1(4):213-220. **10.** Data on file. JYN-011. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **11.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD.

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September 2021 10US21EBP0219