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

Is there a benefit in using JYNARQUE in ADPKD patients with CKD stage 4 or an estimated glomerular filtration rate (eGFR) <25 mL/min/1.73 m^2?

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 6–7.

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

JYNARQUE® (tolvaptan) slowed eGFR decline in subjects with ADPKD in pivotal trials, but the effects in subjects with eGFR of 15–24 mL/min/1.73 m^2 were not investigated[1]

REPRISE Trial[1]
N=1519

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

Evaluated the impact of JYNARQUE on kidney function

eGFR Inclusion Criteria

Subjects younger than 56 years
eGFR 25–65 mL/min/1.73 m^2

Subjects 56 to 65 years
eGFR 25–44 mL/min/1.73 m^2, plus eGFR decline >2 mL/min/1.73 m^2

In the randomized period of REPRISE, the change of eGFR from pretreatment baseline to post-treatment follow-up was −2.3 mL/min/1.73 m^2/year with JYNARQUE (n=668) as compared with −3.6 mL/min/1.73 m^2/year with placebo (n=663), corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year (95% CI, 0.86 to 1.68, *P*<0.0001).

Understanding the use of JYNARQUE in patients with CKD stage 4 in pivotal clinical trials

- In REPRISE, there were 267 patients with CKD stage 4 (eGFR 25–29 mL/min/1.73 m^2) at baseline[1]
  - Prespecified subgroup analyses showed a beneficial effect of JYNARQUE across this subgroup of patients (treatment effect of 0.81 mL/min/1.73 m^2; *P*=0.02)

The Full Prescribing Information for JYNARQUE does not specify a lower eGFR limit for eligible patients, but use of the medication is contraindicated in patients with anuria.

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

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

The effects of JYNARQUE® (tolvaptan) in patients with baseline eGFR of 15 to 29 mL/min/1.73 m^2 were retrospectively investigated in a post hoc analysis[2]

STUDY DESIGN[2]

- A post hoc analysis retrospectively investigated eGFR decline in patients from the REPRISE trial who at the time of enrollment in an open-label extension (OLE) trial had a baseline eGFR of 15 to 29 mL/min/1.73 m^2
  - The analysis included data from the first 12 months of JYNARQUE therapy during the OLE
- Cohort included patients with eGFR decline with placebo in REPRISE and JYNARQUE in OLE with eGFR of 15 to 29 mL/min/1.73 m^2

Patient subsets

Subset 1
N=148
Received placebo in REPRISE and began JYNARQUE in OLE*

Subset 2
N=148
Received JYNARQUE in REPRISE and in OLE and matched to REPRISE placebo-treated subjects

Annualized eGFR slopes were compared within the subsets

*Patients served as self-controls.

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.

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

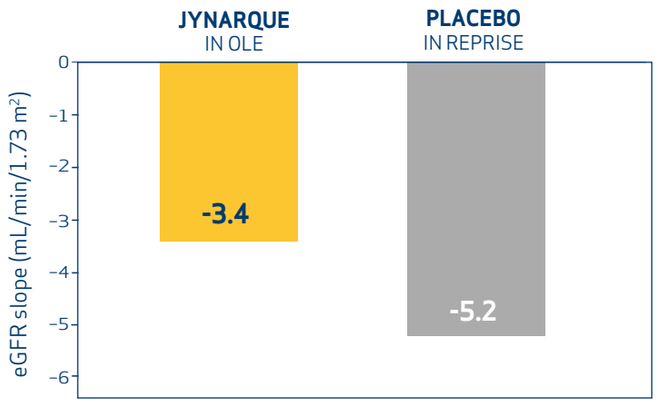
POST HOC ANALYSIS

JYNARQUE® (tolvaptan) in ADPKD patients with very low kidney function[2]

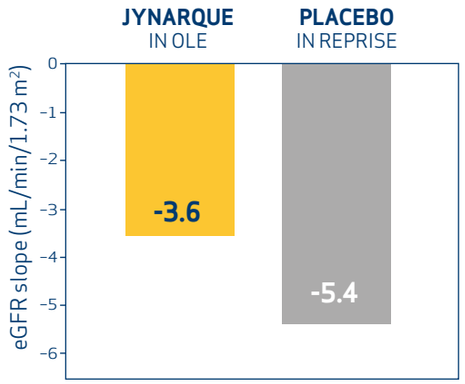
Comparative mean annualized eGFR slope[2]

mL/min/1.73 m²

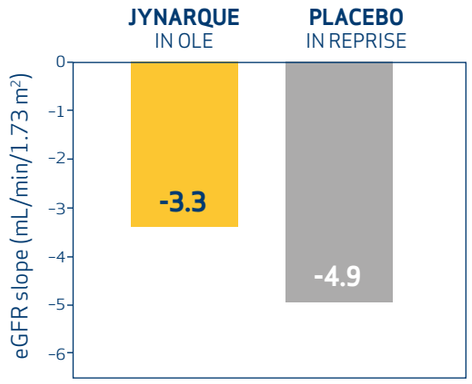
Baseline eGFR 15–29 mL/min/1.73 m²
n=148



Baseline eGFR 15–24 mL/min/1.73 m²
n=75



Baseline eGFR 25–29 mL/min/1.73 m²
n=73



Treatment effect was maintained in REPRISE JYNARQUE subjects continuing JYNARQUE in OLE

Initiating or maintaining JYNARQUE therapy delayed eGFR decline in subjects with baseline eGFR of 15 to 24 and 25 to 29 mL/min/1.73 m²

Although these data support the use of JYNARQUE in patients with more severe impairments in kidney function, expert opinion notes that patients with higher eGFR will benefit the most from therapy[3,4]

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

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.

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

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

- **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**

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

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).

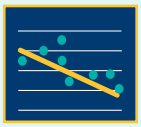
Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING.**

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

Exploring the benefit of JYNARQUE in patients with eGFR <25 mL/min/1.73 m^2

Although JYNARQUE slowed eGFR decline in subjects with ADPKD in the REPRISE trial, the effects of JYNARQUE in subjects with eGFR of 15 to 24 mL/min/1.73 m^2 were not investigated.[1]

The Full Prescribing Information for JYNARQUE does not specify a lower eGFR limit for eligible patients, but use of the medication is contraindicated in patients with anuria.



A post hoc analysis retrospectively investigated the impact of JYNARQUE on eGFR decline in patients from the REPRISE trial with very low eGFR.[2]

Results of this post hoc analysis suggest that initiating or maintaining JYNARQUE therapy delayed eGFR decline in subjects with baseline eGFR of 15 to 29 mL/min/1.73 m^2.[2]

Although these data support the use of JYNARQUE in patients with more severe impairments in kidney function, expert opinion notes that patients with higher eGFR will benefit the most from therapy.[3,4]

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**

References: 1. Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. **2.** Torres VE, Gansevoort RT, Perrone RD, et al. *Kidney Int Rep*. 2021;6(8):2171-2178. **3.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **4.** Chebib FT, Torres VE. *Am J Kidney Dis*. 2021;78(2):282-292.

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

Otsuka
Otsuka America Pharmaceutical, Inc.

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

February 2023 10US23EBP0047