Data in Patients >55 Years

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

Can I initiate JYNARQUE in older patients (>55 years) with ADPKD?

What is the risk-to-benefit profile of JYNARQUE treatment in older patients?

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 Program**

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

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 the REPRISE clinical trial[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 in 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).

In REPRISE subgroup analyses, a treatment effect of JYNARQUE was not observed in patients older than 55 years (N=200). These results, however, should be viewed in context of the relatively slow progression of disease observed in placebo-treated older patients (2.34 mL/min/1.73 m^2 decline vs 4.60 mL/min/1.73 m^2 among patients aged ≤55 years), and the relatively short duration of follow-up.[1,2]

There is no upper age limit within the Full Prescribing Information for JYNARQUE.

US expert opinion suggests that therapy with JYNARQUE may be continued until reaching the need for kidney replacement therapy regardless of age.[3]

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; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; REPRISE=Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy.

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

The clinical benefit of JYNARQUE® (tolvaptan) in patients aged >55 years were retrospectively investigated from a pooled database[2]

Study Overview

This post hoc pooled subgroup analysis aimed to assess the long-term effect of JYNARQUE compared with SOC on kidney function in older patients (aged >55 years) with ADPKD with CKD Stages 3 and 4

- Pooled database was constructed with data from 11 studies
- Data across studies were linked longitudinally to allow long-term follow-up
- Subjects on JYNARQUE were matched 1:1 with subjects on SOC based on baseline CKD stage, sex, age, and eGFR
- The annual rate of change in eGFR was estimated using CKD-EPI*

MATCHED ANALYSIS STUDY POPULATION

Subjects who were randomized to JYNARQUE from REPRISE (n=95†) were matched 1:1 with SOC subjects (n=53 from HALT-PKD and n=42 from OVERTURE):

Mean age:	Age range:	CKD stage 3:	CKD stage 4:
60.2 years	**56 to 65 years**	**69%**	**31%**

2.4 years **Mean duration of JYNARQUE with a mean gap of 29 days between REPRISE and the extension study**

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.

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; HALT-PKD=HALT Progression of Polycystic Kidney Disease; OVERTURE=Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease; SOC=standard of care.

*Estimation was done using a mixed model that included treatment, time, baseline eGFR, and time-by-treatment interaction.

†Who were randomized to JYNARQUE treatment in the REPRISE clinical trial were included in the matched analysis.

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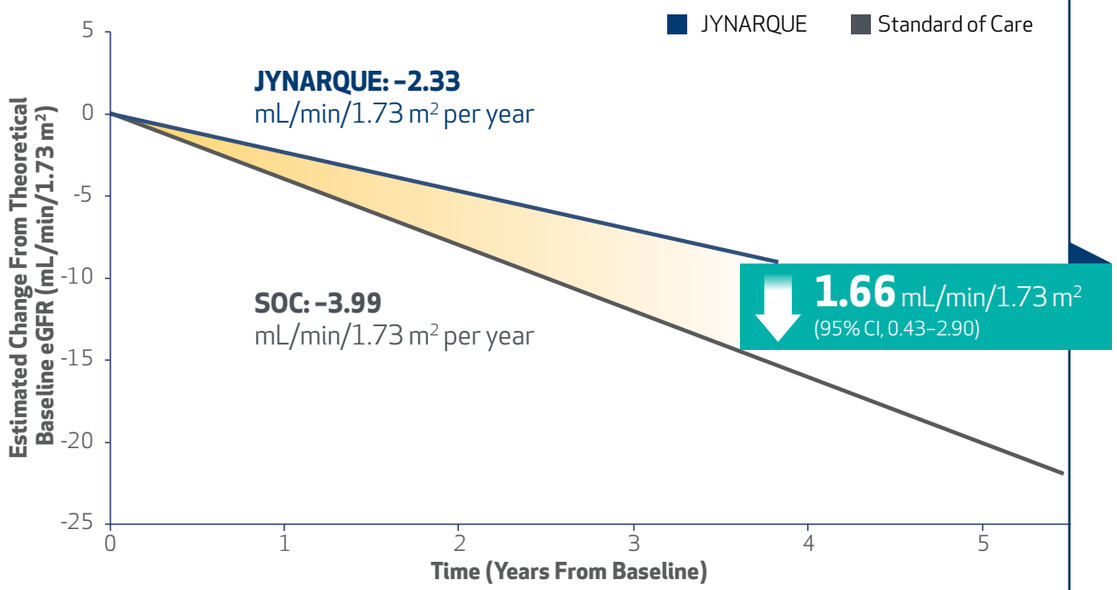
POST HOC RETROSPECTIVE ANALYSIS

Effect of JYNARQUE® (tolvaptan) in ADPKD patients >55 years[2]*

Estimated annual rate of eGFR change in the matched analysis set



The annual rate of change of eGFR was estimated using a mixed model that included treatment, time, baseline eGFR, and time-by-treatment interaction as fixed effects and subject-specific intercept and slope (for time) as random effects with an unstructured variance-covariance matrix. Data after 5.5 years were excluded.

JYNARQUE reduced the annual rate of eGFR decline by 1.66 mL/min/1.73 m²

These data provide evidence to support the efficacy of JYNARQUE in patients aged 56–65 years

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.

*Who were randomized to JYNARQUE treatment in the REPRISE clinical trial were included in the matched analysis.

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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

TEMPO=Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; 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)

INDICATION

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IMPORTANT SAFETY INFORMATION

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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 use of JYNARQUE in older patients (>55 years) with ADPKD

There is no upper age limit within the Full Prescribing Information for JYNARQUE, and therapy with JYNARQUE in patients aged 55–65 years can be supported by the efficacy outcomes seen in a retrospective, pooled, long-term analysis.[2]

In the REPRISE subgroup analysis of nearly 200 patients between 56–65 years of age, a treatment effect of JYNARQUE was not observed. These results, however, should be viewed in context of the relatively slow progression of disease observed in placebo-treated older patients (2.34 mL/min/1.73 m^2 decline vs 4.60 mL/min/1.73 m^2 among patients aged ≤55 years), and the relatively short duration of follow-up.[1,2]

Efficacy of JYNARQUE was retrospectively studied in ADPKD patients between ages 56 and 65. Results from the pooled analysis showed that treatment with JYNARQUE reduced annual rate of eGFR decline in these older patients.[2]

US expert opinion suggests that therapy with JYNARQUE may be continued until reaching the need for kidney replacement therapy regardless of age.[3]

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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.** Chebib FT, Zhou X, Garbinsky D, et al. Presented at: National Kidney Foundation Spring Clinical Meetings; Boston, MA. April 6–10, 2022. Abstract 350. **3.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol.* 2018;29(10):2458-2470.

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Otsuka
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