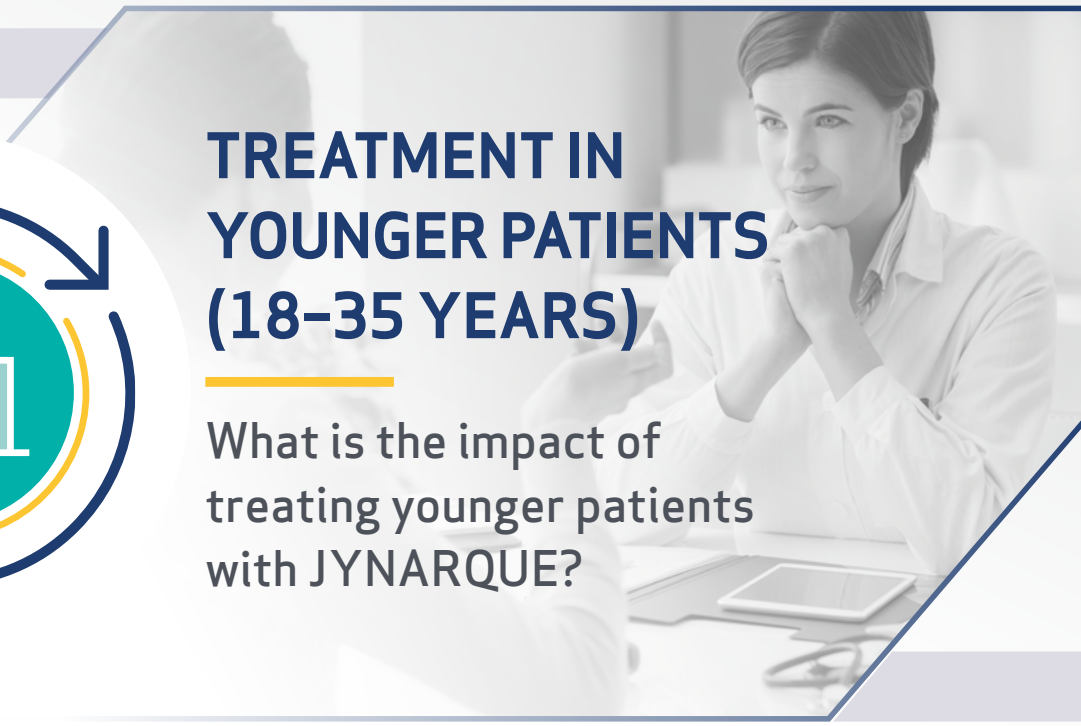
An evidence-based answer (EBA) to a

common clinical question about JYNARQUE® (tolvaptan)



TREATMENT IN YOUNGER PATIENTS (18–35 YEARS)

What is the impact of treating younger patients with JYNARQUE?

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 10–11.

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

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 in eGFR from pretreatment baseline to posttreatment follow-up, annualized by dividing each participant's treatment duration

Patients treated with JYNARQUE by CKD stage[1,2,4]

CKD stage GFR (mL/min/1.73 m²)	**Stage 1** ≥90	**Stage 2** 89–60	**Stage 3a** 59–45	**Stage 3b** 44–30	**Stage 4** 29–15
TEMPO 3:4 36-month trial, n=961	35%	48%	14%	3%	
REPRISE 12-month trial, n=681		5%	31%	44%	20%

Please see clinical trial efficacy and safety data on pages 8–9.

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; GFR=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.

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

Treatment effects of JYNARQUE® (tolvaptan) in younger patients (18–35 years)[5]

The clinical impact of JYNARQUE vs placebo in younger subjects (aged 18–35) was retrospectively assessed from a pooled database

Primary objective:

Assess treatment effect of JYNARQUE compared with standard of care (SOC)* alone on the annual rate of change of kidney function decline (eGFR) for up to 5.5 years.

Rationale:

Previous data among patients aged 18–35 years with ADPKD were limited to 3 years of follow-up in the TEMPO 3:4 study.

Limited data exist on the long-term effect of treatment with JYNARQUE on kidney function among patients aged 18–35 years. Linking patient data from multiple clinical trials and observational studies increases the duration of follow-up and facilitates evaluation of the long-term treatment effect of JYNARQUE.

CRISP=Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; HALT-PKD=HALT Progression of Polycystic Kidney Disease; OVERTURE=Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease.

*SOC in the following trials was: OVERTURE, patients were controlled for blood pressure (BP); CRISP was noninterventional; and in HALT-PKD, patients received an angiotensin-converting enzyme inhibitor (ACEi) with or without an angiotensin receptor blocker (ARB) with standard BP control.

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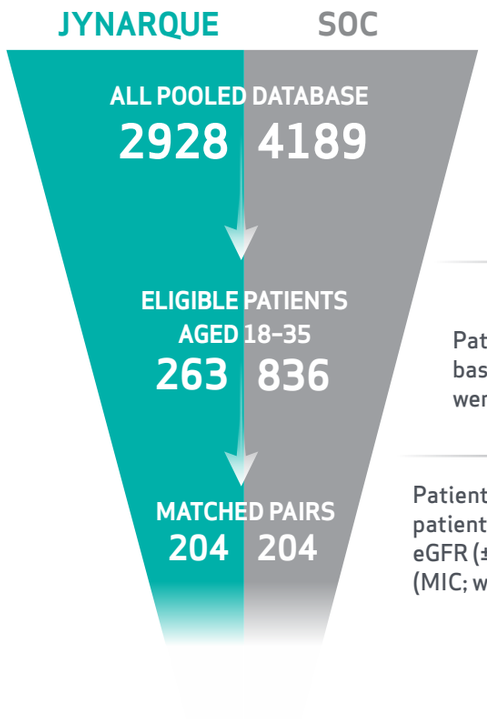
STUDY DESIGN FOR POOLED, 5.5-YEAR ANALYSIS

A pooled database consisting of existing data from clinical trials and observational studies was used for the analysis (tolvaptan: n=2928; SOC: n=4189). Data from patients participating in multiple studies were linked longitudinally to maximize the duration of follow-up (5.5 years).[5]



The number of patients in a pooled database consisting of data from clinical trials and observational studies that were analyzed for this study. Studies included:

- **JYNARQUE:** TEMPO 3:4, TEMPO 4:4, REPRISE, and long-term, open-label phase 3 safety study
- **Natural history or SOC:** CRISP, HALT-PKD Study A, HALT-PKD Study B, OVERTURE

Patients aged 18–35 years at baseline who had baseline and ≥1 postbaseline eGFR assessment were eligible for inclusion

Patients in the tolvaptan cohort were matched 1:1 with patients in the SOC cohort on CKD stage, sex, age (± 2 years), eGFR (± 5 mL/min/1.73 m^2), and Mayo Imaging Classification (MIC; when available)

THE ANALYSIS COMPRISED 3 STEPS

1. **MATCH** patients 1:1 from the JYNARQUE and SOC cohorts to minimize confounding
2. **ESTIMATE** the effects of JYNARQUE vs SOC on kidney function decline over 5.5 years of follow-up*
3. **EXTRAPOLATE** predicted kidney function decline to 35 years†

- Although the ability of JYNARQUE to slow the rate of eGFR decline has been demonstrated in clinical trials, to date, no outcomes-driven clinical trials have been conducted to document the impact of JYNARQUE on time to ESKD
- The absence of prospectively collected trial data examining the impact of JYNARQUE on time to ESKD is due to the large number of patients and long duration of follow-up that would be required for adequate statistical analysis
- In the absence of such data, predicted eGFR is extrapolated out to 35 years by assuming the same relationship as seen in the first 5.5 years and a baseline eGFR of 93 mL/min/1.73 m^2

ESKD=end-stage kidney disease.

*The annual rate of change of eGFR was estimated using a mixed model that included time (continuous), treatment, baseline eGFR, time-by-treatment interaction, and patient-specific slopes and intercepts with an unstructured variance-covariance matrix.

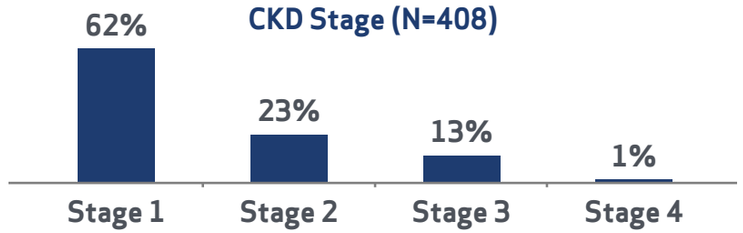
†Extrapolations of predicted eGFR values for up to 35 years were performed assuming the same relationship as in the first 5.5 years and a baseline eGFR of 93 mL/min/1.73 m^2.

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

PATIENT CHARACTERISTICS OF THE MATCHED COHORT[5]

	JYNARQUE® (tolvaptan) (N=204)	SOC (N=204)
Age, years, mean (SD)	**30.2** (4.1)	**30.1** (4.1)

CKD stage characteristics[5]



Other characteristics

Sex (N=408):
55% male
45% female

Mayo Imaging Classification* (N=360):
1C: 26%
1D: 37%
1E: 37%

eGFR (mL/min/1.73 m^2 [mean (SD)]):

JYNARQUE (n=204)
92.7 (25.1)

SOC (n=204)
92.7 (25.3)

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.

*MIC was available for 180 (88.2%) of the matched patients in the JYNARQUE cohort.
Percentages may not add up to 100% because of rounding.

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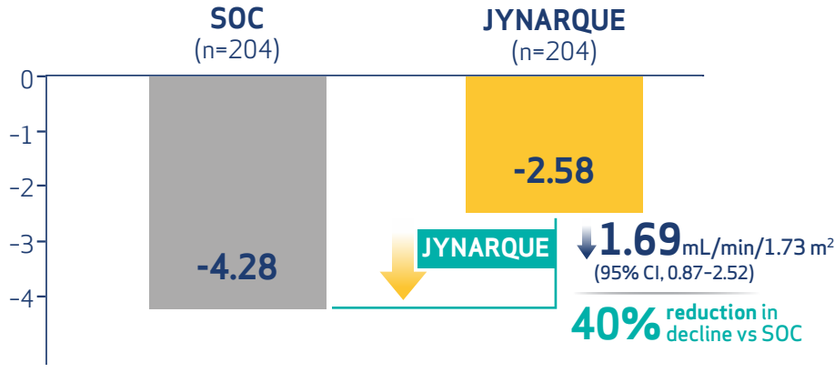
Impact of JYNARQUE® (tolvaptan) treatment in younger patients[5]

Estimated annual rate of change in eGFR*
(mL/min/1.73 m²)



Mean duration of JYNARQUE exposure: 4.4 years (SD=2.7)

Estimated eGFR change from baseline over time*

Cumulative reduction in decline of eGFR (JYNARQUE – SOC)

Year 1	Year 3	Year 5
1.69 (95% CI, 0.87–2.52)	5.09 (95% CI, 2.61–7.55)	8.47 (95% CI, 4.35–12.59)

Treatment in younger patients (18–35 years) with JYNARQUE may produce notable differences in the rate of change in eGFR over time.

SELECT IMPORTANT SAFETY INFORMATION:

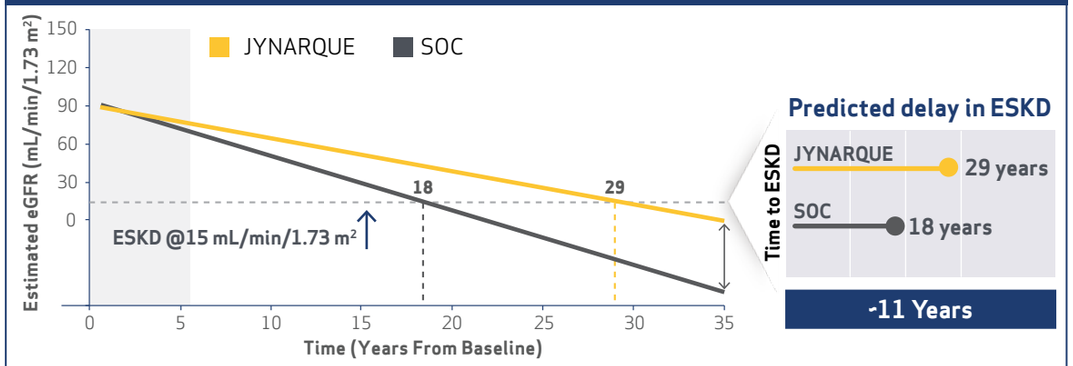
Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because 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.

*Change from baseline eGFR was estimated based on the theoretical baseline value estimated from the mixed model. Positive values of the difference indicate slower rates of decline in eGFR for the JYNARQUE cohort (values shown reflect eGFR for JYNARQUE – eGFR for SOC).

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

Extrapolation of predicted effects of JYNARQUE® (tolvaptan) on eGFR out to 35 years[5]

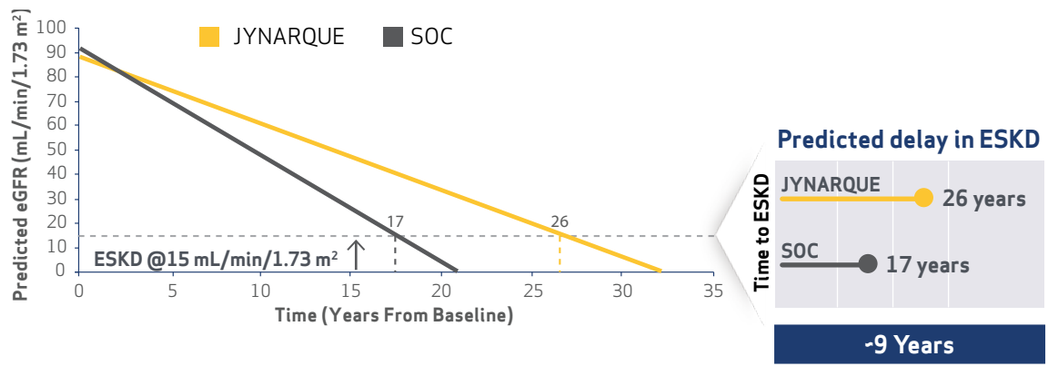
MIXED MODEL*



The extrapolations were performed using a mixed model that assumed patients had a baseline eGFR of 93 mL/min/1.73 m² and assumed maintenance of the same relationship as observed in the first 5.5 years.

Extrapolations suggest that patients receiving JYNARQUE may see a potential delay to kidney failure onset of -11 years relative to patients receiving SOC

EXTRAPOLATIONS BASED ON THE IRAZABAL EQUATION (Sensitivity Analysis)†



Irazabal equation[7] yielded a similar result, with a projected potential delay of -9 years in time to onset of kidney failure for patients receiving JYNARQUE vs SOC

The prediction intervals for the estimates were wide, indicating large variability. Therefore, these projections need to be interpreted with caution.

*Extrapolations were based on the mixed model including treatment, time, treatment-by-time interaction, and baseline eGFR for a patient with baseline eGFR of 93 mL/min/1.73 m². 95% prediction intervals were based on the empirical best linear unbiased predictor.

†Extrapolation for SOC was based on the Irazabal equation for a predicted mean based on the sample means/proportions of the matched analysis set. The coefficients of the treatment (–3.90) and time-by-treatment interaction (1.69) terms estimated from the mixed model were added to predict the eGFR means for JYNARQUE.

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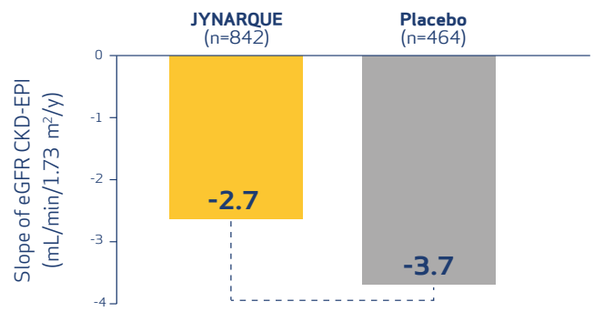
The TEMPO 3:4 and REPRISE trials showed JYNARQUE® (tolvaptan) effectiveness in slowing kidney function decline in ADPKD over a broad range of CKD stages[1,2]

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

Change in kidney function (slope of eGFR CKD-EPI)



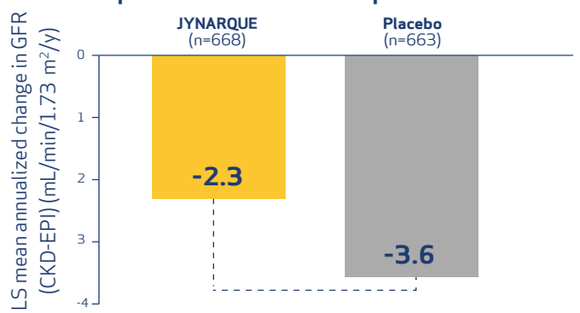
26%
reduction in decline of kidney function[8]

Treatment effect:
1.0 mL/min/1.73 m^2/y (95% CI, 0.6 to 1.4, *P*<0.0001)

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. JYNARQUE 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

Change in eGFR from pretreatment baseline to posttreatment follow-up over 12 months



35%
reduction in decline of kidney function[9]

Treatment effect:
1.3 mL/min/1.73 m^2/y (95% CI, 0.86 to 1.68, *P*<0.0001)

CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; LS=least squares; TKV=total kidney volume.

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

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 2 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

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

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 JYNARQUE 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:** JYNARQUE 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 Impact of Treatment in Younger Patients (18–35 Years) With JYNARQUE® (tolvaptan)

Clinical impact of JYNARQUE in younger patients (18–35 years) with ADPKD and early-stage CKD (stages 1–3)

JYNARQUE slowed eGFR decline in subjects with ADPKD in pivotal trials. However, previous long-term data for the subgroup of patients aged 18–35 years with ADPKD were limited to 3 years of follow-up in the TEMPO 3:4 study[1,2]

The clinical impact of JYNARQUE vs placebo in younger subjects (aged 18–35) was retrospectively assessed from a pooled database[5]

- Data from patients participating in multiple studies were linked longitudinally

JYNARQUE slowed the estimated annual rate of eGFR decline by 1.69 mL/min/1.73 m^2 per year compared with SOC[5]

- This difference represented a 40% reduction in eGFR decline for JYNARQUE compared with SOC
- The change from baseline eGFR was estimated based on the theoretical baseline value estimated from the mixed model

Extrapolations suggest a potential delay in kidney failure. For patients receiving JYNARQUE, the projected potential long-term benefit is a delay in kidney failure onset (eGFR=15 mL/min/1.73 m^2) of ~11 years relative to patients receiving SOC[5,*]

*Extrapolations were based on the mixed model including treatment, time, treatment-by-time interaction, and baseline eGFR for a patient with baseline eGFR of 93 mL/min/1.73 m^2. 95% prediction intervals were based on the empirical best linear unbiased predictor. The prediction intervals for the estimates were wide, indicating large variability. Therefore, the data should be interpreted with caution.

Treatment with JYNARQUE may produce notable differences in the rate of change in eGFR over time

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

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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**

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. TOL-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **4.** Torres VE, Higashihara E, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *Clin Am Soc Nephrol*. 2016;11(5):803-811. **5.** Chebib FT, Dahl N, Zhou X, et al. Poster presented at: PKD Connect 2023; June 23-25, 2023; Denver, CO. **6.** Chebib FT, Perrone RD, Chapman AB, et al. *J Am Soc Nephrol*. 2018;29(10):2458-2470. **7.** Irazabal MV, Rangel JL, Bergstralh EJ, et al. *J Am Soc Nephrol*. 2015;26(1):160-172. **8.** Data on file. TOL-011. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **9.** Data on file. TOL-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD.

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

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