Long-Term Data

An evidence-based answer to a

common clinical question about JYNARQUE® (tolvaptan)

Are there any data showing long-term effects (safety and benefits) of 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 Tolvaptan for ADPKD Shared System REMS**

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Please see **IMPORTANT SAFETY INFORMATION** on pages 14–15.

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 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 11-12.

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 14-15

The long-term treatment effects of JYNARQUE® (tolvaptan)

STUDY 206 – LONG-TERM TREATMENT EFFECTS[5]

A 5.5-year retrospective, pooled, matched-control analysis of JYNARQUE in patients with ADPKD

The primary objective was to evaluate the longer-term effects of JYNARQUE on rate of change of kidney function decline and total kidney volume (TKV) in ADPKD

Limitations of the pooled analysis

- Differences between treatment groups may have affected the outcomes
  - Use of matching and multiple regression adjustment for the relative comparison helped to reduce this bias, but residual confounding possibly still exists
- Patients enrolled at different times and in clinical studies may have had differences in characteristics or lifestyle factors not reflected in baseline characteristics
- Subjects who did not perform well may have dropped off earlier, especially among observational studies. Therefore, observations after 5.5 years of follow-up were excluded to reduce potential bias caused by informative missingness

STUDY 211 – LONG-TERM SAFETY[6]

3.9 up to 11 years of total exposure of JYNARQUE in patients with ADPKD

- n=28 patients for cumulative JYNARQUE exposure of up to 11 years
- n=520 patients on JYNARQUE for 7.5 years

The primary objective was to evaluate the long-term safety and tolerability of JYNARQUE in the treatment of ADPKD

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.

Retrospective pooled longitudinal study[5]

Method and Cohort	Intervention
Pooled longitudinal analysis • 8 studies with JYNARQUE • 5 studies with SOC **Subjects with ADPKD** **JYNARQUE vs SOC*** **Follow-up over 5.5 years**	**Long-term effects of JYNARQUE on:** • **Kidney Function** • **Kidney Volume**

To control for heterogeneity in disease characteristics between JYNARQUE and SOC treatment groups, analysis populations were matched for baseline demographic and disease characteristics

The 8 JYNARQUE studies	5 studies without JYNARQUE (natural history or SOC*)
• **TEMPO 2:4** (n=46 JYNARQUE) • **TEMPO 3:4** (n=961 JYNARQUE) • **Phase 1 trial** (n=20 JYNARQUE) • **Phase 2 trial** (n=29 JYNARQUE) • **NOCTURNE** (n=133 JYNARQUE) • **REPRISE** (n=1496 JYNARQUE) • **TEMPO 4:4** (n=1083 JYNARQUE) • **Long-term, open-label, phase 3 safety study** (n=1803 JYNARQUE)	• **CRISP** (n=241 SOC) • **HALT-PKD, Studies A and B** (n=1044 SOC) • **OVERTURE** (n=3409 SOC) • **TEMPO 3:4** (n=484 placebo patients) • **NOCTURNE** (n=44 placebo patients)

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.

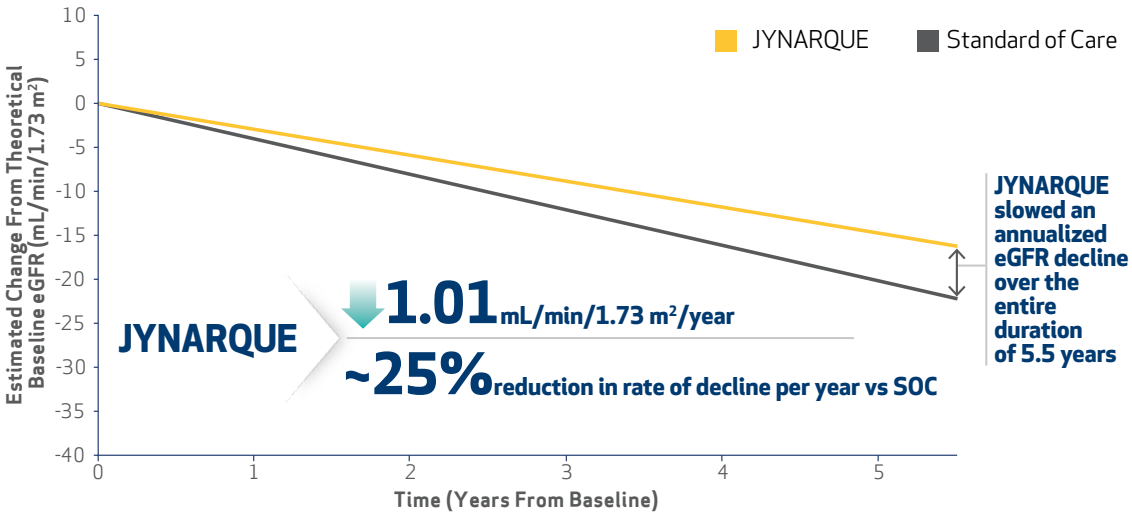
CRISP=Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; HALT-PKD=HALT Progression of Polycystic Kidney Disease; OVERTURE=Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease; SOC= standard of care.

*The SOC subjects from CRISP and HALT-PKD studies A and B were randomized to various antihypertensive regimens involving blockade of the renin-angiotensin-aldosterone system. The other SOC subjects were included from Otsuka-sponsored studies (the observational study OVERTURE and subjects randomized to placebo in TEMPO 3:4 and NOCTURNE).

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15

Retrospective pooled longitudinal analysis: decline in annualized eGFR and growth in estimated TKV over 5.5 years[5]

Change in Kidney Function



Matched analysis showed JYNARQUE slowed annualized eGFR decline

Estimated TKV (% of Baseline) at Years 1, 3, and 5

Estimated TKV(% of baseline) over time*

JYNARQUE	SOC	
97	107	1 Year
110	121	3 Years
124	138	5 Years

The difference between treatment groups was most prominent within the first year. In TEMPO 3:4, the difference was minimal in years 2 and 3. JYNARQUE had little effect on kidney size beyond what accrued during the first year of treatment*

In the matched TKV analysis sets, estimated TKV at Years 1, 3, and 5 was smaller with JYNARQUE than with SOC

*Percent change from baseline.

JYNARQUE® (tolvaptan)
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Retrospective pooled longitudinal analysis of the JYNARQUE® (tolvaptan) treatment gap[5]

A secondary objective of Study 206 was to analyze this group of patients to understand the impact of JYNARQUE treatment gaps on disease progression

Off-treatment days were primarily due to the gap between JYNARQUE titration/run-in period for subjects on placebo in REPRISE and resumption of JYNARQUE at the start of the long-term safety trial

Median off-treatment gap was 55 days

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15

Impact of the JYNARQUE® (tolvaptan) treatment gap showed direct effect in slowing the rates of eGFR and TKV growth[5]

Impact of the JYNARQUE treatment gap on disease progression

The estimated rate of eGFR decline during the JYNARQUE treatment gap was similar to the rate of decline while on SOC

−3.64 vs −3.70 mL/min/1.73 m^2 per year

The estimated rate of TKV growth during the JYNARQUE treatment gap was larger than the growth rate while on treatment

This may reflect the return of fluid to kidney cysts, in addition to continued growth after subjects interrupted JYNARQUE

Impact of the JYNARQUE treatment gap or treatment interruption supports long-term and consistent benefits of JYNARQUE

The long-term safety and tolerability of JYNARQUE® (tolvaptan) in patients with ADPKD was investigated in a prospective, open-label safety study[6]

Key Inclusion Criteria

Participants continued from:

- **REPRISE** (JYNARQUE [n=506] or placebo [n=570])

or

- **TEMPO 4:4 extension study** (JYNARQUE [n=718])

or

- **TEMPO 3:4** (JYNARQUE [n=4] or placebo [n=3])

or

- **Phase 2 trial** (JYNARQUE [n=2])

JYNARQUE (N=1800)

- 1311 (73%) of the 1800 participants had >18 months of exposure
- Median (range) of JYNARQUE exposure: 651 (1–1435) days
- Cumulative JYNARQUE exposure: up to 11 years (n=28)
  - 520 patients were on JYNARQUE for 7.5 years
  - Subjects with longest duration of exposure were from TEMPO 4:4

Safety assessment of liver function test

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15

OPEN-LABEL EXTENSION STUDY

Long-term safety assessments included monthly liver enzyme testing during the first 18 months of JYNARQUE exposure and every 3 months thereafter[6]

Safety outcome of LFT

Liver enzyme elevation	ALT (%)	AST (%)
≥3x ULN	1.6	3.5
≥5x ULN	0.7	1.8
≥10x ULN	0.3	0.9
≥20x ULN	0.2	0.3

No patient met Hy's Law criteria during the study*

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

SELECT IMPORTANT SAFETY INFORMATION:

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.

DILI=drug-induced liver injury; LFT=liver function test; ULN=upper limit of normal.

*Meeting Hy's Law criteria indicates the development of potentially severe DILI defined by:
- ALT or AST >3 times the ULN and total bilirubin >2 times the ULN in the absence of cholestasis (ALT <2 times the ULN)[1]

JYNARQUE® (tolvaptan)
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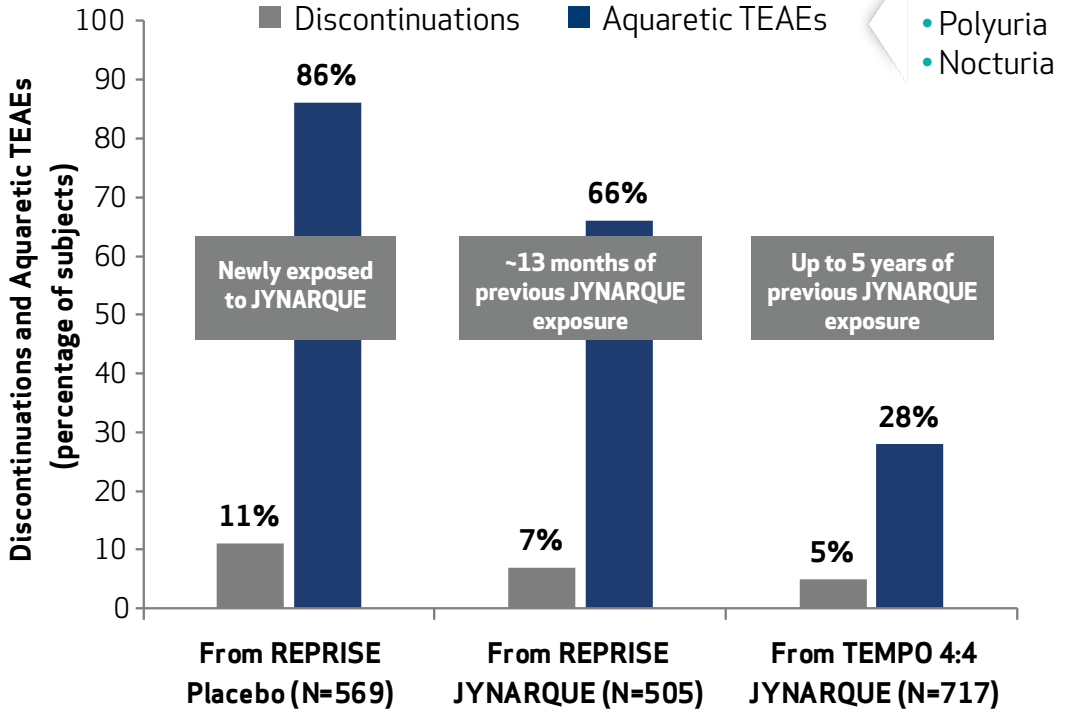
Discontinuations and aquaretic treatment emergent adverse events (TEAEs) decreased with longer exposure to JYNARQUE® (tolvaptan)[6]

Discontinuations due to aquaretic TEAEs were more common in newer patients



Discontinuations and aquaretic TEAEs decreased with longer exposure to JYNARQUE

SELECT IMPORTANT SAFETY INFORMATION:

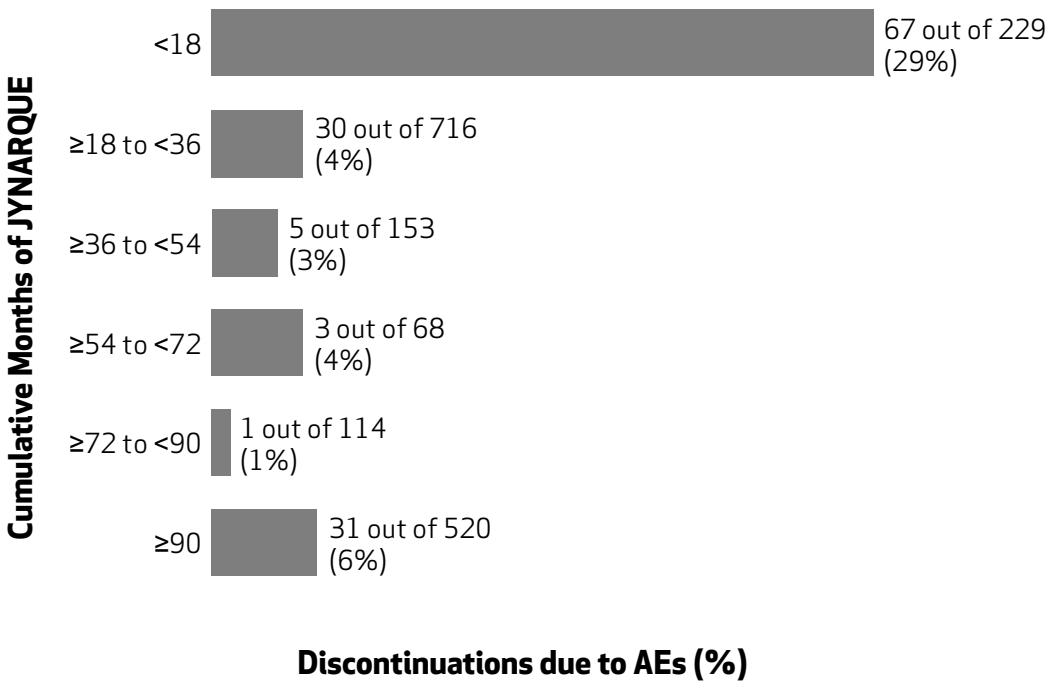
Other Drug Interactions:

- **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

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15

Discontinuations decreased with longer exposure to JYNARQUE® (tolvaptan)[6]

Most discontinuations due to AEs occurred in the first 18 months



Frequency of AEs decreased with longer exposure

Percentages are based on the number of subjects treated for each cumulative exposure period

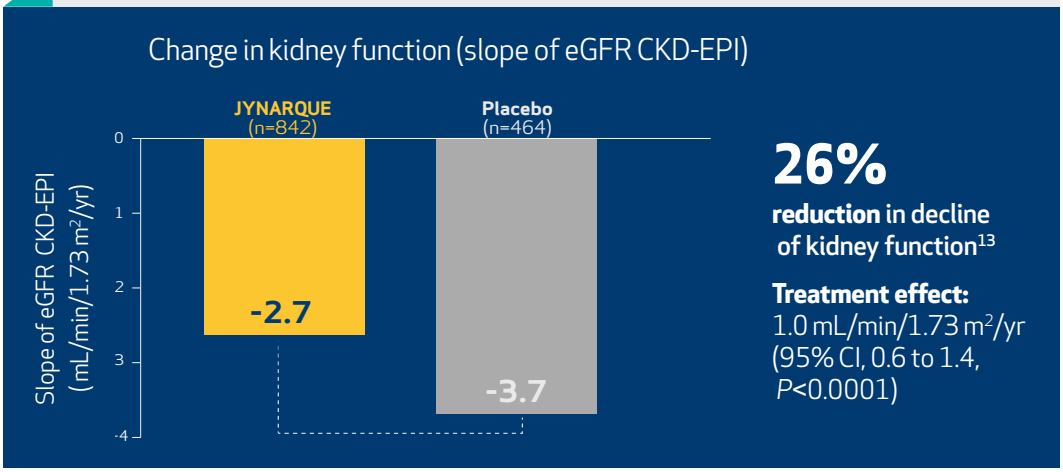
SELECT IMPORTANT SAFETY INFORMATION:

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.

AE=adverse event.

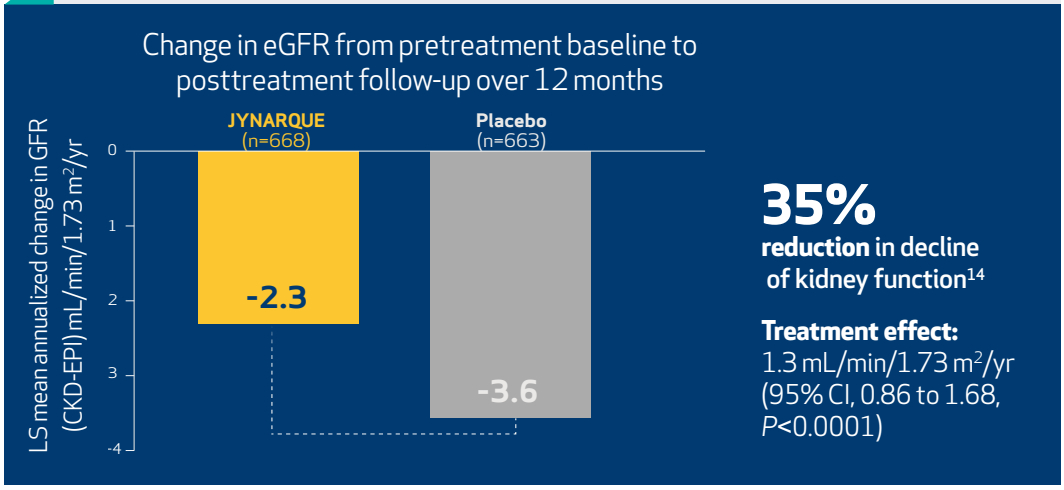
The TEMPO 3:4 and REPRISE trials showed JYNARQUE® (tolvaptan) effectiveness in slowing kidney function decline in ADPKD over a broad range of CKD stages[1,2]

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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15

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.

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 Tolvaptan for ADPKD Shared System REMS**

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.

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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**.

Long-term evaluation of JYNARQUE in patients with ADPKD

The treatment effects of JYNARQUE were consistent with findings from controlled clinical trials and substantiate the disease-modifying effects of JYNARQUE[5]

Most common adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia[1,2]

Retrospective, pooled data analysis provided evidence to support long-term efficacy of JYNARQUE in patients with ADPKD[5]

- JYNARQUE slowed annualized eGFR decline by 1.01 mL/min/1.73 m^2 or approximately by 25% per year vs SOC over 5.5 years
- Estimated TKV at years 1, 3, and 5 was smaller with JYNARQUE than with SOC
  - The difference between treatment groups was most prominent within the first year. In TEMPO 3:4, the difference was minimal in years 2 and 3

The results of Study 211 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[6]

- Aquaretic TEAEs and discontinuations decreased with longer exposure to JYNARQUE

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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.** 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.** Zhou X, Davenport E, Ouyang J, et al. *Kidney Int Rep.* 2022;7(5):1037-1048. **6.** Torres VE, Chapman AB, Devuyst O, et al. *Clin J Am Soc Nephrol.* 2021;16(1):48-58.

Please see **IMPORTANT SAFETY INFORMATION** on pages 14-15.

Otsuka
Otsuka America Pharmaceutical, Inc.

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

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