

Tacrolimus exposure was also associated with higher hemoglobin A_{1c}: 37.4 mmol/mol versus 33.6 mmol/mol. Cardiovascular events and cardiovascular risk factors were not significantly different between groups.

Tacrolimus, in combination with mycophenolate and corticosteroids, is an effective treatment option for patients with active lupus nephritis. CNIs have known renal and cardiovascular adverse effects in kidney transplant recipients. However, in the absence of long-term follow-up data, there are persistent concerns about the safety of tacrolimus in lupus nephritis.

The new study shows “clinically meaningful” long-term declines in kidney func-

tion associated with tacrolimus treatment in patients with lupus nephritis. The effect on an eGFR decline is greater with longer duration of treatment but appears independent of indications of tacrolimus therapy. The researchers conclude: “[O]ur study supports the need for increased vigilance [toward] tacrolimus treatment, especially in [patients with lupus nephritis] with an increased risk of developing ESKD [end stage kidney disease]” [van Schaik M, et al. Long-term renal and cardiovascular risks of tacrolimus in patients with lupus nephritis. *Nephrol Dial Transpl*, published online May 20, 2024. doi: 10.1093/ndt/gfae113]. ■

Anti-CD38 Shows Safety in Antibody-Mediated Rejection

The investigational CD38 monoclonal antibody felzartamab has a low rate of serious adverse events in the treatment of antibody-mediated kidney transplant rejection, according to a clinical trial report in *The New England Journal of Medicine*.

The phase 2 randomized, double-blind trial included 22 kidney transplant recipients with antibody-mediated rejection occurring after at least 180 days. Median time from transplant to study enrollment was 9 years. In equal numbers, patients were as-

signed to felzartamab (nine infusions at a dose of 16 mg/kg of body weight) or to placebo. Treatment continued for 6 months, followed by a 6-month observation period.

Safety and side-effect profiles were evaluated as the primary outcome. A range of secondary efficacy outcomes were evaluated as well, including resolution of antibody-mediated rejection.

Eight patients in the felzartamab group

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JYNARQUE® (tolvaptan) has been proven effective in the 2 largest clinical trials of over 2800 patients with ADPKD across CKD stages 1–4¹⁻³

TEMPO 3:4 Trial— A 36-month trial in patients with CKD Stages 1, 2, and 3^{2,4}

49% reduction
of total kidney volume vs placebo at the end of 3 years*

(P<0.001; month 36 treatment effect: -9.2%)

The difference in TKV between treatment groups was most prominent within the first year, at the earliest assessment; 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.*

Study design: TEMPO 3:4 was a double-blind, placebo-controlled randomized trial of 1445 patients with ADPKD. The inclusion criteria were: 18 to 50 years of age; early, rapidly progressing ADPKD (meeting modified Ravine criteria¹); TKV ≥750 mL; creatinine clearance ≥60 mL/min. Patients were treated for up to 3 years. **The primary endpoint was annual rate of change in the total kidney volume.**⁴

REPRISE Trial— A 12-month trial of patients with CKD late Stage 2 to early Stage 4^{3,5}

35% reduction
in decline of kidney function vs placebo

(treatment effect: 1.3 mL/min/1.73 m²/year; 95% CI: 0.86 to 1.68; P<0.0001)

Study design: REPRISE was a double-blind, placebo-controlled randomized withdrawal trial of 1370 patients with ADPKD. The inclusion criteria were: CKD with an eGFR between 25 and 65 mL/min/1.73 m² if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m², plus eGFR decline >2.0 mL/min/1.73 m²/year if between ages 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess renal function. **The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing each subject's treatment duration.**^{3,6}

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

*Data only included those patients who remained in the study for 3 years; effect in those who discontinued is unknown.²

¹In 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.

²Ravine criteria defined as at least 2 unilateral or bilateral kidney cysts in at-risk individuals between 15 and 30 years of age; 2 cysts in each kidney in individuals between 30 and 59 years of age; and at least 4 cysts in each kidney in individuals older than 60 years of age.^{7,8}

(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
- **V₂-Receptor Agonist:** Tolvaptan interferes with the V₂-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V₂-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 Brief Summary of FULL PRESCRIBING INFORMATION, including BOXED WARNING, on the following page.

CKD=chronic kidney disease; CI=confidence interval; eGFR=estimated glomerular filtration rate; REPRISE= Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO= Tolvaptan Efficacy and Safety Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV=total kidney volume.



References: 1. Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. 2. Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med*. 2012;367(25):2407-2418. 3. Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med*. 2017;377(20):1930-1942. 4. Torres VE, Meijer E, Bae KT, et al. *Am J Kidney Dis*. 2011;57(5):692-699. 5. Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD. 6. Torres VE, Devuyst O, Chapman AB, et al. *Am J Nephrol*. 2017;45(3):257-266. 7. Belibi FA, Edelstein CL. *J Am Soc Nephrol*. 2009;20(1):6-8. 8. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. *Lancet*. 1994;343(8901):824-827.



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Findings

Anti-CD38 Shows Safety in Antibody-Mediated Rejection

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experienced mild to moderate infusion reactions. Serious adverse events, primarily infection-related, occurred in one patient with felzartamab versus four patients with placebo. Graft loss occurred in one patient in the placebo group; there were no deaths in either group.

Renal biopsy performed at 24 weeks showed resolution of morphologic antibody-

mediated rejection in 82% of patients (9 of 11) assigned to felzartamab versus 20% (2 of 10) in the placebo group. Other efficacy outcomes also favored felzartamab: microvascular inflammation, median score of 0 versus 25; a molecular score indicating probability of antibody-mediated rejection, 0.17 versus 0.77; and donor-derived cell-free DNA level, 0.31% versus 0.82%.

At 52 weeks, antibody-mediated rejection occurred in three of the nine patients who responded to felzartamab. Recurrence was associated with rising rejection-related molecular scores and natural killer cell burden.

CD38 is a promising target for depletion of plasma cells producing donor-specific an-

tibodies and natural killer cells, which are believed to contribute to microvascular inflammation. A different anti-CD38 therapy has been approved for depletion of malignant plasma cells in multiple myeloma.

The new phase 2 trial shows “an acceptable safety profile” and “potential therapeutic benefit” of felzartamab for late active or chronic active antibody-mediated rejection after kidney transplantation. “[F]elzartamab may have the potential to effectively and safely reverse ongoing antibody-mediated rejection,” the investigators conclude. The study “underscores the potential of felzartamab as a therapeutic option warranting further investigation in the context of late or even early rejection after organ transplantation”

[Mayer KA, et al. A randomized phase 2 trial of felzartamab in antibody-mediated rejection. *N Engl J Med*, published online May 25, 2024. doi: 10.1056/NEJ-Moa2400763]. ■

No Decrease in CKD Admissions With “ICD-Pieces”

A primary care intervention to promote guideline-based care for patients with the “kidney dysfunction triad” does not lead to reduced rates of hospitalization due to chronic kidney disease (CKD), reports a pragmatic trial in *The New England Journal of Medicine*.

The cluster-randomized Improving Chronic Disease Management with Pieces (ICD-Pieces) trial evaluated a multidisciplinary intervention to promote guideline-directed therapy for patients with CKD. The intervention included a personalized algorithm, based on electronic health record data, to identify patients with the triad of CKD, type 2 diabetes, and hypertension, as well as practice facilitators who assisted primary care practitioners in implementing evidence-based interventions.

A total of 11,182 patients at 141 clinics in four large health systems were assigned to intervention or usual-care groups. All-cause hospitalization at 1 year was compared between groups, along with secondary outcomes. Patient characteristics were similar between intervention and usual-care groups.

Rates of hospitalization for any cause were not significantly different between groups: 20.7% for patients assigned to the ICD-Pieces intervention and 21.1% in the usual-care group. Secondary outcomes were similar as well, including emergency department visits, hospital readmissions, cardiovascular events, dialysis, and death from any cause.

The ICD-Pieces intervention was associated with a higher rate of acute kidney injury: 12.7% versus 11.3%. Other adverse events were comparable between groups.

Patients with the kidney dysfunction triad are at high risk for cardiovascular events and kidney failure. Although several guideline-directed therapies targeting these patients have been developed, few studies have evaluated the effects on morbidity and mortality.

The new pragmatic trial shows no significant effect of ICD-Pieces implementation on CKD hospitalization rates. “[T]he use of an EHR [electronic health record]-based algorithm and practice facilitators embedded in primary care clinics did not translate into reduced hospitalization at 1 year,” the researchers write. They discuss implications for future clinical trials of multicomponent interventions for patients with multiple chronic diseases [Vazquez MA, et al.; ICD-Pieces Study Group. Pragmatic trial of hospitalization rate in chronic kidney disease. *N Engl J Med* 2024; 390:1196–1206. doi: 10.1056/NEJMoA2311708]. ■

JYNARQUE® (tolvaptan) tablets for oral use
Brief summary of PRESCRIBING INFORMATION. See full prescribing information for JYNARQUE.

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 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 restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

INDICATIONS AND USAGE: JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

- CONTRAINDICATIONS:** JYNARQUE is contraindicated in patients:
- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease.
 - Taking strong CYP 3A inhibitors.
 - With uncorrected abnormal blood sodium concentrations.
 - Unable to sense or respond to thirst.
 - Hypovolemia.
 - Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product.
 - Uncorrected urinary outflow obstruction.
 - Anuria.

WARNINGS AND PRECAUTIONS

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 initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter. At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN.

Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.

In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

JYNARQUE REMS Program: JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury. Notable requirements of the JYNARQUE REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving JYNARQUE about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

Hypertremia, Dehydration and Hypovolemia: JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypertremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

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. During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.

Co-Administration with Inhibitors of CYP 3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies. **TEMPO 3:4 -NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD.** The TEMPO3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to JYNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 g daily. Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the JYNARQUE group and 5.0% (24/483) of subjects in the placebo group. Aqueatic effects were the most common reasons for discontinuation of JYNARQUE. These included polyuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo. Table 1 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%) ^a	Annualized Rate ^b	Number of Subjects	Proportion (%) ^a	Annualized Rate ^b
Increased urination ^c	668	69.5	28.6	135	28.0	10.3
Thirst ^d	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1

Table 1: TEMPO 3:4, Treatment Emergent Adverse Reactions in ≥3% of JYNARQUE Treated Subjects with Risk Difference ≥ 1.5%, Randomized Period

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%) ^a	Annualized Rate ^b	Number of Subjects	Proportion (%) ^a	Annualized Rate ^b
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

^a100x (Number of subjects with an adverse event/N)
^b100x (Number of subjects with an adverse event/Total subject years of drug exposure)
^cThirst includes polydipsia and thirst
^dIncreased urination includes micturition urgency, nocturia, polyuria, polyuria

REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD. 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 subjects discontinued the study, 52 (3.5%) were due to aqueatic 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. **Liver Injury:** 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] versus 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.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

Hepatobiliary Disorders: Liver failure requiring transplant

Immune System Disorders: Anaphylaxis

DRUG INTERACTIONS

CYP 3A Inhibitors and Inducers: CYP 3A Inhibitors: Tolvaptan's AUC was 5.4 times as large and C_{max} was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated. Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE. **Strong CYP 3A Inducers:** Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers.

V₂-Receptor Agonist: As a V₂-receptor antagonist, tolvaptan will interfere with the V₂-agonist activity of desmopressin (DDAVP). Avoid concomitant use of JYNARQUE with a V₂-agonist.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure. Advise pregnant women of the potential risk to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Lactation: Risk Summary: There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypertremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE.

Pediatric Use: Safety and effectiveness of JYNARQUE in pediatric patients have not been established.

Geriatric Use: Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in Patients with Hepatic Impairment: Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease.

Use in Patients with Renal Impairment: Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with eGFR_{MDL} ≥25 to 65 mL/min/1.73m².

OVERDOSAGE: Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia. In patients with suspected JYNARQUE overdose, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaresis abates. Dialysis may not be effective in removing JYNARQUE because of its high binding affinity for human plasma protein (>98%).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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