

in adverse events, including transplant thrombosis or infectious complications.

Kidneys from DCD donors are an important source of organs for transplantation but are susceptible to cold ischemic injury, which may lead to DGF. In the emerging NMP technique, donor kidneys are perfused with a warmed, oxygenated, red cell-based solution, producing a near-physiologic state that enables functional testing. To date, the new report is the first randomized, multicenter trial comparing NMP with conventional SCS in DCD kidney transplantation.

The results show no reduction in DGF with a period of NMP before transplantation of DCD kidneys. The researchers write, “Nonetheless, we have demonstrated that this new technology for kidney preservation is feasible, safe and suitable for clinical application” [Hosgood SA, et al. Normothermic machine perfusion versus static cold storage in donation after circulatory death kidney transplantation: A randomized controlled trial. *Nat Med* 2023; 29:1511–1519. doi: 10.1038/s41591-023-02376-7]. ■

Model Predicts Kidney Failure Risk After Nephrectomy

A validated, six-item equation performs well in predicting the 5-year risk of kidney failure in patients undergoing surgery for localized kidney cancer, according to a study in the *American Journal of Kidney Diseases*.

The model was developed in a population-based cohort of 1026 adults in Manitoba, Canada, who underwent partial or radical nephrectomy for non-metastatic

kidney cancer from 2004 through 2016. All patients underwent at least one measurement of estimated glomerular filtration rate (eGFR) both before and after surgery. Models were created to identify factors associated with the 5-year risk of incident kidney failure, defined as dialysis, transplantation, or eGFR less than 15 mL/min/1.73 m².

The resulting Kidney Cancer Risk Equation (KCRE) comprised six readily accessible variables: age, sex, eGFR, type of nephrectomy, diabetes, and urine albumin-to-creatinine ratio. In the development cohort, the equation showed good predictive performance, with an area under the curve (AUC) of 0.85. The KCRE performed similarly well in a validation cohort of 12,043 patients undergoing kidney cancer surgery in Ontario, Canada, between 2008 and 2018: AUC, 0.86. The findings were consistent in sensitivity analyses, and the model showed excellent calibration after adjustment of the baseline hazard.

Nephrectomy is an effective treatment for kidney cancers but carries a risk of later decreased kidney function or kidney failure. The KCRE was developed to meet the need for pre-operative tools to predict the long-term risk of kidney failure after surgery for localized kidney cancer.

The new study describes the KCRE as a simple, validated model to predict the risk of developing kidney failure after nephrectomy for kidney cancer. “The KCRE is an easy-to-use tool for urologists and nephrologists to apply in the pre-operative period for risk stratification and patient-centric counselling to identify those at risk of developing post-operative kidney failure in the next 5 years,” the researchers write. They call for further validation in diverse patient samples [Harasemiw O, et al. A predictive model for kidney failure after nephrectomy for localized kidney cancer: The Kidney Cancer Risk Equation. *Am J Kidney Dis*, published online ahead of print June 30, 2023. doi: 10.1053/j.ajkd.2023.06.002; [https://www.ajkd.org/article/S0272-6386\(23\)00695-9/fulltext](https://www.ajkd.org/article/S0272-6386(23)00695-9/fulltext)]. ■

Index to Advertisers

American College of Rheumatology . . . Page 7
nephCentric Page 3
Novartis Back Cover
Otsuka Pages 24-26

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.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. 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 cobicistat) 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: 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, pollakiuria, 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 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.

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., hypernatremia), 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 eGFR₃₀₋₅₉ 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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