HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JYNARQUE safely and effectively. See full prescribing information for JYNARQUE.

JYNARQUE® (tolvaptan) tablets for oral use

Initial U.S. Approval: 2009

WARNING: RISK OF SERIOUS LIVER INJURY

See full prescribing information for complete boxed warning.

• JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported (5.1).

• Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter (5.1).

• JYNARQUE is available only through a restricted distribution program called the JYNARQUE REMS Program (5.2).

INDICATIONS AND USAGE

JYNARQUE is a selective vasopressin V₂-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) (1).

DOSAGE AND ADMINISTRATION

• Recommended dosage (2.1)

Initial Dosage Titration Step Target Dosage
1st Dose 45 mg 1st Dose 60 mg 1st Dose 90 mg
2nd Dose (8 hours later) 15 mg 2nd Dose (8 hours later) 30 mg 2nd Dose (8 hours later) 30 mg
Total Daily Dose 60 mg Total Daily Dose 90 mg Total Daily Dose 120 mg

• Dose adjustment is recommended for patients taking moderate CYP 3A inhibitors (2.4, 5.4, 7.1).

DOSAGE FORMS AND STRENGTHS

• Tablets: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg (3).

CONTRAINDICATIONS

• History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease (4).

• Concomitant use of strong CYP 3A inhibitors is contraindicated (4).

• Uncorrected abnormal blood sodium concentrations (4, 5.3).

• Unable to sense or respond to thirst (4).

• Hypovolemia (4).

• Hypersensitivity to tolvaptan or any of its components (4).

• Uncorrected urinary outflow obstruction (4).

• Anuria (4).

WARNINGS AND PRECAUTIONS

• Hypernatremia, dehydration and hypovolemia: May require intervention (5.3).

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 (6.1).

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.

DRUG INTERACTIONS

Avoid concomitant use with:

• Strong CYP 3A Inducers (7.1).

• OATP1B1/3 and OAT3 Transporter Substrates (7.2).

• BCRP Transporter Substrates (7.3).

• V₂-Receptor Agonists (7.4).

USE IN SPECIFIC POPULATIONS

• Pregnancy: May cause fetal harm (8.1).

• Lactation: Breastfeeding not recommended (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

REVISED: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS LIVER INJURY

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Monitoring
2.3 Missed Doses
2.4 Co-Administration with CYP 3A Inhibitors
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Liver Injury
5.2 JYNARQUE REMS Program
5.3 Hypernatremia, Dehydration and Hypovolemia
5.4 Co-Administration with Inhibitors of CYP 3A
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 CYP 3A Inhibitors and Inducers
7.2 OATP1B1/3 and OAT3 Transporter Substrates
7.3 BCRP Transporter Substrates
7.4 V₂-Receptor Agonist
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Use in Patients with Hepatic Impairment
8.7 Use in Patients with Renal Impairment
10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
1 INICATIONS AND USAGE
JYNARQUE® (tolvaptan) is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The initial dosage for JYNARQUE is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

2.2 Monitoring
To mitigate the risk of significant or irreversible liver injury, perform blood testing for ALT, AST and bilirubin prior to initiation of JYNARQUE, at 2 and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter. Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

5.1 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 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.

In a 3-year placebo-controlled trial and its open-label extension (in which patients’ liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan treated patients compared to none of the placebo treated patients. 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 ALT or AST, 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.

5.2 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 [see Warnings and Precautions (5.1)]. 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 [see Warnings and Precautions (5.1)].
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

Further information, including a list of qualified pharmacies/distributors, is available at www.JYNARQUEREMS.com or by telephone at 1-877-726-7220.

5.3 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.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hypernatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4.0% versus 0.6% and 1.4% versus 0% of tolvaptan-treated versus placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% versus 0.7% and 2.3% versus 0.4% for tolvaptan-treated versus placebo-treated patients, respectively.

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.

5.4 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 [see Drug Interactions]
6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious Liver Injury [see Boxed Warning and Warnings and Precautions (5.1)]
- Hypernatremia, Dehydration and Hypovolemia [see Warnings and Precautions (5.3)]
- Drug Interactions with Inhibitors of CYP 3A [see Warnings and Precautions (5.4)]

6.1 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.

**Table 2: TEMPO 3:4, Treatment Emergent Adverse Reactions in ≥3% of JYNARQUE Subjects (N=483)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Tolvaptan (N=483)</th>
<th>Placebo (N=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects</strong></td>
<td><strong>Proportion (%)</strong></td>
<td><strong>Annualized Rate</strong></td>
</tr>
<tr>
<td>Increased urination&lt;sup&gt;5&lt;/sup&gt;</td>
<td>668</td>
<td>69.5</td>
</tr>
<tr>
<td>Thirst&lt;sup&gt;6&lt;/sup&gt;</td>
<td>612</td>
<td>63.7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>154</td>
<td>16.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>131</td>
<td>13.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>128</td>
<td>13.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>109</td>
<td>11.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>76</td>
<td>7.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>69</td>
<td>7.2</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>47</td>
<td>4.9</td>
</tr>
<tr>
<td>Dry skin</td>
<td>47</td>
<td>4.9</td>
</tr>
<tr>
<td>Rash</td>
<td>40</td>
<td>4.2</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>37</td>
<td>3.9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>34</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*100x (Number of subjects with an adverse event/N)
*100x (Number of subjects with an adverse event/Total subject years of drug exposure)
<sup>1</sup>Thirst includes polydipsia and thirst
<sup>2</sup>Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

7 DRUG INTERACTIONS

7.1 CYP 3A Inhibitors and Inducers

CYP 3A Inhibitors

Tolvaptan's AUC was 5.4 times as large and Cmax was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]. 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 [see Contraindications (4)].

Dose reduction of JYNARQUE is recommended for patients taking moderate CYP 3A inhibitors [see Dosage and Administration (2.4)]. 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 [see Clinical Pharmacology (12.3)]. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers [see Dosage and Administration (2.4)].

7.2 OATP1B1/3 and OAT3 Transporter Substrates

The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/3 and OAT3 in vitro. Patients who take JYNARQUE should avoid concomitant use with OATP1B1/3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, metformin, furosemide), as the plasma concentrations of these substrates may be increased [see Clinical Pharmacology (12.3)].

7.3 BCRP Transporter Substrates

Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE should avoid concomitant use with BCRP substrates (e.g., rosuvastatin) [see Clinical Pharmacology (12.3)].

7.4 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with JYNARQUE use in pregnant women is 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, skeletal malformations occurred at approximately 3-times the human exposure (see Data). Advance 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.
In patients with suspected JYNARQUE overdosage, 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%).

11 DESCRIPTION

JYNARQUE contains tolvaptan, a selective vasopressin V2-receptor antagonist in saline, orange, and white tablets for oral administration available in 15 mg, 30 mg, 45 mg, 60 mg and 90 mg strengths. Tolvaptan is (1S,4S)-4′-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-y) carbonyl]-o-toluyl-m-toluidide. The empirical formula is C24H22ClIN2O5. Molecular weight is 448.49. The chemical structure is:

Inactive ingredients include corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and FD&C Blue No. 2 Aluminum Lake as colorant.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V2-receptor is 29 times that for the V1a-receptor. Decreased binding of vasopressin to the V2-receptor in the kidney lowers adenylate cyclase activity resulting in a decrease in intracellular adenosine 3′,5′-cyclic monophosphate (cAMP) concentrations. Decreased cAMP concentrations prevent aquaporin 2 containing vesicles from fusing with the plasma membrane, which in turn causes an increase in urine water excretion, an increase in free water clearance (aquarexis) and a decrease in urine osmolality. In human ADPKD cyst epithelial cells, tolvaptan inhibited AVP-stimulated in vitro cyst growth and chloride-dependent fluid secretion into cysts. In animal models, decreased CAMP concentrations were associated with decreases in the rate of growth of total kidney volume and the rate of formation and enlargement of kidney cysts. Tolvaptan metabolites have no or weak antagonistic activity for human V2-receptors compared with tolvaptan.

12.2 Pharmacodynamics

In healthy subjects or patients with eGFRs as low as 10 mL/min/1.73 m² receiving a single dose of tolvaptan, the onset of the aquaretic effects occurs within 1 to 2 hours post-dose. In healthy subjects, single doses of 60 mg and 90 mg produce a peak effect of about a 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose. Higher doses of tolvaptan do not increase the peak effect in urine excretion rate but sustain the effect for a longer period of time.

Urinary excretion rate returns to baseline within 24 hours following the maximum recommended 90 mg dose of tolvaptan.

Changes in free water clearance mirror the changes in urine excretion rate. Increased free water clearance causes an increase in serum sodium concentration unless fluid intake is increased to match urine output.

Increases in urine excretion rate and free water clearance are positively correlated with baseline glomerular filtration rate with increases in both values observed in patients with creatinine clearance as low as 15 mL/min.

With the recommended split-dose regimen, tolvaptan inhibits vasopressin from binding to the V2-receptor in the kidney for the entire day, as indicated by increased urine output and decreased urine osmolality. Following a 90/30 mg split-dose regimen in patients with eGFR >60 mL/min/1.73 m², the change in mean daily urine volume was about 4 L for a mean total daily volume of about 7 L. In patients with eGFR <30 mL/min/1.73 m², the mean change in daily urine volume was about 2 L for a total daily urine volume of about 5 L. Plasma concentrations of native AVP may increase (avg. 2-9 pg/mL) with tolvaptan treatment and return to baseline levels when treatment is stopped.

During tolvaptan treatment, small changes in renal function are expected and the changes are independent of baseline renal function. Glomerular filtration rate is decreased about 6%-10% and uric acid clearance is decreased about 20%-25%.

Percent changes in renal plasma flow are highly correlated to percent changes in GFR. These changes are reversed upon discontinuation of tolvaptan.

Cardiac Electrophysiology

No prolongation of the QT interval was observed with tolvaptan following multiple doses of 300 mg/day for 5 days.
12.3 Pharmacokinetics

In healthy subjects, the pharmacokinetics of tolvaptan after single doses of up to 480 mg and multiple doses up to 300 mg once daily have been studied. In ADPKD patients, single doses up to 120 mg and multiple split-doses up to 90/30 mg have been studied.

Absorption:

In healthy subjects, peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Peak concentrations increase less than dose proportionally with doses greater than 240 mg. The absolute bioavailability of tolvaptan decreases with increasing doses. The absolute bioavailability of tolvaptan following an oral dose of 30 mg is 56% (range 42-80%).

Co-administration of 90 mg JYNARQUE with a high-fat meal (~1000 calories, of which 50% are from fat) doubles peak concentrations but has no effect on the AUC of tolvaptan; tolvaptan may be administered with or without food.

Distribution:

Tolvaptan binds to both albumin and $\alpha_1$-acid glycoprotein and the overall protein binding is >98%; binding is not affected by disease state. The volume of distribution of tolvaptan is about 3 L/kg. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the $S$-(-) to the R-(+) enantiomer of about 3. When administered as multiple once-daily 300 mg doses to healthy subjects or as split-dose regimens to patients with ADPKD, tolvaptan's accumulation factor is <1.2. There is marked inter-subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30 and 60%.

Metabolism and Elimination:

Tolvaptan is metabolized almost exclusively by CYP 3A. Fourteen metabolites have been identified in plasma, urine and feces; all but one were also metabolized by CYP 3A and none are pharmacodynamically active. After oral administration of radiolabeled tolvaptan, tolvaptan was a minor component in plasma representing 3% of total plasma radioactivity; the oxobutyric acid metabolite was present at 52.5% of total plasma radioactivity with all other metabolites present at lower concentrations than tolvaptan. The oxobutyric acid metabolite shows a plasma half-life of ~180 hours. About 40% of radioactivity was recovered in urine (<1% as unchanged tolvaptan) and 59% in feces (19% as unchanged tolvaptan). Following intravenous infusion, tolvaptan half-life is approximately 3 hours. Following single oral doses to healthy subjects, the estimated half-life of tolvaptan increases from 3 hours for a 15 mg dose to approximately 12 hours for 120 mg and higher doses due to more prolonged absorption of tolvaptan at higher doses; apparent clearance is approximately 4 mL/min/kg and does not appear to change with increasing dose.

Specific Populations

Age, Gender and Race

Age, gender and race have no effect on tolvaptan pharmacokinetics.

Hepatic Impairment

In studies involving patients with hepatic impairment (Child-Pugh class A-C), but without ADPKD; moderate (class A, B) or severe (class C) hepatic impairment decreases the clearance and increases the volume of distribution of tolvaptan.

Renal Impairment

In subjects with creatinine clearances ranging from 10-124 mL/min administered a single dose of 60 mg tolvaptan, the AUC and $C_{max}$ of plasma tolvaptan was increased 90% and 10%, respectively, for subjects with clearances of <30 mL/min compared to subjects with clearances >60 mL/min [see Use in Special Populations (8.7)].

In ADPKD patients with estimated creatinine clearance >60 mL/min, pharmacokinetics were similar to healthy subjects.

Drug Interactions:

Impact of Other Drugs on Tolvaptan

Strong CYP 3A Inhibitors

Tolvaptan’s $C_{max}$ and AUC were, respectively, 3.5 times and 5.4 times as high following ketoconazole 200 mg given one day prior to and concomitantly with 30 mg tolvaptan.

Moderate CYP 3A4 Inhibitors

Fluconazole: Fluconazole 400 mg given one day prior and 200 mg given concomitantly produced an 80% and 200% increase in tolvaptan $C_{max}$ and AUC, respectively.

Grapefruit Juice: When 60 mg tolvaptan was taken with 240 mL regular strength grapefruit juice, tolvaptan $C_{max}$ and AUC increased 90% and 60%, respectively.

CYP 3A Inducers

Rifampin: Rifampin 600 mg once daily for 7 days followed by a single 240 mg dose of tolvaptan decreased both tolvaptan $C_{max}$ and AUC about 85%.

Other Drugs

Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with tolvaptan has no clinically relevant impact on the exposure to tolvaptan.

Impact of Tolvaptan on Other Drugs

CYP 3A Substrates

Co-administration of lovastatin and tolvaptan increases the AUC of lovastatin and its active metabolite lovastatin-β hydroxy acid by 40% and 30%, respectively. These are non-clinically significant increases in exposure.

P-gp Substrates

Digoxin: Digoxin 0.25 mg was administered once daily for 12 days. Tolvaptan 60 mg, was co-administered once daily on Days 8 to 12. Digoxin $C_{max}$ and AUC were increased 30% and 20%, respectively.

Other Drugs

Co-administration of other drugs did not meaningfully alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amidorane (or its active metabolite, desethylamidorane).
The primary endpoint was the intergroup difference for rate of change of TKV normalized as a percentage. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category).

At baseline, average estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m² (CKD-Epidemiology formula) and mean TKV was 1692 mL (height adjusted 972 mL/m). Approximately 35% had an eGFR of 90 mL/min/1.73 m² or greater, 48% had an eGFR between 60-89 mL/min/1.73 m², 14% had an eGFR of 45-60 mL/min/1.73 m², and 3% had an eGFR of <45 mL/min/1.73 m². The subjects' mean age was 39 years, 48% were female, 84% were Caucasian, 13% were Asian, and 1.7% were Black or African-American. Approximately 80% had hypertension and approximately 71% were taking an agent that acts on the renin-angiotensin system. Of the 770 subjects who submitted to genetic analysis in TEMPO 3.4's open-label run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.

Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.

A total of 1519 subjects were enrolled in the study. Of these, 1370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis.

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m² (CKD-Epidemiology formula) and historical TKV, available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m² or greater, between 30-59 mL/min/1.73 m², and between 25 and 29 mL/min/1.73 m², respectively. The subjects' mean age was 47 years, 50% were female, 92% were Caucasian, 4% Black or African-American and 3% were Asian, 93% had hypertension, and 87% of subjects were taking antihypertensive agents affecting the angiotensin converting enzyme or receptor. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was −2.3 mL/min/1.73 m²/year with tolvaptan as compared with −3.6 mL/min/1.73 m²/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m²/year (p=0.0001). The key secondary endpoint (eGFR slope in mL/min/1.73 m²/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 mL/min/1.73 m²/year which was also statistically significant (p=0.0001).

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

**JYNARQUE** (tolvaptan) is supplied as non-scored, blue, shallow-convex, immediate release tablets, debossed with “OTSUKA” and the tablet strength (mg) on one side. **JYNARQUE** (tolvaptan) tablets are square, 60 mg tablets are rectangular, and 90 mg tablets are pentagonal.

**JYNARQUE** (tolvaptan) tablets are supplied as non-scored, blue, shallow-convex, immediate release tablets, debossed with “OTSUKA” and the tablet strength (mg) on one side. **JYNARQUE** (tolvaptan) tablets are square, 60 mg tablets are rectangular, and 90 mg tablets are pentagonal.

### 16.2 Storage

**JYNARQUE** (tolvaptan) tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F) and protected from light and moisture.

### 16.3 Handling

**JYNARQUE** (tolvaptan) tablets should be handled in a dry and dust-free environment and should not be exposed to moisture or humidity.

### Table: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Total Number of Events (Events per 100 person-years)</th>
<th>Number of Subjects with an Event (percentage)</th>
<th>Hazard Ratio, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>1049 (43.9)</td>
<td>572 (59.5)</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td>Worsening Kidney Function</td>
<td>44 (1.9)</td>
<td>42 (4.6)</td>
<td>0.39 (0.26, 0.57)</td>
</tr>
<tr>
<td>Kidney Pain</td>
<td>113 (4.7)</td>
<td>95 (9.9)</td>
<td>0.64 (0.47, 0.89)</td>
</tr>
<tr>
<td>Onset or progression of hypertension</td>
<td>734 (30.7)</td>
<td>426 (44.3)</td>
<td>0.94 (0.81, 1.10)</td>
</tr>
<tr>
<td>Worsening Albuminuria</td>
<td>195 (8.2)</td>
<td>195 (20.3)</td>
<td>1.04 (0.84, 1.28)</td>
</tr>
</tbody>
</table>

**Note:** These data are from a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) and 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 age 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 by each subject's treatment duration.

Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.

Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.

A total of 1519 subjects were enrolled in the study. Of these, 1370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis.

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m² (CKD-Epidemiology formula) and historical TKV, available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m² or greater, between 30-59 mL/min/1.73 m², and between 25 and 29 mL/min/1.73 m², respectively. The subjects' mean age was 47 years, 50% were female, 92% were Caucasian, 4% Black or African-American and 3% were Asian, 93% had hypertension, and 87% of subjects were taking antihypertensive agents affecting the angiotensin converting enzyme or receptor. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was −2.3 mL/min/1.73 m²/year with tolvaptan as compared with −3.6 mL/min/1.73 m²/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m²/year (p=0.0001). The key secondary endpoint (eGFR slope in mL/min/1.73 m²/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 mL/min/1.73 m²/year which was also statistically significant (p=0.0001).

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.
16.2 Storage and Handling
Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
As part of patient counseling, healthcare providers must review the JYNARQUE Medication Guide with every patient [see Medication Guide].

Serious Liver Injury
Advise patients that blood testing is required before starting JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly during the first 18 months of therapy and every 3 months thereafter as a requirement to reduce the risk of serious liver injury [see Boxed Warning and Warning and Precautions (5.1)].

Advises patients to immediately stop taking JYNARQUE and notify their healthcare provider if they have symptoms or signs (e.g., abnormal transaminase elevations) of hepatic injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort or tenderness, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) [see Warning and Precautions (5.1)].

JYNARQUE REMS Program
Advise patients that JYNARQUE is only available through a restricted program called the JYNARQUE REMS Program [see Warning and Precautions (5.2)]. Inform the patient of the following notable requirement:

• Patients must enroll in the program and comply with ongoing monitoring requirements [see Warning and Precautions (5.1)]

Advises patients that JYNARQUE is only available only through restricted distribution from certified specialty pharmacies participating in the JYNARQUE REMS program. Therefore, provide patients with the telephone number and web site for information on how to obtain the product [see Warning and Precautions (5.2)].

Hypernatremia, Dehydration and Hypovolemia
Advise patients to drink water to avoid thirst, throughout the day and night. Patients should stop taking JYNARQUE and notify their healthcare provider if they have symptoms or signs of sodium imbalance or dehydration (e.g., dizziness, fainting, weight loss, palpitations, confusion, weakness, gait instability) [see Warning and Precautions (5.3)]. Advise the patient that if they cannot drink enough water for any reason (no access to water, cannot sense thirst, unable to maintain hydration due to vomiting, diarrhea) they should stop taking JYNARQUE and inform their health care provider right away [see Warning and Precautions (5.3)].

Pregnancy
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise women not to breastfeed during treatment with JYNARQUE [see Use in Specific Populations (8.2)].
What is the most important information I should know about JYNARQUE?  

JYNARQUE can cause serious side effects, including:

- **Serious liver problems.** JYNARQUE can cause serious liver problems that can lead to the need for a liver transplant or can lead to death. Stop taking JYNARQUE and call your healthcare provider right away if you get any of the following symptoms:
  
  - feeling tired
  - loss of appetite
  - nausea
  - right upper stomach (abdomen) pain or tenderness
  - vomiting
  - fever
  - rash
  - itching
  - yellowing of the skin and white part of the eye (jaundice)
  - dark urine

To help reduce your risk of liver problems, your healthcare provider will do a blood test to check your liver:

- before you start taking JYNARQUE
- at 2 weeks and 4 weeks after you start treatment with JYNARQUE
- then monthly for 18 months during treatment with JYNARQUE
- and every 3 months from then on

It is important to stay under the care of your healthcare provider during treatment with JYNARQUE.

Because of the risk of serious liver problems JYNARQUE is only available through a restricted distribution program called the JYNARQUE Risk Evaluation and Mitigation Strategy (REMS) Program.

- Before you start treatment with JYNARQUE, you must enroll in the JYNARQUE REMS Program. Talk to your healthcare provider about how to enroll in the program.
- JYNARQUE can only be dispensed by a certified pharmacy that participates in the JYNARQUE REMS Program. Your healthcare provider can give you information on how to find a certified pharmacy.

What is JYNARQUE?  

JYNARQUE is a prescription medicine used to slow kidney function decline in adults who are at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).  

It is not known if JYNARQUE is safe and effective in children.

Do not take JYNARQUE if you:

- have a history of liver problems or have signs or symptoms of liver problems, excluding polycystic liver disease.
- cannot feel if you are thirsty or cannot replace fluids by drinking.
- have been told that the amount of sodium (salt) in your blood is too high or too low.
- are dehydrated.
- are allergic to tolvaptan or any of the ingredients in JYNARQUE. See the end of this Medication Guide for a complete list of ingredients in JYNARQUE.
- are unable to urinate.
**Before taking JYNARQUE, tell your healthcare provider about all your medical conditions, including if you:**

- have a history of sodium levels that are too low.
- are pregnant or plan to become pregnant. It is not known if tolvaptan will harm your unborn baby. Tell your healthcare provider if you become pregnant or think that you may be pregnant.
- are breast-feeding or plan to breastfeed. It is not known if tolvaptan passes into your breast milk. Do not breastfeed during treatment with JYNARQUE. Talk to your healthcare provider about the best way to feed your baby during this time.

**Tell your healthcare provider about all the medicines you take** including prescription medicines, over-the-counter medicines, vitamins and herbal supplements.

- Taking JYNARQUE with certain medicines could cause you to have too much tolvaptan in your blood. JYNARQUE should not be taken with certain medications. Your healthcare provider can tell you if it is safe to take JYNARQUE with other medicines.
- Do not start taking a new medicine without talking to your healthcare provider.
- Keep a list of your medicines to show your healthcare provider and pharmacist.

### How should I take JYNARQUE?

- Take JYNARQUE exactly as your healthcare provider tells you to.
- Take JYNARQUE orally two times each day. Take the first dose of JYNARQUE when you wake up and take the second dose 8 hours later.
- Be sure to drink enough water so that you will not get thirsty or become dehydrated.
- If you miss a dose of JYNARQUE, take the next dose at your regular time.
- If you take too much JYNARQUE, call your healthcare provider or go to the nearest hospital emergency room right away.

### What should I avoid while taking JYNARQUE?

- Do not drink grapefruit juice during treatment with JYNARQUE. This could cause you to have too much tolvaptan in your blood.

### What are the possible side effects of JYNARQUE?

**JYNARQUE may cause serious side effects, including:**

See “What is the most important information I should know about JYNARQUE?”

- Too much sodium in your blood (hypernatremia) and loss of too much body fluid (dehydration). In some cases, dehydration can lead to extreme loss of body fluid called hypovolemia. You should drink water when you are thirsty and throughout the day and night. Stop taking JYNARQUE and call your healthcare provider if you cannot drink enough water for any reason, such as not having access to water, or vomiting or diarrhea. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fainting
  - weight loss
  - a change in the way your heart beats
  - feel confused or weak

The most common side effects of JYNARQUE include:

- thirst and drinking more fluid than normal
- making large amounts of urine, urinating often and urinating at night

These are not all the possible side effects of JYNARQUE.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

### How should I store JYNARQUE?

JYNARQUE comes in a child-resistant package. Store JYNARQUE between 68°F to 77°F (20°C to 25°C).

Keep JYNARQUE and all medicines out of the reach of children.
**JYNARQUE® (tolvaptan)**

<table>
<thead>
<tr>
<th>General information about the safe and effective use of JYNARQUE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JYNARQUE for a condition for which it was not prescribed. Do not give JYNARQUE to other people, even if they have the same symptoms you have. It may harm them.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What are the ingredients in JYNARQUE?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient:</strong> tolvaptan</td>
</tr>
<tr>
<td><strong>Inactive ingredients:</strong> corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose, and FD&amp;C Blue no. 2 Aluminum Lake as colorant.</td>
</tr>
</tbody>
</table>

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

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For more information about JYNARQUE, go to www.JYNARQUEREMS.com or call 1-877-726-7220.