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):

<table>
<thead>
<tr>
<th>Initial Dosage</th>
<th>Titration Step</th>
<th>Target Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Dose 45 mg</td>
<td>1st Dose 60 mg</td>
<td>1st Dose 90 mg</td>
</tr>
<tr>
<td>2nd Dose (8 hours later) 15 mg</td>
<td>2nd Dose (8 hours later) 30 mg</td>
<td>2nd Dose (8 hours later) 30 mg</td>
</tr>
<tr>
<td>Total Daily Dose 60 mg</td>
<td>Total Daily Dose 90 mg</td>
<td>Total Daily Dose 120 mg</td>
</tr>
</tbody>
</table>

- 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

- Hyponatremia, 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).

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: 04/2018
FULL PRESCRIBING 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 [see Warnings and Precautions (5.1)].

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 [see Warnings and Precautions (5.1)]. 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 [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

JYNARQUE 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, monthly for 18 months and every 3 months thereafter. Monitor for concurrent symptoms that may indicate liver injury [see Warnings and Precautions (5.1)].

2.3 Missed Doses

If a dose of JYNARQUE is not taken at the scheduled time, take the next dose at its scheduled time.

2.4 Co-Administration with CYP 3A Inhibitors

CYP 3A Inhibitors

Concomitant use of strong CYP 3A inhibitors is contraindicated [see Contraindications (4) and Warnings and Precautions (5.4)].

In patients taking concomitant moderate CYP 3A inhibitors, reduce the dose of JYNARQUE per Table 1. Consider further reductions if patients cannot tolerate the reduced dose [see Warnings and Precautions (5.4) and Drug Interactions (7.1)]. Interrupt JYNARQUE temporarily for short term therapy with moderate CYP 3A inhibitors if the recommended reduced doses are not available.

Table 1: Dose adjustment for patients taking moderate CYP 3A inhibitors

<table>
<thead>
<tr>
<th>Standard Morning and Afternoon Dose (mg)</th>
<th>Dose (mg) with Moderate CYP 3A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 mg and 30 mg</td>
<td>45 mg and 15 mg</td>
</tr>
<tr>
<td>60 mg and 30 mg</td>
<td>30 mg and 15 mg</td>
</tr>
<tr>
<td>45 mg and 15 mg</td>
<td>15 mg and 15 mg</td>
</tr>
</tbody>
</table>

3 DOSAGE FORMS AND STRENGTHS

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 15 mg tablets are triangular, 30 mg tablets are round, 45 mg tablets are square, 60 mg tablets are rectangular, and 90 mg tablets are pentagonal.

4 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 [see Warnings and Precautions (5.1)]
- Taking strong CYP 3A inhibitors
- With uncorrected abnormal blood sodium concentrations [see Warnings and Precautions (5.3)]
- Unable to sense or respond to thirst [see Warnings and Precautions (5.3)]
- Hypovolemia [see Warnings and Precautions (5.3)]

5 WARNINGS AND PRECAUTIONS

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 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.

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 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.

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 Hyponatremia, Dehydration and Hypovolemia

JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hyponatremia. 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, hyponatremia (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, monitor for weight loss, tachycardia and hypotension because they may signal dehydration.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hyponatremia (defined as any 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.

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)]
- Hyponatremia, 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 on JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo. TEMPO 3:4, Treatment Emergent Adverse Reactions in JYNARQUE Treated Subjects with Risk Difference ≥1.5%, Randomized Period ≥3% of ADPKD subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo. JYNARQUE. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects. Adverse events that led to discontinuation were reported for 15.4% (148/961) of (77%) subjects who were treated with JYNARQUE remained on treatment for at least 12 months across both studies.

Table 2: TEMPO 3:4, Treatment Emergent Adverse Reactions in JYNARQUE Treated Subjects with Risk Difference ≥1.5%, Randomized Period

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Tolvaptan (N=961)</th>
<th>Placebo (N=483)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Subjects</td>
<td>Proportion (%)*</td>
</tr>
<tr>
<td>Increased urination§</td>
<td>668</td>
<td>69.5</td>
</tr>
<tr>
<td>Thirst‡</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)
‡Thirst includes polydipsia and thirst
§Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

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, methotrexate, 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., rosvastatin) [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 and not castrate 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, maternal non-toxic doses, tolvaptan and not castrate any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure (see Data). 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.
Oral administration of tolvaptan during the period of organogenesis in Sprague-Dawley rats produced no evidence of teratogenesis at doses up to 100 mg/kg/day. Lower body weights and delayed ossification were seen at 1000 mg/kg, which is approximately 17-times the exposure in humans at the 90/30 mg dose (AUCτ, 6570 ng h/mL). The fetal effects are likely secondary to maternal toxicity (decreased food intake and low body weights). In a prenatal and postnatal study in rats, tolvaptan had no effect on physical development, reflex function, learning ability or reproductive performance at doses up to 1000 mg/kg/day.

In New Zealand White rabbits, placental transfer was demonstrated with Cτ, values in the yolk sac fluid approximating 22.7% of the value in maternal rabbit serum. In embryo-fetal studies, teratogenicity (microphthalmia, embryo-fetal mortality, cleft palate, brachymelia and fused phalanx) was evident in rabbits at 1000 mg/kg (approximately 3 times the exposure at the 90/30 mg dose). Body weights and food consumption were lower in dams at all doses, equivalent to 0.6 to 3-times the human exposure at the 90/30 mg dose.

8.2 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 (see Data). 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.

Data

In lactating rats administration of radiolabeled tolvaptan, lactate radioactivity concentrations reached the highest level at 8 hours after administration and then decreased gradually with time with a half-life of 27.3 hours. The level of activity in milk ranged from 1.5- to 15.8-fold those in blood over the period of 72 hours post-dose. In a prenatal and postnatal study in rats, maternal toxicity was noted at 100 mg/kg/day or higher (>4.4 times the human exposure at the 90/30 mg dose). Increased perinatal death and decreased body weight of the offspring were observed during the lactation period and after weaning at approximately 17.3 times the human exposure at the 90/30 mg dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 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 based on age, as well as on a host of other factors such as severity of disease and other drug therapy.

8.6 Use in Patients with Hepatic Impairment

Because of the risk of hepatic 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 [see Contraindications (4)].

8.7 Use in Patients with Renal Impairment

Efficacy studies included patients with normal and reduced renal function [see Clinical Studies (14); TEMPO 3:4]. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with eGFR <60 mL/min/1.73 m².

10 OVERDOSAGE

Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple oral 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. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hyperthermia.

No prolongation of the QT interval was observed with tolvaptan following multiple doses of 300 mg/day for 5 days.
JYNARQUE™ (tolvaptan)

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 α1-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 stereosepecific, 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 h. 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 Cmax 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_{ss} and AUC were increased 30% and 20%, respectively.

**Transporter Substrates**

Tolvaptan is a substrate of P-gp and an inhibitor of P-gp and BCRP. The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/83 and OAT3; in vitro studies indicate that tolvaptan or the oxobutyric acid metabolite of tolvaptan may have the potential to increase exposure of drugs that are substrates of these transporters [see Drug Interactions (7.2), (7.3)].

**Other Drugs**

Co-administration of tolvaptan did not meaningfully alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of JYNARQUE was assessed in 2-year carcinogenicity studies in mice and rats. Tolvaptan was not tumorigenic in male or female rats at doses up to 1000 mg/kg/day (1.9-5.1 times the human exposure at the 90/30 mg dose), in male mice at doses up to 60 mg/kg/day (0.4 times the human exposure at the 90/30 mg dose) and to female mice at doses up to 100 mg/kg/day (0.7 times the human exposure at the 90/30 mg dose).

Mutagenesis

Tolvaptan was not clastogenic in the in vitro chromosomal aberration test in Chinese hamster lung fibroblast cells or the in vivo rat micronucleus assay and was not mutagenic in the in vitro bacterial reverse mutation assay.

Impairment of fertility

In a fertility study in which male and female rats were administered tolvaptan orally at 100, 300 or 1000 mg/kg/day, altered estrous cycles due to prolongation of diestrus were observed in dams given 300 and 1000 mg/kg/day (9.7- and 17.3 times the human exposure at the 90/30 mg dose). Tolvaptan had no effect on copulation or fertility indices. There were also no effects on the incidences of early or late resorption, dead fetuses, pre- or post-implantation loss, external anomalies, or fetal body weights.

14 CLINICAL STUDIES

JYNARQUE™ was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages. The findings from these trials, when taken together, suggest that JYNARQUE slows the loss of renal function progressively through the course of the disease.

TEMPO 3:4-NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

In TEMPO 3:4, 1445 adult patients (age >18 years) with early (estimated creatinine clearance [eCrCl] ≥60 mL/min), rapidly-progressing (total kidney volume [TKV] ≥750 mL and age <51 years) ADPKD (diagnosed by modified Ravine criteria) were randomized 2:1 to treatment with tolvaptan or placebo. Patients were treated for up to 3 years; patients who discontinued medication prematurely were only required to attend clinic visits to assess renal function for up to 42 days after treatment withdrawal and to attend telephone visits at all scheduled visits for up to 36 months. Patients who completed treatment at the 3-year visit had treatment interrupted for 2-6 weeks to assess renal function post treatment. Patients received treatment twice a day (first dose on waking, second dose approximately 9 hours later). Patients were initiated on 45 mg/15 mg, and up-titrated weekly to 60 mg/30 mg and then to 90 mg/30 mg as tolerated. Patients were to maintain the highest tolerated dose for 3 years, but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to drink adequate water to avoid thirst or dehydration and before bedtime.
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/m²). 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 extension, 749 (97%) had an identifiable mutation in the PKD1 (656 or 88%), or PKD2 (93 or 12%) gene.

The trial 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, the earliest assessment, with little further difference in years two and three. 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.

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; p=0.0095). As shown in the table below, the result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. Few subjects in either arm required a radiologic or surgical intervention for kidney pain. Most kidney pain events reflected use of a medication to treat pain such as use of paracetamol, tricyclic antidepressants, narcotics and other non-narcotic agents.

The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0 mL/min/1.73 m²/year with a 95% confidence interval of (0.6, 1.4). Of the subjects enrolled in the trial, 5% of subjects in the tolvaptan arm and 2% in the placebo arm either had missing baseline data or discontinued from treatment prior to the end of the titration visit and hence were excluded from the analysis. In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of JYNARQUE treatment.

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)].

Advise 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)]

Advise 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)].

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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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
  - 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>
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<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>
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<tr>
<th>What are the ingredients in JYNARQUE?</th>
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<tbody>
<tr>
<td><strong>Active ingredient:</strong> tolvaptan</td>
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<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>
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For more information about JYNARQUE, go to www.JYNARQUEREMS.com or call 1-877-726-7220.