PDL DRUG REVIEW

Proprietary Name: Jynarque®
Common Name: tolvaptan
PDL Category: Vasopressins

Summary

Pharmacology/Usage: Tolvaptan, the active ingredient of Jynarque®, 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. In humans, tolvaptan inhibited AVP-stimulated in vitro cyst growth and chloride-dependent fluid secretion into cysts.

Indication: To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

There is no pregnancy category for this medication; however, the risk summary indicates that the available data with use in pregnant women are not sufficient to determine if there is a drug associated risk of adverse developmental outcomes. Advise pregnant women of the potential risk to the fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Immediate-release Tablets: 15mg, 30mg, 45mg, 60mg, 90mg

Recommended Dosage: It is recommended to perform blood testing for ALT, AST, and bilirubin prior to starting Jynarque®, at 2 and 4 weeks after starting therapy, monthly for 18 months, and every 3 months thereafter. Monitor for concurrent symptoms that may indicate liver injury.

Take 60mg PO QD, as 45mg taken on waking and 15mg taken 8 hours later. Titrate to 60mg plus 30mg, increasing to 90mg plus 30mg per day if tolerated, with at least weekly intervals between titrations. Down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

Drug Interactions: Concomitant use of tolvaptan with strong CYP3A inhibitors is contraindicated. Dose reduction of Jynarque® is recommended while taking concomitant moderate CYP3A inhibitors (refer to the prescribing information for additional information). Patients should avoid grapefruit juice beverages while taking Jynarque®. In addition, concomitant use of Jynarque® with strong CYP3A inducers should be avoided. Avoid concomitant use of Jynarque® with a V2-agonist and BCRP substrates (e.g. rosuvastatin). Last, avoid concomitant use of Jynarque® with OATP1B1/B3 and OAT3 substrates (e.g. statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (tolvaptan) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included increased urination (41.5%), thirst (40.3%), dry mouth (3.6%), fatigue (3.9%), diarrhea (2.3%), dizziness (2.6%), dyspepsia (4.6%), decreased appetite (6.2%), abdominal distension (1.6%), dry skin (3.2%), rash (2.3%), hyperuricemia (2%), and palpitations (2.3%).

Jynarque® has a box warning regarding the increased risk of serious livery injury, as it can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported. It is recommended to measure ALT, AST, and bilirubin before starting 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 the risk of serious hepatoxicity. Due to 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.

For the Jynarque® REMS program, prescribers must be certified and enrolled in the program, as well as inform the patients about the risk of hepatotoxicity with use and appropriate actions to take if it occurs. Patients must enroll and comply with ongoing monitoring requirements, and pharmacies must also be certified by enrolling in the REMS program.

Jynarque® increases free water clearance and as a result may cause dehydration, hypovolemia, and hypernatremia. Thus, ensure abnormalities in sodium concentrations are corrected prior to starting therapy. Drink water when thirsty and monitor for weight loss, tachycardia and hypotension as they may be a signal of dehydration.

Contraindications: In patients: with a history, signs or symptoms of significant liver impairment or injury (this does not apply to uncomplicated polycystic liver disease); taking strong CYP3A inhibitors; with uncorrected abnormal blood sodium concentrations; unable to sense or respond to thirst; hypovolemia; hypersensitivity to tolvaptan or any component of the product; uncorrected urinary outflow obstruction; anuria

Manufacturer: Otsuka America Pharmaceutical, Inc

Analysis: Jynarque® was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in 2 trials, including the TEMPO 3:4 study that included patients at earlier stages of disease and the REPRISE study that included patients at later stages.

The *TEMPO 3:4 study* was a phase 3, double-blind, placebo-controlled randomized study that included adults >18 years of age with early (eCrCl ≥60ml/min), rapidly-progressing (total kidney volume [TKV] ≥750ml and age <51 years) ADPKD (N=1445) who were randomized to tolvaptan or placebo for up to 3 years. All 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 TVK normalized as a percentage. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of worsening kidney function (defined as persistent 25% reduction in reciprocal serum creatinine during treatment from end of titration to last on-drug visit); medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); worsening hypertension (defined as persistent increase in blood pressure category or an increased anti-hypertensive prescription); and worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category). At baseline, average eGFR was 82ml/min/1.73m^2 and mean TKV was 1692ml. The mean age of subjects was 39 years, while 48% were female and 84% were Caucasian.

Results suggested that 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, HR 0.87; p=0.0095). As can be seen in the table below, the result of the main secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. However, there was no effect of tolvaptan on either progression of hypertension or albuminuria. Results can be seen in the table below, which was adapted from the prescribing information.

Event	Tolvaptan		Placebo		HR
	Total # events (events/100-PY)	# of subjects with event (%)	Total # events (events/100-PY)	# of subjects with event (%)	
Composite	1049 (43.9)	572 (59.5%)	665 (50.0)	341 (70.6%)	0.87

Event	Tolvaptan		Placebo		HR
	Total # events (events/100-PY)	# of subjects with event (%)	Total # events (events/100-PY)	# of subjects with event (%)	
Worsening Kidney Function	44 (1.9)	42 (4.6%)	64 (4.8)	61 (12.8%)	0.39
Kidney Pain	113 (4.7)	95 (9.9%)	97 (7.3)	78 (16.2%)	0.64
Onset or Progression of Hypertension	734 (30.7)	426 (44.3%)	426 (32.1)	244 (50.5%)	0.94
Worsening albuminuria	195 (8.2)	195 (20.3%)	103 (7.8)	101 (20.9%)	1.04

The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment. The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0ml/min/1.73m^2/year. Of the subjects enrolled in the trial, 5% in the tolvaptan group and 2% in the placebo group either had missing baseline data or discontinued from treatment prior to the end of the titration visit and were excluded in the analysis. In the extension trial, eGFR differences produced by the third year were maintained over the next 2 years of Jynarque® treatment.

The *REPRISE* was a phase 3, double-blind, placebo-controlled randomized withdrawal study that included adults aged 18-65 years with CKD with an eGFR between 25 and 65ml/min/1.73m^2 if younger than age 56 or an eGFR between 25 and 44ml/min/1.73m^2 plus eGFR decline >2ml/min/1.73m^2/year if between age 56-65. 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.

Patients were maintained on the 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 were encouraged to begin drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration. Of the 1519 enrolled in the study, 1370 successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. For subjects randomized, the baseline average eGFR was 41 ml/min/1.73m^2 and historical TKV (available in 318 subjects) averaged 2026ml. Approximately 5%, 75%, and 20% had an eGFR 60 ml/min/1.73m^2 or greater, between 30-59 ml/min/1.73m^2, and between 25-29 ml/min/1.73m^2, respectively.

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was -2.3 ml/min/1.73m^2/year with tolvaptan as compared with -3.6 ml/min/1.73m^2/year, corresponding to a treatment effect of 1.3 ml/min/1.73m^2/year ($p<0.0001$). The key secondary endpoint (eGFR slope in ml/min/1.73m^2/year assessed using a linear mixed effect model of annualized eGFR) demonstrated a difference between treatment groups of 1.0ml/min/m^2/year that was also statistically significant ($p<0.0001$).

Place in Therapy: 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). It is the first and only treatment approved for this indication. Due to the risk of elevations of liver enzymes, Jynarque® will be available only through a restricted distribution program and liver enzymes will need to be monitored.

It is recommended that Jynarque® remain non-preferred to ensure it is used in clinically appropriate situations.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Jynarque [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc; 2018.