Tolvaptan (JYNARQUE)
Criteria for Use
August 2018

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at the *PBM INTERnet* or *PBM Formulary Management - Home (sharepoint.com)* site for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive tolvaptan (JYNARQUE).

- ☐ History, signs or symptoms of significant liver impairment or injury (Note: this does not apply to uncomplicated polycystic liver disease)
- ☐ Strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan)
- ☐ Uncorrected abnormal blood sodium concentrations (see Issues for Consideration; Hypernatremia)
- ☐ Unable to sense or respond to thirst (see Issues for Consideration; Dehydration)
- ☐ Hypovolemia (see Issues for Consideration)
- ☐ Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
- ☐ Uncorrected urinary outflow obstruction
- ☐ Anuria
- ☐ Advanced diabetes (e.g., glycosylated hemoglobin > 7.5%)
- ☐ Significant kidney disease (i.e., currently active glomerulonephritides), renal cancer, single kidney, or recent (within the past 6 months) renal surgery or acute kidney injury
- ☐ Chronic kidney disease stage 5 (estimated glomerular filtration rate [eGFR] < 15 ml/min/1.73m^2), end-stage kidney disease
- ☐ Inability to adhere to a twice daily treatment regimen

Inclusion Criteria

Each of the following must be fulfilled in order to meet criteria.

- ☐ Restricted to a VA authorized Nephrologist
- ☐ Restricted to JYNARQUE REMS Program and VA Specific Ordering Process [refer to JYNARQUE (Tolvaptan) folder on PBM Formulary Management Sharepoint Specialty Distribution Meds]
- ☐ Diagnosis of autosomal dominant polycystic kidney disease (ADPKD) (See Issues for Consideration)

AND one of the following, indicating a high risk of progression of kidney disease:

☐ Age ≥ 18 to 50 years with eGFR ≥ 60 ml/min/1.73m^2 AND total kidney volume (TKV) ≥ 750 ml* (See Issues for Consideration)

☐ Age ≥ 18 to 55 years with eGFR ≥ 25 to ≤ 65 ml/min/1.73m^2*

OR

☐ Age ≥ 56 to < 66 years with eGFR ≥ 25 to ≤ 44 ml/min AND eGFR decline > 2ml/min/1.73m^2 per year

[**Note: the above criterion including age and eGFR are per the inclusion criteria of the clinical trials of tolvaptan in ADPKD (TEMPO 3:4 and REPRISE); either may be used as the qualifying criterion in patients who overlap (e.g., 18 to 50 years with eGFR 60 to 65 ml/min/1.73m^2)*]

For women of childbearing potential

☐ Per the manufacturer's prescribing information, available data with tolvaptan (JYNARQUE) in pregnant women is insufficient to determine if there is a drug associated risk of adverse developmental outcomes. Based on animal data, tolvaptan (JYNARQUE) may cause fetal harm. In addition, breastfeeding is not recommended.

Dosage and Administration

- Tolvaptan (JYNARQUE) is available in 7-day blister cards of the following tablet strengths for morning and afternoon doses:
  - 45 mg and 15 mg
  - 60 mg and 30 mg
  - 90 mg and 30 mg
- The initial recommended dosage of tolvaptan (JYNARQUE) is 60 mg orally per day which is divided as 45 mg upon awakening and 15 mg taken 8 hours later.
- It is recommended to titrate the dose to 60 mg plus 30 mg, then 90 mg plus 30 mg per day, if tolerated, with at least a weekly interval between dose titrations.
- The dose may be down-titrated based on tolerability (the tablets are not scored).
- If a dose is not taken at the scheduled time, it is recommended to take the next dose at the scheduled time.
- Dose adjustment for patients taking moderate CYP 3A inhibitors:

Standard Morning and Afternoon Doses (mg)	Dose (mg) with Moderate CYP 3A Inhibitors
90 mg and 30 mg	45 mg and 15 mg
60 mg and 30 mg	30 mg and 15 mg
45 mg and 15 mg	15 mg and 15 mg

Monitoring

Risk of Serious Liver Injury [Boxed Warning]

- Monitoring of ALT, AST, and bilirubin should be performed prior to initiation of tolvaptan, at 2 and 4 weeks after initiation, monthly for 18 months, and every 3 months thereafter, to reduce the risk for significant or irreversible liver injury (refer to Safety section in the Monograph; manufacturer Prescribing Information; and JYNARQUE REMS Program requirements/VA Specific Ordering Process for obtaining tolvaptan (JYNARQUE).

Issues for Consideration

FDA Indication

- Tolvaptan (JYNARQUE) is indicated to slow kidney function decline in adults at risk for rapidly progressing ADPKD. (Note: Tolvaptan (SAMSCA) is not to be used for ADPKD)

Diagnosis of ADPKD

- Various criteria are available that can be used in the diagnosis of ADPKD. The example provided below is per the inclusion criteria of the clinical trials of tolvaptan in ADPKD, TEMPO 3:4 and REPRISE (modified Pei-Ravine criteria):
  - With family history: several cysts per kidney (3 if by sonography, 5 if by computed tomography or magnetic resonance imaging).

    OR
  - Without family history: 10 cysts per kidney (by any radiologic method above) and exclusion of other cystic kidney diseases. Conditions to be excluded include: multiple simple renal cysts, renal tubular acidosis, cystic dysplasia of the kidney, multicystic kidney, multilocular cysts of the kidney, medullary cystic kidney and acquired cystic disease of the kidney.
- Other examples of diagnostic criteria include:
  - With family history: 15 to 39 years of age - presence of 3 or more (unilateral or bilateral) renal cysts; 40 to 59 years of age - 2 or more cysts in each kidney; $\geq$ 60 years of age – 4 or more cysts in each kidney.
  - Refer to Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol 2009;20:205-12 for additional criteria and estimated accuracy based on diagnostic criterion.

Total Kidney Volume

- Total kidney volume has been suggested as one of several factors that may be used as a marker to assess the risk for rapid disease progression in patients with ADPKD. Although TKV has been approved by the FDA as a biomarker for studies in the treatment of ADPKD, routine or standardized use of imaging studies to evaluate TKV in clinical practice is limited. As TKV can be calculated from an MRI or CT scan of the patient's kidneys, the manufacturer's web site provides information on the requested measurements for calculation of TKV.

Drug-Drug Interactions

Impact of other drugs on tolvaptan

- CYP 3A inhibitors and inducers:
  - Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated.
  - Reduction in dose of tolvaptan is recommended in patients taking moderate CYP 3A inhibitors.
  - Patients should avoid grapefruit juice while being treated with tolvaptan.
  - Avoid use of strong CYP 3A inducers during treatment with tolvaptan.
  - Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with tolvaptan had no clinically relevant impact on exposure to tolvaptan.

Impact of tolvaptan on other drugs

- OATP1B1/3 and OAT3 transporter substrates
  - The manufacturer's product information recommends avoiding concomitant use of tolvaptan with OATP1B1/3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide) due to the potential increase in plasma concentrations of these substrates from inhibition by the oxybutyric metabolite of tolvaptan.
- BCRP transporter substrates
  - The manufacturer's product information recommends avoiding concomitant use of tolvaptan with BCRP substrates (e.g., rosuvastatin) as tolvaptan is an inhibitor of BCRP.
- P-gp substrates
  - When digoxin was administered with tolvaptan, digoxin Cmax was increased by 30% and AUC by 20%.
- V2-receptor agonist
  - Tolvaptan, as a V_2-receptor antagonist, will interfere with the agonist activity of desmopressin; avoid concomitant use of tolvaptan with a V_2-agonist.
- Other drugs
  - Co-administration of tolvaptan did not meaningfully alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone.

Hypernatremia, Dehydration and Hypovolemia

- Tolvaptan (JYNARQUE) may cause dehydration, hypovolemia and hypernatremia. Abnormalities in serum sodium should be corrected prior to initiation of tolvaptan (JYNARQUE).
- Patients should be instructed to drink water when thirsty, throughout the day and night while awake.
- If serum sodium increases above normal during treatment, or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, tolvaptan (JYNARQUE) should be temporarily suspended until serum sodium, hydration and volume status is within normal range.
- In clinical trials with tolvaptan (JYNARQUE) in ADPKD, patients were instructed to limit dietary salt intake to < 5 grams/day, and to ingest at least 2 to 3 liters of fluid per day (including 1 to 2 cups of water at bedtime regardless of perceived thirst, and to replenish fluids after each episode of nocturia).

Discontinuation Criteria

- Inability to adhere to liver function test monitoring at 2 and 4 weeks after initiation of treatment with tolvaptan (JYNARQUE), monthly for 18 months, then every 3 months thereafter
- Inability to adhere to twice daily therapy with tolvaptan (JYNARQUE)
- Inability to tolerate treatment with tolvaptan (JYNARQUE)
- Development of chronic kidney disease stage 5 (eGFR < 15 ml/min/1.73m^2), end-stage kidney disease

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