

PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Jynarque® (tolvaptan tablets – Otsuka)

TAC APPROVAL DATE: 06/12/2019

OVERVIEW

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

Disease Overview

ADPKD is a heterogeneous, inherited kidney disorder associated with the development of kidney cysts, which result in kidney pain, hypertension, renal failure, and other clinical sequelae.⁵⁻⁸ The condition is a common cause of end-stage renal disease (ESRD); however, other organs are also impacted (e.g., hepatic and vascular systems). Progressive kidney enlargement occurs; however, manifestations generally do not occur until later in life (fourth decade) due to compensatory renal mechanisms. If a parent has the condition, a child has a 50% chance of inheritance. Approximately 600,000 people in the US have this condition.

Clinical Efficacy

Jynarque was shown to slow the rate of decline in renal function in adults at risk of rapidly-progressing ADPKD in two trials.¹⁻⁴ TEMPO 3:4 (n = 1,445) [published] involved adults (18 to 50 years of age) with early, rapidly-progressing (total kidney volume \geq 750 mL and aged < 51 years) ADPKD who received Jynarque or placebo for up to 3 years.¹⁻² Patients had an average estimated glomerular filtration rate (eGFR) of 82 mL/min/1.73 m². The prespecified primary endpoint of 3-year change in total kidney volume was achieved with Jynarque therapy (P < 0.0001).¹ During the 3-year period, total kidney volume increased by 2.8% per year with Jynarque vs. 5.5% per year with placebo (P < 0.001).² The difference in total kidney volume occurred mainly in Year 1, with little additional differences noted in Year 2 and 3.¹ The relative rate of ADPKD-related events were decreased by 13.5% in patients randomized to Jynarque compared with placebo (44 vs. 50 events per 100 person-years; P = 0.0095). This composite endpoint was primarily driven by decreases in worsening kidney function and kidney pain events.¹⁻² TEMPO 4:4 (n = 871) [published] involved patients completing TEMPO 3:4 and provided an additional 2 years of data regarding the effects of Jynarque, as all patients were given active therapy.^{1,3} The difference between groups in total kidney volume was not maintained.¹ The percent changes in total kidney volume from the baseline of TEMPO 3:4 to Month 24 of TEMPO 4:4 were 29.9% among those previously receiving Jynarque vs. 31.6% who were given placebo prior [P = 0.38]).

REPRISE (n = 1,370) [published] involved adults (18 to 65 years of age) with later stage ADPKD who received Jynarque or placebo for up to 1 year.^{1,4} The trial included a prerandomization phase to assess tolerability, as well as a 3-week randomized withdrawal period to evaluate renal function. Patients had an average eGFR of 41 mL/min/1.73 m². In the randomized period, the change in eGFR from pretreatment baseline to post-treatment follow-up was -2.3 mL/min/1.73 m²/year with Jynarque compared with -3.6 mL/min/1.73 m²/year with placebo, with a treatment effect of 1.3 mL/min/1.73 m²/year (P < 0.0001). The eGFR slope (with adjustment per trial duration), a key secondary endpoint, also demonstrated a difference between treatment groups of 1.0 mL/min/m²/year (P < 0.0001).

Guidelines

The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Working Groups on Inherited Kidney Disorders and European Renal Best Practice published a position statement regarding use of tolvaptan in ADPKD (2016).¹⁰ A confirmed eGFR decline ≥ 5 mL/min/1.73 m² in 1 year, and/or ≥ 2.5 mL/min/1.73 m² per year over a period of 5 years defines rapid progression. Also, a total kidney volume increase $> 5\%$ per year by repeated measurements (preferably three or more, each at least 6 months apart and by magnetic resonance imaging) defines rapid progression.¹⁰ The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m² or receiving dialysis).

The National Kidney Foundation and the Polycystic Kidney Disease Foundation, list tolvaptan as an FDA-approved treatment option for patient with ADPKD.^{8,11}

Safety

Jynarque has a Boxed Warning regarding a risk of serious liver injury which can be fatal.¹ Monitor transaminases and bilirubin levels prior to therapy initiation, at 2 weeks and 4-weeks after initiation, then continuing monthly for the first 18 months and once every 3 months thereafter. Other Warnings/Precautions for Jynarque include hypernatremia, dehydration, and hypovolemia; intervention may be required. Due to the potential risk of liver injury, Jynarque has a REMS program which restricts distribution. The program has many components involving the prescriber, patient, and pharmacies. The most common adverse events in patients treated with Jynarque (incidence $> 10\%$ and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria, and polydipsia.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Jynarque. All approvals are provided for the duration noted below. Due to the specialized skills required for evaluation and diagnosis of patients treated with Jynarque as well as the monitoring required for adverse events and long-term efficacy, approval requires Jynarque to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Jynarque is recommended in those who meet the following criteria:

FDA-Approved Indication

- 1. Autosomal Dominant Polycystic Kidney Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C and D):
 - A)** The patient is ≥ 18 years of age; AND
 - B)** The agent is prescribed by or after consultation with a nephrologist; AND
 - C)** According to the prescribing physician, the patient has rapidly-progressing autosomal dominant polycystic kidney disease (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); AND
 - D)** The patient does not have Stage 5 chronic kidney disease (glomerular filtration rate < 15 mL/min/1.73 m² or receiving dialysis).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Jynarque has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

1. **Patient is Currently Receiving Samsca® (tolvaptan tablets).** Samsca is a tolvaptan product that is indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and syndrome of inappropriate antidiuretic hormone.⁹ Concomitant use is not recommended.
2. **Hyponatremia.** Samsca is another tolvaptan product indicated for the treatment of clinically-significant hypervolemic and euvolemic hyponatremia (serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction and fluid restriction), including patients with heart failure and syndrome of inappropriate antidiuretic hormone (SIADH). Samsca should be used for this condition.
3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Jynarque® tablets for oral use [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; February 2019.
2. Torres VE, Chapman AB, Devuyst O, et al, for the TEMPO 3:4 trial investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med.* 2012;367(25):2407-2418. [Supplementary Appendix].
3. Torres VE, Chapman AB, Devuyst O, et al, for the TEMPO 4:4 trial investigators. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 trial. *Nephrol Dial Transplant.* 2018;33(3):477-489.
4. Torres VE, Chapman AB, Devuyst O, et al, for the REPRISÉ trial investigators. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med.* 2017;377(20):1930-1942. [Supplementary Appendix].
5. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2015;88:17-27.
6. Ong ACM, Devuyst O, Knebelmann B, et al, on behalf of the ERA-EDTA Working Group for Inherited Kidney Diseases. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet.* 2015;385:1993-2002.
7. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. In Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Last Updated: June 11, 2015. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1246/> Accessed on April 27, 2018.
8. National Kidney Foundation. Polycystic kidney disease. Available at: <https://www.kidney.org/atoz/content/polycystic>. Accessed on June 3, 2019.
9. Samsca® tablets [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; April 2018.
10. Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dis Transplant.* 2016;31:337-348. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4762400/pdf/gfv456.pdf>. Accessed on May 7, 2018.
11. Polycystic Kidney Disease Foundation. Tolvaptan. Available at: <https://pkdcure.org/tolvaptan/>. Accessed on June 3, 2019.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	05/09/2018
Early annual revision	Added the diagnosis of hyponatremia in the Conditions Not Recommended for Approval section.	06/27/2018
Annual review	No change to the criteria.	06/12/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee.