

tolvaptan (Jynarque[™], generics)

Policy # 00647

Original Effective Date: 11/21/2018

Current Effective Date: 01/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider tolvaptan (Jynarque[™], generics)[†] for the treatment of rapidly progressing autosomal dominant polycystic kidney disease to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for tolvaptan (Jynarque, generics) will be considered when the following criteria are met:

- Patient has a diagnosis of autosomal dominant polycystic kidney disease; AND
- According to the prescribing physician, the patient's disease is rapidly progressing (e.g., reduced or declining renal function, high or increasing total kidney volume) (See Policy Guidelines section); AND
*(Note: This specific patient selection criterion is an additional Company requirement and will be denied as not medically necessary** if not met).*
- Patient is 18 years of age or older; AND
- Patient does NOT have any of the following:
 - Hypovolemia; OR
 - Anuria; OR
 - Uncorrected urinary outflow obstruction; OR
 - History of signs or symptoms of significant liver impairment or injury (not including uncomplicated polycystic liver disease); OR
 - Uncorrected abnormal blood sodium concentrations.
- If the request is for brand Jynarque, patient has tried and failed (e.g., intolerance or inadequate response) GENERIC tolvaptan unless there is clinical evidence or patient history that suggests GENERIC tolvaptan will be ineffective or cause an adverse reaction to the patient.
*(Note: This specific patient selection criterion is an additional Company requirement and will be denied as not medically necessary** if not met).*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of tolvaptan (Jynarque, generics) when the patient's ADPKD is not rapidly progressing to be **not medically necessary.****

Based on review of available data, the Company considers the use of brand Jynarque when the patient has not tried and failed GENERIC tolvaptan to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tolvaptan (Jynarque) when patient selection criteria are not met (except those denoted to be **not medically necessary****) to be **investigational.***

Policy 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). In this guidance, rapid progression has been defined as:

- Confirmed eGFR decline ≥ 5 mL/min/1.73 m² in 1 year; OR
- Confirmed eGFR decline ≥ 2.5 mL/min/1.73 m² per year over a period of 5 years; OR
- Total kidney volume increase $> 5\%$ per year by repeated measurements (preferably 3 or more, at least 6 months apart and by magnetic resonance imaging).

Background/Overview

Jynarque is a formulation of the selective vasopressin V₂-receptor antagonist, tolvaptan. It is indicated to slow kidney disease function decline in adults at risk of rapidly-progressing autosomal dominant polycystic kidney disease (ADPKD), and works by reducing intracellular adenosine 3', 5'-cyclic monophosphate (cAMP). The reduced cAMP concentrations lead to an increase in urine water excretion, more free water clearance, and a decrease in urine osmolality. In human ADPKD cyst epithelial cells, Jynarque inhibits AVP-stimulated in vitro cystic growth and chloride-dependent fluid secretion into cysts. Due to the risk of serious liver injury, Jynarque is only available through a risk evaluation and mitigation strategy (REMS) program. The program has many components involving the prescriber, patient, and pharmacies. Jynarque should be dosed initially at 45 mg orally upon waking and 15 mg administered 8 hours later then titrated to 90 mg plus 30 mg as tolerated with at least weekly intervals between titrations.

Tolvaptan is marketed under two brand names, Jynarque and Samsca, which both now have generics available. Jynarque is available as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg tablets and indicated for the treatment of ADPKD. It has a black box warning and REMS program due to its risk of liver injury. Samsca is available as 15 and 30 mg tablets and is indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia. The use of Samsca does not require a REMS program.

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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. The condition is a common cause of end-stage renal disease (ESRD); however, other organs are also impacted (e.g. hepatic and vascular system disease). Progressive kidney enlargement occurs throughout the disease course, but 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 an approximate 50% chance of inheritance. ADPKD impacts around 600,000 people in the United States. Prior to the availability of Jynarque, management of ADPKD emphasized treating disease complications that occur (e.g., hypertension, flank pain, kidney decline). Patients that experience severe decreases in renal function could also consider some form of dialysis, or if appropriate, kidney transplantation. Curative options are not currently available.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Jynarque was approved in April 2018 to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Efficacy of Jynarque in slowing the rate of decline in renal function in patients at risk of rapidly progressing ADPKD was established in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages.

TEMPO 3:4 included 1445 adult patients with early (estimated $\text{CrCl} \geq 60 \text{ mL/min}$), rapidly-progressing (total kidney volume $\geq 750 \text{ mL}$ and age < 51 years) ADPKD were randomized 2:1 to treatment with Jynarque or placebo. Patients were treated for up to 3 years at the highest dose tolerated (max 90 mg at waking and 30 mg 9 hours later). The primary endpoint was the intergroup difference for rate of change of total kidney volume normalized as a percentage. In the Jynarque group the total kidney volume increased by 2.8% compared to 5.5% in the placebo group ($P < 0.001$). Therefore this trial did meet its prespecified primary endpoint; however, the difference in total kidney volume 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 total kidney volume was not maintained. Jynarque has little effect on kidney size beyond what accrues during the first year of treatment.

REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65 years) with chronic kidney disease with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56 or eGFR between 25 and 44 mL/min/1.73 m^2 plus eGFR decline > 2.0

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mL/min/1.73 m² per year if between age 56-65 years. A total of 1370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. 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. This difference was found to be -2.3 mL/min/1.73 m² per year in the Jynarque group compared with -3.6 mL/min/1.73 m² per year in the placebo group. This corresponds to a treatment effect of 1.3 mL/min/1.73 m² per year which was statistically significant (p < 0.0001).

References

1. Jynarque [package insert]. Otsuka America Pharmaceutical, Inc. Rockville MD. October 2018.
2. Jynarque Drug Evaluation. Express Scripts. Updated August 2018.
3. 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 Practis. *Nephrol Dis Transplant*. 2016;31:337-348.

Policy History

Original Effective Date: 11/21/2018

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11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. New policy.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Clarified criteria regarding the definition of rapidly progressing disease and added policy guidelines section with reference.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2022	Medical Policy Committee review
12/14/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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12/04/2025 Medical Policy Committee review

12/10/2025 Medical Policy Implementation Committee approval. Title changed from “tolvaptan (Jynarque)” to “tolvaptan (Jynarque, generics)”. Generic added to policy with new criterion requiring trial of generic prior to brand.

Next Scheduled Review Date: 12/2026

***Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.