BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

JYNARQUE™ (tolvaptan) oral
SAMSCA® (tolvaptan) oral
Tolvaptan oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for JYNARQUE (tolvaptan)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Nephrologist or in consultation with a Nephrologist

Indication
- Diagnosis of autosomal dominant polycystic kidney disease (ADPKD) and is at risk for rapidly progressing kidney dysfunction

ORIGINAL EFFECTIVE DATE: 07/16/2015 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/15/2024

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Age Requirement

- 18 years of age and less than or equal to 55 years of age

Baseline Clinical Evaluation

- Individual has **ONE** of the following risks for progression to end stage renal disease:
  - Estimated glomerular filtration rate (eGFR) between 25 mL/min/1.73m² and less than 65 mL/min/1.73m²
  - Historical annual eGFR decline of greater than or equal to 3 mL/min/1.73m² based on 5 measurements over a period of greater than or equal to 4 years
  - Mayo Clinic class (a measurement of total kidney volume (TKV) growth) 1C, 1D, or 1E
  - PROPKD score greater than 6
  - Bilateral total kidney volume (TKV) at least 750 mL or greater (by MRI or CT)
  - Bilateral kidney length greater than 16.5 cm (by ultrasound, MRI, or CT) in individuals between 18 and less than 50 years of age
- Transaminases (ALT, AST) and bilirubin
- Serum sodium within normal limits

Alternative Therapies

- Failure (trial for at least three months duration), contraindication, intolerance to **ONE** of the following:
  - Angiotensin converting enzyme (ACE) inhibitor
  - Angiotensin receptor blocker (ARB)

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No FDA labeled contraindications such as:
  - History of significant liver impairment or injury (does not apply to uncomplicated polycystic liver disease)
  - Concurrent use with strong CYP3A inhibitors (e.g., clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone)
  - Uncorrected abnormal blood sodium concentrations
  - Inability to sense or respond to thirst
  - Hypovolemia
  - Uncorrected urinary outflow obstruction
  - Anuria
- No eGFR less than 25 mL/min/1.73m²

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- No concomitant use with CYP3A inducers (e.g., barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort)
- Will not be used with desmopressin, vasopressin, Samsca (tolvaptan), or Vaprisol (conivaptan)

Documentation Requirements
- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (e.g., eGFR, transaminases, bilirubin, serum sodium)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration
- 3 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)
Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications
- Continues to be seen by a Nephrologist or in consultation with a Nephrologist

Clinical Response
- Achieved and maintains **TWO** of the following:
  - Blood pressure less than 130/80
  - At least a 25% improvement in serum creatinine from baseline
  - No albuminuria
  - Reduction in kidney pain

Adherence
- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety
- No new contraindications or significant adverse drug effects including:
  - History of significant liver impairment or injury (does not apply to uncomplicated polycystic liver disease)

  - Concurrent use with strong CYP3A inhibitors (e.g., clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone)
  - Uncorrected abnormal blood sodium concentrations
  - Inability to sense or respond to thirst
  - Hypovolemia
  - Uncorrected urinary outflow obstruction
  - Anuria
  - ALT or AST greater than 3 times the upper limit of normal (unless resolved or explained)
  - Need for renal replacement therapy
- No eGFR less than 25 mL/min/1.73m²
- No concomitant use with CYP3A inducers
- Will not be used with desmopressin, vasopressin, Samsca (tolvaptan), or Vaprisol (conivaptan)

Documentation Requirements
- Chart notes
- Supporting clinical documentation with evidence of improvement in ADPKD
- Lab values confirming safe use

Continuation Therapy Criteria Approval Duration
- 12 months OR end of plan year

Medical Necessity Requirements for SAMSCA (tolvaptan) and Tolvaptan generic

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by or in consultation with a Nephrologist, Cardiologist, or Endocrinologist

Indication
- Diagnosis of clinically significant hypervolemic **OR** euvolemic hyponatremia as evidenced by **ONE** of the following:
  - Serum sodium less than 125 mEq/L
  - OR serum sodium between 125–134 mEq/L with symptoms of hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion) resistant to fluid restriction

Age Requirement
- 18 years of age

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Baseline Clinical Evaluation

- Therapy is initiated OR re initiated in a hospital setting AND/OR individual is pending hospital discharge
- Individual has not already received 30 days of tolvaptan therapy from a recent previous hospitalization
- Drug induced causes of hyponatremia have been discontinued

Alternative Therapies

- Failure, contraindication, intolerance to:
  - Fluid restriction
  - Loop diuretics (bumetanide, furosemide, torsemide)
  - Saline infusion
- **For brand Samsca**: failure, contraindication, intolerance to generic tolvaptan. Note: Any failure, contraindication, or intolerance to the generic drugs should be reported to the Food and Drug Administration (FDA)

Safety

- No FDA labelled contraindications such as:
  - Use in autosomal dominant polycystic kidney disease outside FDA approved Risk Evaluation and Mitigation Strategy (REMS)
  - Hypovolemic hyponatremia
  - Anuria
  - Use with strong CYP3A inhibitors such as clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone
- No need to raise serum sodium acutely or urgently
- No underlying liver disease, including cirrhosis
- No creatinine clearance less than 10 mL/min
- Will not be used with CYP3A inducers such as barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort
- Will not be used with moderate CYP3A inhibitors such as amiodarone, cyclosporine, diltiazem, erythromycin, fluconazole, verapamil, others
- Will not be used with desmopressin, vasopressin, Jynarque (tolvaptan), or Vaprisol (conivaptan)

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (e.g., serum sodium)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- Total of 30 days only including inpatient days

- No renewal or continuation beyond 30 days

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Samsca (tolvaptan) is 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 with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with Samsca (tolvaptan). It has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients. Hyponatremia may present with nausea, headache, lethargy, muscle cramps, altered gait or falls, mental status changes, seizures, or coma.

Jynarque (tolvaptan) is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

Samsca (tolvaptan) should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., > 12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Arterial vasodilatation is involved in the development of hyponatremia. With arterial vasodilatation there is a reduction in the effective arterial blood volume, this in turn leads to the stimulation of several neurohumoral systems [the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS)] and the non-osmotic release of an antidiuretic hormone, arginine vasopressin (AVP or vasopressin). The activation of the RAAS and SNS results in sodium retention and renal vasoconstriction. Increased levels of AVP causes activation of vasopressin 2 (V2) receptors within the renal tubules. These receptors play a major role in the rate of solute-free water excretion. Depending on the daily water intake, patients cannot excrete enough free water and they develop water retention, which generates serum dilution and hypo-osmolality.

Hyponatremia can be hypovolemic, euvolemic (normovolemic), or hypervolemic. Hypovolemic hyponatremia is a result of fluid losses either from the kidneys (most commonly due to iatrogenic over-diuresis) or loss from the gastrointestinal tract (such as diarrhea). Patients typically will have signs of dehydration and findings of pre-renal

azotemia due to the contraction of the total plasma volume. Patients with hypovolemic hyponatremia should be treated with the withdrawal of diuretics and the infusion of isotonic solutions to normalize the total body sodium level.

In euvolemic hyponatremia the total body sodium level is normal or near normal. Asymptomatic patients need only have their free water restricted.

Hypervolemic hyponatremia is characterized by a pronounced deficit of free water excretion and leads to inappropriate water retention in comparison with the sodium concentration. This imbalance results in an expanded extracellular volume and dilutional hyponatremia. Patients with hypervolemic hyponatremia usually have ascites and/or edema and may have concurrent kidney injury. Hypervolemic hyponatremia should be managed by restricting free water ingestion, by increasing renal excretion of solute-free water, and by correcting the vasodilatation and the resultant decreased effective arterial blood volume. Causes of this type of hyponatremia include congestive heart failure, liver cirrhosis, and renal diseases such as renal failure and nephrotic syndrome.

Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-receptor that is 1.8 times that of native AVP. Tolvaptan affinity for the V2-receptor is 29 times greater than that for the V1a-receptor. When taken orally, 15-60 mg doses of tolvaptan antagonize the effect of AVP and cause an increase in urine water excretion that results in an increase in free water clearance (so called aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations. Urinary excretion of sodium and potassium and plasma potassium concentration are not significantly changed. Doses above 60 mg do not increase aquaresis or serum sodium further.

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous fluid filled cysts in both kidneys. The progressive expansion of cysts occurs slowly which replaces much of the normal mass of the kidneys, reducing kidney function and ultimately leading to kidney failure. Cysts may also develop in other organs such as the liver, pancreas, spleen, heart, and blood vessels of the brain. ADPKD patients suffer from acute or chronic pains (mostly caused by infection or intracystic bleeding), hematuria, urinary tract infections, nephrolithiasis, and hypertension.

Autosomal dominant polycystic kidney disease (ADPKD) is diagnosed by ultrasound, CT scan, or MRI. The Ravine's diagnostic criteria for individuals who have a 50% risk of developing ADPKD type 1 include:

- At least two unilateral (cysts in one kidney) or bilateral (cysts in both kidneys) cysts in individuals who are younger than age 30 for individuals with a positive family history of ADPK. Individuals with a negative family history of ADPKD need at least 5 cysts.
- At least two cysts in each kidney in individuals who are between 30 and 59 years for individuals with a positive family history of ADPK. Individuals with a negative family history of ADPKD need at least 5 cysts.
- At least four cysts in each kidney in individuals who are 60 years old or older for individuals with a positive family history of ADPK. Individuals with a negative family history of ADPKD need at least 8 cysts.

There are two genes known to be associated with ADKPD; *PKD1* and *PKD2*. *PKD1* is found in approximately 85 percent of individuals with ADPKD.

In human ADPKD cyst epithelial cells, tolvaptan inhibits AVP-stimulated *in vitro* cyst growth and chloride-dependent fluid secretion into cysts. In animal models, decreased cAMP concentrations were associated with

decreases in the rate of growth of total kidney volume (TKV) and decreases in the rate of formation and enlargement of kidney cysts.

In 2013 the manufacturer and Food & Drug Administration (FDA) issued a warning on the potential of significant liver injury with the use of Samsca (tolvaptan) that was seen in patients with autosomal dominant polycystic kidney disease (ADPKD). The FDA safety announcement recommended limiting the duration of Samsca (tolvaptan) to no longer than 30 days and that it should not be used in patients with underlying liver disease. Because of the risks of serious liver injury, Jynarque (tolvaptan) is available only through a Risk Evaluation and Mitigation Strategy (REMS) program.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Mayo Clinic Classification (http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754)

Class	Estimated kidney growth rate: yearly percentage increase	Risk for eGFR decline	Estimated eGFR slope (mL/min/1.73m^2 per year: male	Estimated eGFR slope (mL/min/1.73m^2 per year: female
1A	< 1.5	Low	- 0.23	0.03
1B	1.5- < 3	Intermediate	- 1.33	- 1.13
1C	3- < 4.5	High	- 2.33	- 2.43
1D	4.5- < 6	High	- 3.48	-3.29
1E	≥ 6	High	- 4.78	- 4.58
Classification only applies to patients with typical morphology of ADPKD as defined by diffuse bilateral cystic involvement of the kidneys.				

In the absence of Cockcroft-Gault GFR, CKD-EPI >45 mL/min may be used, and in the absence of TKV, ultrasound kidney length >16.5 cm may be used.[6,7]

Progression score for Polycystic Kidney Disease:

PROPKD	
Variable:	Points
Male	1
HTN before age 35 years	2
First urological event: Gross hematuria, cyst infections, and flank pain related to cysts	2
Mutation:	
PKD2	0
Non-truncating *PKD1*	2
Truncating *PKD1*	4

PROPKD Score	0	1	2	3	4	5	6	7	8	9
Risk of Progression to ESRD	Low Risk				Intermediate Risk			High Risk		
Median age for ESRD onset	70.6				56.9			49		

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Five Stages of Kidney Disease:

- Stage 1 with normal or high GFR (GFR > 90 mL/min)
- Stage 2 Mild CKD (GFR = 60-89 mL/min)
- Stage 3A Moderate CKD (GFR = 45-59 mL/min)
- Stage 3B Moderate CKD (GFR = 30-44 mL/min
- Stage 4 Severe CKD (GFR = 15-29 mL/min)
- Stage 5 End Stage CKD (GFR <15 mL/min)

Resources:

Jynarque (tolvaptan) product information, revised by Otsuka America Pharmaceutical, Inc. 10-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 11, 2025.

Samsca (tolvaptan) product information, revised by Otsuka America Pharmaceutical, Inc. 04-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 11, 2025.

Tolvaptan product information, revised by Apotex Corp. 11-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed J April 11, 2025.

Torres VE, Bennett WM. Autosomal dominant polycystic kidney disease (ADPKD) in adults: Epidemiology, clinical presentation, and diagnosis. In: UpToDate, Perrone RD, Taylor RD (Eds), UpToDate, Waltham, MA.: UpToDate Inc. http://uptodate.com. Literature current through May 2025. Topic last updated October 24, 2024. Accessed June 15, 2025.

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Müller RM, Messchendorp AL, Birn H, et al.: An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrology Dialysis Transplantation 2022 May; 37 (5): 825–839. Assessed July 08, 2024. Re-evaluated June 15, 2025.