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 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.

Criteria:

JYNARQUE (tolvaptan)

➢ **Criteria for initial therapy:** Jynarque (tolvaptan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist

2. Individual is between 18 years of age and 55 years of age

3. Individual has a confirmed diagnosis autosomal dominant polycystic kidney disease (ADPKD) and is at risk for rapidly progressing kidney dysfunction

4. Individual has **ONE** of the following risks for progression to end-stage renal disease:
    a. Individual is between 18 years of age and less than or equal to 55 years of age with an estimated glomerular filtration rate (eGFR) between 25 mL/min/1.73m^2 less than 65 mL/min/1.73m^2
    b. Individual has a historical annual eGFR decline of greater than or equal to 3 mL/min/1.73m^2 based on 5 measurements over a period of greater than or equal to 4 years
    c. Mayo Clinic class (a measurement of total kidney volume (TKV) growth) is 1C, 1D, or 1E
    d. Individual has a PROPKD score > 6
    e. Bilateral TKV $\geq$ 750 mL (by magnetic resonance imaging [MRI], or computed tomography [CT])
    f. Bilateral kidney length > 16.5 cm (by ultrasound, MRI, or CT) in an individual is between 18 years of age and less than 50 years of age

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Transaminases (ALT, AST) and bilirubin
    b. Serum sodium are within normal limits

6. Individual has documented failure (after 3 months of use), contraindication per FDA label, intolerance, or is not a candidate for angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)

7. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

8. There are **NO** FDA-label contraindications such as:
    a. A history of signs or symptoms of significant liver impairment or injury. This contraindication does not apply to *uncomplicated* polycystic liver disease
    b. Concurrent use with strong CYP 3A inhibitors such as clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone, and others
    c. Use in uncorrected abnormal blood sodium concentrations
    d. Individual is unable to sense or appropriately respond to thirst
    e. Individual with hypovolemia
    f. Uncorrected urinary outflow obstruction
    g. Anuria

9. Individual does not have an estimated glomerular filtration rate (eGFR) of less than 25 mL/min/1.73m^2

10. There are no significant interacting drugs such as CYP3A inducers (e.g., barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort and others)

11. Will not be used with desmopressin or vasopressin or tolvaptan (brand Samsca or generic) or Vaprisol (conivaptan)

PHARMACY COVERAGE GUIDELINE

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

Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Jynarque (tolvaptan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist

2. Individual's condition has responded while on therapy with response defined as achieved and maintains **TWO** of the following:
    a. Blood pressure is < 130/80
    b. At least a 25% improvement on serum creatinine from baseline
    c. No albuminuria
    d. Reduction in kidney pain

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Hepatic injury
        ii. Individual with signs and symptoms consistent with hepatic injury
        iii. Individual whose ALT or AST exceeded 3 times the upper limit of normal unless there is another explanation for the injury, or it has resolved
    c. Individual needs renal replacement therapy

6. Individual does not have an estimated glomerular filtration rate (eGFR) of less than 25 mL/min/1.73m^2

7. There are no significant interacting drugs such as CYP3A inducers (e.g., barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort and others)

8. Will not be used with desmopressin or vasopressin or tolvaptan (brand Samsca or generic) or Vaprisol (conivaptan)

Renewal duration: 12 months

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

- 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**

SAMSCA (tolvaptan)
Tolvaptan

- **Criteria for therapy:** Samsca (tolvaptan) and generic tolvaptan are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist, Cardiologist, or Endocrinologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of clinically significant hypervolemic **OR** euvolemic hyponatremia as evidenced by **ONE** of the following:
     a. Serum sodium prior to initiation is < 125 mEq/L
     b. Serum sodium prior to initiation is 125-134 mEq/L **and** individual is symptomatic for hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion, etc.) that is resistant to fluid restriction

  4. Therapy is initiated **OR** re-initiated in a hospital setting **AND/OR** individual is pending hospital discharge

  5. Individual has not already received 30 days of tolvaptan therapy from a recent previous hospitalization

  6. Individual has documented failure, contraindication per FDA label, or intolerance such that the individual is unable to use therapies to control hyponatremia such as:
     a. Fluid restriction
     b. Loop diuretics such as bumetanide, furosemide, torsemide
     c. Saline infusion

  7. **For brand Samsca:** Individual has failure, contraindication per FDA label, intolerance, or is not a candidate for **generic tolvaptan** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  8. Drug-induced causes of hyponatremia have been discontinued

  9. There are **NO** FDA-label contraindications such as:
     a. Use in patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved Risk Evaluation and Mitigation Strategy (REMS)
     b. Individual is unable to sense or appropriately respond to thirst

c. Hypovolemic hyponatremia
d. An individual who is anuric
e. Use with strong CYP3A inhibitors such as clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone

10. Individual does not need to raise serum sodium acutely or urgently

11. Individual does not have underlying liver disease, including cirrhosis

12. Individual does have a creatinine clearance of less than 10 mL/min

13. Will not be used with CYP3A inducers such as barbiturates, carbamazepine, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort

14. Will not be used with moderate CYP3A inhibitors such as amiodarone, cyclosporine, diltiazem, erythromycin, fluconazole, verapamil, others

15. Will not be used with desmopressin or vasopressin or Jynarque (tolvaptan) or Vaprisol (conivaptin)

Approval duration:
Total of 30 days only including the number of days while inpatient
No renewal or continuation beyond 30 days

- 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).

PHARMACY COVERAGE GUIDELINE

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

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		

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 May 31, 2024.

Samsca (tolvaptan) product information, revised by Otsuka America Pharmaceutical, Inc. 04-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 31, 2024.

Tolvaptan product information, revised by Camber Pharmaceuticals, Inc. 08-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 09, 2024.

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.

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 June 2024. Topic last updated July 25, 2022. Accessed July 9, 2024.

Chapman AB, Rahbari-Oskoui FF, Bennett WM. Autosomal dominant polycystic kidney disease (ADPKD): Treatment. In: UpToDate, Perrone RD, Taylor EN (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated September 11, 2023. Accessed July 09, 2024.

Sterns RH. Overview of the treatment of hyponatremia in adults. In: UpToDate, Emmett M, Forman JP (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated on October 25, 2023. Accessed July 09, 2024.

Sterns RH. Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat. In: UpToDate, Emmett M, Forman JP (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated February 13, 2024. Accessed July 09, 2024.