BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 8/15/19**
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	ARCHIVE DATE:

JYNARQUE™ (tolvaptan) oral tablet
SAMSCA® (tolvaptan) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Jynarque (tolvaptan)

Criteria:

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

1. Prescriber is a physician specializing in kidney disease or is in consultation with a Nephrologist or Geneticist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of autosomal dominant polycystic kidney disease (ADPKD)

4. Individual has failure, contraindication or intolerance such that the individual is unable to use **ALL** the following preferred step therapy agents:
   - Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
   - Calcium channel blocker **or** beta-blocker

5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - Measure ALT, AST, bilirubin as required by the Jynarque REMS Program
   - Comprehensive metabolic panel
   - Correction of any abnormalities of serum sodium
   - Blood pressure

6. There are **NO** contraindications
   - Contraindications include:
     - With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
     - Concurrent use with strong CYP 3A inhibitors
     - Use in uncorrected abnormal blood sodium concentrations
     - Individual is unable to sense or appropriately respond to thirst
     - Individual with hypovolemia
     - Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product
     - Uncorrected urinary outflow obstruction
     - Anuria

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

8. Will not be used with desmopressin or vasopressin or Samsca (tolvaptan) or Vaprisol (conivaptin)

9. Will not be used in individuals with a creatinine clearance of less than 25 mL/min

Initial approval duration: 3 months

- **Criteria for continuation of coverage (renewal request):** Jynarque (tolvaptan) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in kidney disease or is in consultation with a Nephrologist

2. Individual's condition responded while on therapy
    - Response is defined as:
        - Achieved and maintains **TWO** of the following:
            - Blood pressure is < 130/80
            - At least a 25% improvement on serum creatinine from baseline
            - No albuminuria

3. Individual has been adherent with the medication

4. There are no significant interacting drugs

5. Will not be used in individuals with a creatinine clearance of less than 25 mL/min

6. Will not be used with desmopressin or vasopressin or Samsca (tolvaptan) or Vaprisol (conivaptin)

Renewal duration: 12 months

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Samsca (tolvaptan)

Criteria:

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

1. Prescriber is a physician specializing in managing fluid and electrolyte abnormalities or is in consultation with a Nephrologist, Cardiologist, or Endocrinologist
2. Individual is 18 years of age or older
3. Therapy is initiated **OR** re-initiated in a hospital setting **AND/OR** individual is pending hospital discharge
4. A confirmed diagnosis of clinically significant hypervolemic **OR** euvolemic hyponatremia as evidenced by **ONE** of the following:
   - Serum sodium prior to initiation is ≤ 125 mEq/L
   - Serum sodium prior to initiation is 125-134 mEq/L **and** individual is symptomatic for hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion, etc.)
   - Requires ongoing treatment to prevent clinically significant hypervolemic or euvolemic hyponatremia due to conditions such as heart failure or Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
5. Individual has failure, contraindication or intolerance such that the individual is unable to use therapies to control hyponatremia, such as:
   - Fluid restriction
   - Loop diuretics
   - Demeclocycline
   - Saline infusion
6. Drug-induced causes of hyponatremia have been discontinued
7. There are **NO** contraindications:
   - Contraindications include:
     - Use in patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved REMS
     - Need to raise serum sodium acutely or urgently
     - Individual is unable to sense or appropriately respond to thirst
     - Hypovolemic hyponatremia
     - An individual who is anuric
     - Use with strong CYP3A inhibitors such as clarithromycin, telithromycin, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, nefazodone
     - Hypersensitivity (anaphylactic shock, generalized rash) to tolvaptan or any component of the product

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

9. Will not be used in patients with underlying liver disease, including cirrhosis

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

11. Will not be used with hypertonic saline

12. Will not be used in individuals with a creatinine clearance of less than 10 mL/min

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

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.

Resources:

Samsca package insert. Revised by manufacturer 06-2017. Accessed 06-29-2017.

Samsca. Package Insert. Revised by manufacturer February 2014. Accessed 06-02-2015.

Samsca. Package Insert. Revised by manufacturer 04-2018. Accessed 07-07-2018.

Jynarque package insert. Revised by manufacturer 04-2018. Accessed 07-07-2018.

Jynarque (tolvaptan) product information accessed 07-12-19 at DailyMed

Samsca (tolvaptan) product information accessed 07-12-19 at DailyMed

FDA Drug Safety Communications: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death. Safety announcement April 30, 2013 UCM350084.

UpToDate: Treatment of autosomal dominant polycystic kidney disease. Current through Jun 2019

UpToDate: Hypertension in autosomal dominant polycystic kidney disease. Current through Jun 2019

UpToDate: Diagnosis and screening for autosomal dominant polycystic kidney disease. Current through Jun 2019

UpToDate: Overview of the treatment of hyponatremia in adults. Current through Jun 2019