EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Tolvaptan Products – Samsca® (tolvaptan tablets for oral use – Otsuka)

TAC APPROVAL DATE: 06/12/2019

OVERVIEW

Samsca, a selective vasopressin V_2-receptor antagonist, 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 (HF) 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. It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients. The most common adverse reactions with Samsca are thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria, and hyperglycemia. Samsca has a Boxed Warning that patients should be in a hospital for initiation and re-initiation of therapy. Too rapid of a correction of hyponatremia can lead to osmotic demyelination causing dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma, and death. In addition, Samsca has a Boxed Warning that tolvaptan should not be used for the treatment of autosomal dominant polycystic kidney disease (ADPKD) outside of the FDA-approved Risk Evaluation and Mitigation Strategy (REMS), due to the risk of hepatotoxicity. The recommended starting dose is 15 mg once daily (QD). The dose may be increased at intervals ≥ 24 hours to 30 mg QD, and to a maximum of 60 mg QD as needed to raise serum sodium. Limit the treatment duration of Samsca to 30 days. If hepatic injury is suspected, discontinue Samsca. Avoid use of Samsca in patients with underlying liver disease. Samsca may lead to serious and potentially fatal liver injury.[1] In placebo-controlled trials and open-label extension study involving chronically administered Samsca in patients with ADPKD, cases of serious liver injury attributed to Samsca were noted.[1-2] These generally occurred within the first 18 months of tolvaptan therapy.[1] Jynarque™ (tolvaptan tablets) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD.[5] The initial dose of Jynarque is 60 mg per day as 45 mg taken on waking and 15 mg given 8 hours later. The dose should be titrated to 60 mg plus 30 mg, then to 90 mg plus 30 mg per day.

Clinical Data

Two trials (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 [SALT-1 and SALT-2; n = 424]) demonstrated that Samsca increased serum sodium effectively in patients with euvolemic or hypervolemic hyponatremia that was due to many underlying causes (e.g., HF, liver cirrhosis, SIADH).[1,3] Patients (aged ≥ 18 years) received therapy for 30 days with Samsca or placebo and were followed for an additional 7 days after study withdrawal. Patients in the trial had a serum sodium < 135 mEq/L at study entry (baseline 129 mEq/L). In both trials, Samsca therapy led to a greater increase in serum sodium ($P < 0.0001$) compared with baseline for the measured endpoints at Day 4 and Day 30. The effects of sustained serum sodium were demonstrated for up to 1 year in an open-label study.[1] Another long-term analysis (the Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions [SALTWATER]) showed that in 111 patients who received Samsca for approximately 1 year, increases in serum sodium were maintained.[1,4]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Samsca. All approvals are provided for up to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Hyponatremia.** Approve for up to 30 days if patient meets ONE of the following criteria (A, B, or C):
   - **A)** The patient has a serum sodium < 125 mEq/L at baseline; OR
   - **B)** The patient has less marked hyponatremia, defined as serum sodium < 135 mEq/L at baseline, that is symptomatic (e.g., nausea, vomiting, headache, lethargy, confusion); OR
   - **C)** The patient has already been started on Samsca and has received < 30 days of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Samsca 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Autosomal Dominant Polycystic Kidney Disease (ADPKD).** Jynarque (tolvaptan tablets) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. The recommended dosing differs.[5] The Samsca prescribing information states that tolvaptan should not be prescribed or used to treat ADPKD outside of the FDA-approved REMS for ADPKD.

2. **Patient is Currently Receiving Jynarque® (tolvaptan tablets).** Jynarque is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD. Concomitant use is not recommended.

3. **Patients Requiring Intervention to Raise Serum Sodium Urgently to Prevent or to Treat Serious Neurological Symptoms.** Samsca has not been studied in a setting of urgent need to raise serum sodium acutely.[1]

4. 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. Samsca® tablets for oral use [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; April 2018.
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.

3. Schrier RW, Gross P, Gheorghiade M, et al, for the SALT Investigators. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099-2112.
4. Berl T, Quittnat-Pelletier F, Verbalis JG, et al, for the SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol*. 2010;21:705-712.
5. Jynarque™ tablets for oral use [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; February 2019.

OTHER REFERENCES UTILIZED

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes.	06/15/2016
Annual revision	No criteria changes	06/28/2017
Annual revision	Added autosomal dominant polycystic kidney disease and concomitant Jynarque use in the Conditions Not Recommended for Approval section.	06/27/2018
Annual revision	No criteria changes.	06/12/2019

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