SAMSCA® (tolvaptan) (B) NOT FOR USE FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) (B) NOT FOR USE FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

WARNING: (A) INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM (B) NOT FOR USE FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

See full prescribing information for complete boxed warning.

(A) Initiate and re-initiate in a hospital and monitor serum sodium
- SAMSCA 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.

(B) Not for use for autosomal dominant polycystic kidney disease (ADPKD)
- Because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS (4.1)

Boxed Warning and Contraindications
Use in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) outside of FDA-Approved REMS (4.1) 04/2018

Warnings and Precautions
Liver Injury (5.2) 04/2018

INDICATIONS AND USAGE
SAMSCA is a selective vasopressin V1a receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvoletic 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) (1)

Important Limitations:
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA (1)
- It has not been established that SAMSCA provides a symptomatic benefit to patients (1)

ADVERSE REACTIONS
Most common adverse reactions (≥5% placebo) are thirst, dry mouth, asthenia, constipation, polyuria, and hyperglycemia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka at 1-877-726-7220 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2018

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SAMSCA® is indicated for the treatment of clinically significant hypervolemic and euvoletic 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).

Important Limitations
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.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage in Adults
Patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.
The usual starting dose for SAMSCA is 15 mg administered once daily without regard to meals. Increase the dose to 30 mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium. Do not administer SAMSCA for more than 3 days without reducing the risk of liver injury [see Warnings and Precautions (5.2)]. During initiation and titration, frequently monitor for changes in serum electrolytes and volume. Avoid fluid restriction during the first 24 hours of therapy. Patients receiving SAMSCA should be advised that they can continue ingestion of fluid in response to thirst [see Warnings and Precautions (5.1)].

2. Drug Withdrawal

Following discontinuation from SAMSCA, patients should be advised to resume fluid restriction and should be monitored for changes in serum sodium and volume status.

2.3 Co-Administration with CYP 3A Inhibitors, CYP 3A Inducers and P-gp Inhibitors CYP 3A Inhibitors

Tolvaptan is metabolized by CYP 3A, and use with strong CYP 3A inhibitors causes a marked (5-fold) increase in exposure [see Contraindications (4.5)]. The effect of moderate CYP 3A inhibitors on tolvaptan exposure has not been assessed. Avoid co-administration of SAMSCA and moderate CYP 3A inhibitors [see Warnings and Precautions (5.5), Drug Interactions (7.1)].

CYP 3A Inducers

Co-administration of SAMSCA with potent CYP 3A inducers (e.g., rifampin) reduces tolvaptan plasma exposure [see Warnings and Precautions (5.5), Drug Interactions (7.1)].

P-gp Inhibitors

Tolvaptan is a substrate of P-gp. Co-administration of SAMSCA with inhibitors of P-gp (e.g., cyclosporine) may metabolize a decrease in SAMSCA dose [see Warnings and Precautions (5.5), Drug Interactions (7.1)].

3 DOSAGE FORMS AND STRENGTHS

SAMSCA (tolvaptan) is available in 15 mg and 30 mg tablets [see How Supplied/Storage and Handling (16)].

3.1 Oral Solution

SAMSCA is contraindicated in the following conditions:

4.1 Use in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) Outside of FDA-Approved Risk Evaluation and Mitigation Strategy (REMS) for ADPKD

SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely. SAMSCA has not been studied in patients with severe hyponatremia (serum sodium <125 mEq/L) or at a rate at least 2% greater than placebo-treated patients. Hyponatremia was more frequent in placebo-treated patients compared to tolvaptan-treated patients. The incidence of hyponatremia with SAMSCA was 9.2% (21/225) compared to 1.5% (3/220) of placebo-treated patients. Hyponatremia is a known risk of SAMSCA and is not avoided even when SAMSCA is used to maintain serum sodium levels above 12 mEq/L, especially in individuals with no history of hyponatremia. SAMSCA should not be used in patients with severe hyponatremia (serum sodium <125 mEq/L) or at a rate at least 2% greater than placebo-treated patients in treating patients with an acute reduction of the extracellular fluid volume which could result in increased serum potassium levels. SAMSCA should not be used in patients with severe hyponatremia (serum sodium <125 mEq/L) or at a rate at least 2% greater than placebo-treated patients because of an adverse event, compared to 12% (26/220) of placebo-treated patients. SAMSCA should be used with caution in patients whose ability to recover from liver injury may be impaired [see Contraindications (4.1), Drug Interactions (7.1)].

4.5 Tolvaptan is metabolized by CYP 3A, and use with CYP 3A inhibitors may metabolize a decrease in SAMSCA dose [see Warnings and Precautions (5.5), Drug Interactions (7.1)].

4.6 Anuric Patients

Tolvaptan is a substrate of CYP 3A, CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations [see Dosage and Administration (2.3), Drug Interactions (7.1)]. Do not use SAMSCA with strong inhibitors of CYP 3A [see Contraindications (4.5)] and avoid concomitant use with moderate CYP 3A inhibitors.

4.7 Hypermagnesemia

Tolvaptan is a substrate of CYP 3A, CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations [see Dosage and Administration (2.3), Drug Interactions (7.1)].

4.8 Hyperkalemia and Drugs that Increase Serum Potassium

Tolvaptan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium levels. Serum potassium levels should be monitored after initiation of tolvaptan treatment in patients with a serum potassium >3 mEq/L as well as those who are receiving drugs known to increase serum potassium levels.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse event information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium <135 mEq/L) were treated with SAMSCA. The mean age of these patients was 71% of patients were male and 82% were Caucasian. One hundred eighty-nine (189) tolvaptan-treated patients had a serum sodium <130 mEq/L and 52 patients had a serum sodium <125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 patients were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium).

Overall, over 4,000 patients have been treated with oral doses of tolvaptan in open-label or placebo-controlled clinical trials. Approximately 95% of these patients had hyponatremia, approximately 2% had hypernatremia, and 1% had hyponatremia in a setting of urgent need to raise serum sodium acutely. The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/225) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (22/220) of placebo-treated patients. No adverse reaction occurring in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.

Table 1 lists the adverse reactions reported in tolvaptan-treated patients with hyponatremia (serum sodium <135 mEq/L) and at a rate at least 2% greater than placebo-treated patients in two 30-day, double-blind, placebo-controlled trials. In these studies, 223 patients were exposed to tolvaptan (starting dose 15 mg, titrated to 30 and 60 mg as needed to raise serum sodium). Adverse events resulting in death in these trials were 6% in tolvaptan-treated patients and 6% in placebo-treated patients.

Table 1. Adverse Reactions (≥2% more than placebo) in Tolvaptan-Treated Patients in Double-Blind, Placebo-Controlled Hyponatremia Trials

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>MedDRA Preferred Term</th>
<th>Tolvaptan (N = 223)</th>
<th>Placebo (N = 220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>28 (13)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>16 (7)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Thirst*</td>
<td>35 (16)</td>
<td>11 (5)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>19 (9)</td>
<td>9 (4)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>9 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Hyperglycemia*</td>
<td>14 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>8 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Pollakiuria or polyuria*</td>
<td>25 (11)</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/225) of tolvaptan-treated patients discontinued treatment because of an adverse event, compared to 12% (22/220) of placebo-treated patients. No adverse reaction occurring in discontinuation of trial medication occurred at an incidence of >1% in tolvaptan-treated patients.
SAMSCA® (tolvaptan)

The following terms are subsumed under the referenced ADR in Table 1:
- polydipsia
- diabetes mellitus
- decreased appetite
- urine output increased, micturition urgency, nocturia
- dry mouth
- tremor
- hypothermia
- hypernatremia
- dehydration/hypovolemia

In a subgroup of patients with hyponatremia (N = 475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvaptan, 38% placebo), nausea (21% tolvaptan, 16% placebo), thirst (12% tolvaptan, 2% placebo), dry mouth (7% tolvaptan, 2% placebo) and polyuria or polyuria (6% tolvaptan, 2% placebo).

Gastrointestinal bleeding in patients with cirrhosis
In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo treated patients. The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (N = 807 tolvaptan; N = 518 placebo) or in <2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and are not mentioned elsewhere in the label.

Blood and Lymphatic System Disorders: Disseminated intravascular coagulation
Cardiac Disorders: Infraventricular fibrillation
Investigations: Prothrombin time prolonged
Gastrointestinal Disorders: Ischemic colitis
Metabolism and Nutrition Disorders: Diabetic ketoacidosis
Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis
Nervous System Disorders: Cerebrovascular accident
Renal and Urinary Disorders: Urethral hemorrhage
Reproductive System and Breast Disorders (female): Vaginal hemorrhage
Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure
Vascular disorder: Deep vein thrombosis

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of SAMSCA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neurologic: Osmotic demyelination syndrome
Investigations: Hypernatremia
Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with tolvaptan, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hyponatremia is observed, management may include dose decrease or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremic patients, hypernatremia was reported as an adverse event in 0.7% of patients receiving tolvaptan vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hypernatremia of 1.7% in patients receiving tolvaptan vs. 0.6% in patients receiving placebo.

Immune System Disorders: Hypersensitivity reactions including anaphylactic shock and rash

7 DRUG INTERACTIONS
7.1 Effects of Drugs on Tolvaptan

Ketoconazole is a strong inhibitor of CYP3A. Co-administration ofLovastatin and SAMSCA increases the AUC of Lovastatin by approximately 1 -to 2 fold. SAMSCA is a weak inhibitor of CYP3A. Co-administration ofLovastatin and SAMSCA increases the AUC of Lovastatin by approximately 1 -to 2 fold.

Ketoconazole is a strong inhibitor of P-gp. Co-administration of SAMSCA and ketoconazole 200 mg daily results in a 5-fold increase in exposure to tolvaptan. Co-administration of SAMSCA with 400 mg ketoconazole daily increases the AUC of tolvaptan by 12-fold. Co-administration of lovastatin and SAMSCA increases the active metabolite lovastatin-β hydroxycacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.

Pharmacodynamic Interactions
Tolvaptan produces a greater 24 hour urine volume/excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of tolvaptan with furosemide or hydrochlorothiazide produces a 24 hour urine volume/excretion rate that is similar to the rate after tolvaptan administration alone.

Although specific interaction studies were not performed, in clinical studies tolvaptan was used concomitantly with beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics. Adverse reactions of hyperkalemia were approximately 1.7% in patients taking tolvaptan was administered with angiotensin receptor blockers, angiotensin converting enzyme inhibitors and potassium sparing diuretics compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy.

As a V_2-receptor antagonist, tolvaptan may interfere with the V_2 agonist activity of desmopressin (dDAVP) in patients with von Willebrand's disease (vWD), intravenous infusion of desmopressin. In two studies, 2 hours after administration of oral tolvaptan did not produce the expected increases in vWF Factor VIII activity. It is not recommended to administer SAMSCA with a V_2-agonist.

8 USE IN SPECIFIC POPULATIONS
There is no need to adjust dose based on age, gender, race, or cardiac function [see Clinical Pharmacology (12.3)].

8.1 Pregnancy
Pregnancy Category C.
There are no adequate and well controlled studies of SAMSCA use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification occurred at 1.7% in pregnant rabbits treated with tolvaptan (on a body surface area basis), there were reductions in maternal body weight gain and food consumption at all doses, and increased abortions at the mid and high doses (about 57% and 524 times the MRHD). At 324 times the MRHD, there were increased rates of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations [see Nonclinical Toxicology (12.3)].

8.2 Labor and Delivery
The effect of SAMSCA on labor and delivery in humans is unknown.

8.3 Nursing Mothers
It is not known whether SAMSCA is excreted into human milk. Tolvaptan is excreted into the milk of lactating rats. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or SAMSCA, taking into consideration the importance of SAMSCA to the mother.

8.4 Pediatric Use
Safety and effectiveness of SAMSCA in pediatric patients have not been established.

8.5 Geriatric Use
There is no need to adjust dose based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric [see Contraindications (4.6) and Clinical Pharmacology (12.3)].

8.6 Use in Patients with Hepatic Impairment
Moderate and severe hepatic impairment do not affect exposure to tolvaptan to a clinically relevant extent. Avoid use of tolvaptan in patients with underlying liver disease.

8.7 Use in Patients with Renal Impairment
No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric [see Contraindications (4.6) and Clinical Pharmacology (12.3)].

8.8 Use in Patients with Congestive Heart Failure
The exposure to tolvaptan in patients with congestive heart failure is not clinically relevantly increased. No dose adjustment is necessary.

10 OVERDOSE
Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

The oral LD_50 of tolvaptan in rats and dogs is >2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased body weight, polyuria, polydipsia, diarrhea, tremors, and fasciculations.

If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered.

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should occur. Patients should be hydrated with intravenous fluids and be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for...
11 DESCRIPTION
Tolvaptan is (±)-4'-(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carboxylil-o-toluol-toluolide. The empirical formula is C26H25ClN2O3. Molecular weight is 448.94. The chemical structure is:

\[
\text{HO-} \quad \text{C-O} \quad \text{C-O} \quad \text{N} \quad \text{C-O} \quad \text{C-O} \quad \text{Cl} \quad \text{C6H5}
\]

SAMSCA® tablets for oral use contain 15 mg or 30 mg of tolvaptan. Inactive ingredients include lactose monohydrate, sodium lauryl sulfate, hydroxypropyl methylcellulose, starch (corn, microcrystalline cellulose and FD&C Blue No. 2 Aluminum Lake as colorant.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V2-receptor is 29 times greater than for the V1a-receptor. When taken orally, 15 to 60 mg doses of tolvaptan antagonize the effect of vasopressin and cause an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations. Urinary excretion of sodium and potassium and plasma potassium concentrations are not significantly changed. Tolvaptan metabolites have no or weak antagonist activity for human V1a-receptors compared with tolvaptan.

In healthy subjects receiving a single dose of SAMSCA 60 mg, the onset of the aquaretics and sodium increasing effects occurs within 2 to 4 hours post-dose. A peak effect of about a 6 mEq increase in serum sodium and about 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose; thus, the pharmacological activity lags behind the plasma concentrations of tolvaptan. About 60% of the peak effect on serum sodium is sustained at 24 hours post-dose, but the urinary excretion rate is not elevated by this time. Doses above 60 mg tolvaptan do not increase aquaretics or serum sodium further. The effects of tolvaptan in the recommended dose range of 15 to 60 mg once daily appear to be limited to aquaretics and the resulting increase in sodium concentration.

In a parallel-arm, double-blind (for tolvaptan and placebo), placebo- and positive-controlled, multiple dose study of the effect of tolvaptan on the QTc interval, 172 healthy subjects were randomized to tolvaptan 30 mg, tolvaptan 300 mg, placebo, or moxifloxacin 400 mg once daily. At both the 30 mg dose and the 300 mg dose, no significant effect of administering tolvaptan on the QTc interval was detected. In another study of the effect of tolvaptan on the QTc interval, 172 healthy subjects were randomized to tolvaptan 30 mg, tolvaptan 300 mg, placebo, or moxifloxacin 400 mg once daily. At both the 30 mg dose and the 300 mg dose, no significant effect of administering tolvaptan on the QTc interval was detected.

12.2 Pharmacokinetics
In healthy subjects the pharmacokinetics of tolvaptan after single doses of up to 480 mg and multiple doses up to 300 mg once daily have been examined. Area under the curve (AUC) increases proportionally with dose. After administration of doses >60 mg, however, Cmax increases less than proportionally with dose. The pharmacokinetic properties of tolvaptan are stereospecific, with 12.3 Pharmacokinetics
P-gp. Tolvaptan is highly plasma protein bound (99%) and distributed into an apparent volume of distribution of 1.3 L/kg. Tolvaptan is eliminated primarily in the feces (90% for doses up to 60 mg). Unchanged tolvaptan is excreted in the urine. In vitro studies show that tolvaptan is a substrate for the P-gp pump. At the 30 mg dose and 300 mg doses, no significant effect of administering tolvaptan on the QTc interval was detected. In another study of the effect of tolvaptan on the QTc interval, 172 healthy subjects were randomized to tolvaptan 30 mg, tolvaptan 300 mg, placebo, or moxifloxacin 400 mg once daily. At both the 30 mg dose and the 300 mg dose, no significant effect of administering tolvaptan on the QTc interval was detected.

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In the open-label study SALTWATER, 111 patients, 94 of them hyponatremic (serum sodium <135 mEq/L), previously on tolvaptan or placebo therapy were given tolvaptan as a titrated regimen (15 to 60 mg once daily) after having returned to standard care for at least 7 days. By this time, their baseline mean serum sodium concentration had fallen to between their original baseline and post-placebo therapy level. Upon initiation of therapy, average serum sodium concentrations increased to approximately the same levels as observed for those previously treated with tolvaptan, and were sustained for at least a year. Figure 3 shows results from 111 patients enrolled in the SALTWATER Study.

In a phase 3 double-blind, placebo-controlled study (EVEREST), 4133 patients with worsening heart failure were randomized to tolvaptan or placebo as an adjunct to standard of care. Long-term tolvaptan treatment (mean duration of treatment of 0.75 years) had no demonstrated effect, either favorable or unfavorable, on all-cause mortality (HR (95% CI): 0.98 (0.9, 1.1)) or the combined endpoint of CV mortality or subsequent hospitalization for worsening HF (HR (95% CI): 1.0 (0.9, 1.1)).
MEDICATION GUIDE
SAMSCA® (sam-sca)
tolvaptan
Tablets

Read the Medication Guide that comes with SAMSCA before you take it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household.

What is the most important information I should know about SAMSCA?

1) SAMSCA may make the salt (sodium) level in your blood rise too fast. This can increase your risk of a serious condition called osmotic demyelination syndrome (ODS). ODS can lead to coma or death. ODS can also cause new symptoms such as:
   • trouble speaking
   • swallowing trouble or feeling like food or liquid gets stuck while swallowing
   • drowsiness
   • confusion
   • mood changes
   • trouble controlling body movement (involuntary movement) and weakness in muscles of the arms and legs
   • seizures
You or a family member should tell your healthcare provider right away if you have any of these symptoms even if they begin later in treatment. Also tell your healthcare provider about any other new symptoms while taking SAMSCA.

You may be more at risk for ODS if you have:
   • liver disease
   • not eaten enough for a long period of time (malnourished)
   • very low sodium level in your blood
   • been drinking large amounts of alcohol for a long period of time (chronic alcoholism)

To lessen your risk of ODS while taking SAMSCA:
   • Treatment with SAMSCA should be started and re-started only in a hospital, where the sodium levels in your blood can be checked closely.
   • Do not take SAMSCA if you cannot tell if you are thirsty.
   • To prevent losing too much body water (dehydration), have water available to drink at all times while taking SAMSCA. Unless your healthcare provider tells you otherwise, drink when you are thirsty.
   • If your healthcare provider tells you to keep taking SAMSCA after you leave a hospital, it is important that you do not stop and re-start SAMSCA on your own. You may need to go back to a hospital to re-start SAMSCA. Talk to your healthcare provider right away if you stop taking SAMSCA for any reason.
   • It is important to stay under the care of your healthcare provider while taking SAMSCA and follow their instructions.

2) SAMSCA may cause liver problems, including life-threatening liver failure. SAMSCA should not be taken for more than 30 days. Tell your doctor right away if you develop or have worsening of any of these signs and symptoms of liver problems:
   • Loss of appetite, nausea, vomiting
   • Fever, feeling unwell, unusual tiredness
   • Itching
   • Yellowing of the skin or the whites of the eyes (jaundice)
   • Unusual darkening of the urine
   • Right upper stomach area pain or discomfort
   • Very low sodium level in your blood
   • You cannot replace fluids by drinking or you cannot feel if you are thirsty.
   • You are dizzy, faint, or your kidneys are not working normally because you have lost too much body fluid.
   • You have liver problems: These medicines could cause you to have too much SAMSCA in your blood:
     • the antibiotic medicines, clarithromycin (Biaxin, Biaxin XL) or telithromycin (Ketek)
     • the antifungal medicines, ketoconazole (Nizoral) or itraconazole (Sporanox)
     • the anti-HIV medicines, ritonavir (Kaletra, Norvir), indinavir (Crixivan), nelfinavir (Viracept), and saquinavir (Invirase)
     • the antidepressant medicine, nefazodone hydrochloride
   • your body is not able to make urine. SAMSCA will not help your condition.

What should I tell my healthcare provider before taking SAMSCA?
Tell your healthcare provider about all your medical conditions, including if you:
   • have kidney problems and your body cannot make urine.
   • have liver problems
   • cannot feel if you are thirsty. See “What is the most important information I should know about SAMSCA?”
   • have any allergies. See the end of this Medication Guide for a list of the ingredients in SAMSCA.
   • are pregnant or plan to become pregnant. It is not known if SAMSCA will harm your unborn baby.
   • are breast-feeding. It is not known if SAMSCA passes into your breast milk. You and your healthcare provider should decide if you will take SAMSCA or breast-feed. You should not do both.
   • are taking desmopressin (dDAVP).

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Using SAMSCA with certain medicines could cause you to have too much SAMSCA in your blood. See “Who should not take SAMSCA?” SAMSCA may affect the way other medicines work, and other medicines may affect how SAMSCA works.

What is SAMSCA?
SAMSCA is a prescription medicine used to help increase low sodium levels in the blood, in adults with conditions such as heart failure, and certain hormone imbalances. SAMSCA helps raise salt levels in your blood by removing extra body water as urine.

It is not known if SAMSCA is safe or works in children.

Who should not take SAMSCA?
Do not take SAMSCA if:
   • you are allergic to tolvaptan or any of the ingredients in SAMSCA. See the end of this Medication Guide for a complete list of ingredients in SAMSCA.
   • the sodium level in your blood must be increased right away.
   • you cannot replace fluids by drinking or you cannot feel if you are thirsty.
   • you are dizzy, faint, or your kidneys are not working normally because you have lost too much body fluid.
   • you take certain medicines. These medicines could cause you to have too much SAMSCA in your blood:
     • the antibiotic medicines, clarithromycin (Biaxin, Biaxin XL) or telithromycin (Ketek)
     • the antifungal medicines, ketoconazole (Nizoral) or itraconazole (Sporanox)
     • the anti-HIV medicines, ritonavir (Kaletra, Norvir), indinavir (Crixivan), nelfinavir (Viracept), and saquinavir (Invirase)
     • the antidepressant medicine, nefazodone hydrochloride
   • your body is not able to make urine. SAMSCA will not help your condition.

How should I take SAMSCA?
   • See “What is the most important information I should know about SAMSCA?”
   • Take SAMSCA exactly as prescribed by your healthcare provider.
   • Take SAMSCA one time each day.
   • You can take SAMSCA with or without food.
   • Do not drink grapefruit juice during treatment with SAMSCA. This could cause you to have too much SAMSCA in your blood.
SAMSCA® (tolvaptan)

- Certain medicines or illnesses may keep you from drinking fluids or may cause you to lose too much body fluid, such as vomiting or diarrhea. If you have these problems, call your healthcare provider right away.
- Do not miss or skip doses of SAMSCA. If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much SAMSCA, call your healthcare provider right away. If you take an overdose of SAMSCA, you may need to go to a hospital.
- If your healthcare provider tells you to stop taking SAMSCA, follow their instructions about limiting the amount of fluid you should drink.

What are the possible side effects of SAMSCA? SAMSCA can cause serious side effects including:
- See “What is the most important information I should know about SAMSCA?”
- Loss of too much body fluid (dehydration). Tell your healthcare provider if you:
  - have vomiting or diarrhea, and cannot drink normally.
  - feel dizzy or faint. These may be symptoms that you have lost too much body fluid.

Call your healthcare provider right away, if you have any of these symptoms.

The most common side effects of SAMSCA are:
- thirst
- dry mouth
- weakness
- constipation
- making large amounts of urine and urinating often
- increased blood sugar levels

These are not all the possible side effects of SAMSCA. Talk to your healthcare provider about any side effect that bothers you or that does not go away while taking SAMSCA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.