SAMSCA® (tolvaptan) Mechanism of Action Video Transcript

00:00:00 [Beginning of Recorded Material]

00:00:09 Vasopressin, also known as AVP or ADH, is an important mediator of water retention by the kidneys. Vasopressin is synthesized in the hypothalamus, and stored in the posterior pituitary, from which it is released in response to decreased plasma volume and increased serum osmolality. Vasopressin travels through the bloodstream to the kidneys, where it exerts its antidiuretic effects.

00:00:43 Within the nephrons of the kidney, body fluid homeostasis is maintained by transferring water between urine and blood. Collecting tubules are part of the collecting duct system, which connects the nephrons to the renal pelvis and ureters. It is here that vasopressin regulates the transport of water from the urine back into the blood, helping to maintain plasma volume and serum osmolality.

00:01:08 Vasopressin binds and activates V₂-receptors on the outer membranes of collecting tubule cells. This stimulates the synthesis and transport of aquaporin-2 channels from intracellular vesicles to the luminal membrane of the cell. These channels, called aquaporins, allow free water to flow from the collecting tubule lumen through the cell and into the bloodstream, resulting in reduced excretion of water in the urine.

00:01:35 Inappropriate vasopressin release reduces excretion and increases reabsorption of water, which may disproportionately increase plasma water volume and result in dilutional hyponatremia. Dilutional hyponatremia includes euvoletic and hypervolemic hyponatremia, and is a frequently occurring electrolyte disorder in hospitalized patients, associated with certain clinical conditions, including heart failure and syndrome of inappropriate antidiuretic hormone, or SIADH.

00:02:07 Nonspecific neurologic symptoms associated with hyponatremia include nausea, confusion, lethargy, attention deficit, unsteady gait, and falls.

00:02:18 SAMSCA (tolvaptan) is indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia (serum sodium less than one hundred twenty-five milliequivalents per liter 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).

00:02:41 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

00:02:59 SAMSCA selectively blocks the binding of vasopressin to the V₂-receptors in the renal collecting ducts.

00:03:05 Inhibition of vasopressin binding to the V₂-receptor leads to decreased expression and removal of aquaporin-2 from the luminal membrane. Thus, V₂-receptor blockade results in decreased water reabsorption by the kidney.
Diuresis and aquarexis are different. *Diuresis* is an increase in overall urine production due to the alteration of kidney function. SAMSCA provides *aquarexis*, or excretion of water without electrolyte loss. Aquarexis results in increased serum sodium concentration and decreased urine osmolality. This process does not, however, result in a significant change in the urinary excretion of sodium or potassium, nor does it result in increased plasma potassium.

It is important to note that too rapid correction of serum sodium, defined as greater than ten to twelve milliequivalents per twenty-four hours, can cause osmotic demyelination syndrome.

SAMSCA raises serum sodium concentration and osmolality without producing significant effects on electrolyte excretion, blood pressure, or renal function.

SAMSCA is the first and only oral vasopressin V_2-receptor antagonist for treatment of clinically significant hypervolemic and euvoletic hyponatremia.

**INDICATION and IMPORTANT SAFETY INFORMATION for SAMSCA® (tolvaptan)**

**INDICATION**

SAMSCA is indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia (serum sodium less than one hundred twenty-five milliequivalents per liter 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

**IMPORTANT SAFETY INFORMATION**

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 (for example, greater than twelve milliequivalents per liter per twenty-four hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriaparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

**SAMSCA is contraindicated in the following conditions:**

- gent need to raise serum sodium acutely
- nability of the patient to sense or appropriately respond to thirst
— Hypovolemic hyponatremia
— ncomitant use of strong CYP 3A inhibitors
— Anuric patients
— Hypersensitivity (for example: anaphylactic shock, rash generalized) to tolvaptan or its components

- **Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae** – During initiation and after titration monitor patients to assess serum sodium concentrations and neurologic status. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided

- **Liver Injury** – SAMSCA can cause serious and potentially fatal liver injury. In a placebo-controlled and open-label extension study of chronically administered tolvaptan in patients with autosomal dominant polycystic kidney disease (ADPKD), cases of serious liver injury attributed to tolvaptan were observed. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover may be impaired. Limit duration of therapy with SAMSCA to 30 days. **SAMSCA is not approved for use in ADPKD**

- **Dehydration and Hypovolemia** – In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted

- **Co-administration with Hypertonic Saline** – Not recommended

- **Other Drugs Affecting Exposure to SAMSCA**
  — **CYP 3A Inhibitors** – Do not use with strong inhibitors of CYP 3A; avoid concomitant use with moderate CYP 3A inhibitors
  
  — **CYP 3A Inducers** – Avoid concomitant use with CYP 3A inducers. If co-administered, the dose of SAMSCA may need to be increased

  — **P-gp Inhibitors** – The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors

- **Hyperkalemia or Drugs that Increase Serum Potassium** – Monitor serum potassium levels in patients with a serum potassium greater than five milliequivalents per liter and in patients receiving drugs known to increase serum potassium levels

**Pregnancy and Nursing Mothers** – SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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
**Adverse Reactions** - The most common adverse reactions (SAMSCA incidence ≥5% more than placebo, respectively): thirst (16% vs 5%), dry mouth (13% vs 4%), asthenia (9% vs 4%), constipation (7% vs 2%), pollakiuria or polyuria (11% vs 3%) and hyperglycemia (6% vs 1%)  

**Gastrointestinal Bleeding in Patients with Cirrhosis** – In patients with cirrhosis in the hyponatremia trials, GI bleeding was reported in 10% of tolvaptan-treated patients vs 2% for placebo

Please see accompanying FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, beginning on page 5.

**References:**


5. SAMSCA® (tolvaptan) Prescribing Information, Rockville, MD, February 2014.


SAMSCA® (tolvaptan)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SAMSCA safely and effectively. See full prescribing information for SAMSCA.

SAMSCA® (tolvaptan) tablets for oral use
Initial U.S. Approval: 06/2009

WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM
See full prescribing information for complete boxed warning.

- 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 quadriaparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

RECENT MAJOR CHANGES
Contraindications
Hypersensitivity (4.6) 02/2014
Warnings and Precautions
Liver Injury (5.2) 04/2013

INDICATIONS AND USAGE
SAMSCA is a selective vasopressin V2-receptor antagonist indicated for the treatment of clinically significant hyponatremic 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) (1)

Important Limitations:
- Patients requiring intervention to raise serum sodium urgently to prevent or 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)

FULL PRESCRIBING INFORMATION CONTENTS
WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Usual Dosage in Adults
  2.2 Drug Withdrawal
  2.3 Co-Administration with CYP 3A Inhibitors, CYP 3A Inducers and P-gp Inhibitors
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae (see BOXED WARNING)
  5.2 Liver Injury
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  5.5 Drug Interactions
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7 DRUG INTERACTIONS
  7.1 Effects of Drugs on Tolvaptan
  7.2 Effects of Tolvaptan on Other Drugs

WARNING: 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 quadriaparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

1 INDICATIONS AND USAGE
SAMSCA® is indicated for the treatment of clinically significant hyponatremic 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).

Important Limitations
Patients requiring intervention to raise serum sodium urgently to prevent or 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.

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  8.5 Geriatric Use
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  8.7 Use in Patients with Renal Impairment
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*Sections or subsections omitted from the Full Prescribing Information are not listed.

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 quadriaparesis, 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, 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 30 days to minimize 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)].

2.2 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 \( [\text{see Contraindications (4.4)}] \). The effect of moderate CYP 3A
inhibitors on tolvapatan 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 Inhibitors**

Co-administration of SAMSCA with potent CYP 3A inhibitors (e.g., ritonavir) reduces tolvapatan plasma concentrations by 85%. Therefore, the expected clinical effects of SAMSCA may not be observed at the recommended dose. Patient response should be monitored and the dose adjusted accordingly [see Warnings and Precautions (5.5), Drug Interactions (7.1)].

**P-gp Inhibitors**

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

**3 DOSE FORMS AND STRENGTHS**

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

**4 CONTRAINdications**

SAMSCA is contraindicated in the following conditions:

- **4.1 Urgent need to raise serum sodium acutely**
  
  SAMSCA has not been studied in a setting of urgent need to raise serum sodium acutely.

- **4.2 Inability of the patient to sense or appropriately respond to thirst**
  
  Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hyponatremia and hypervolemia.

- **4.3 Hypovolemic hyponatremia**
  
  Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.

- **4.4 Concomitant use of strong CYP 3A inhibitors**
  
  Kept to <24 hrs with tolvapatan increased tolvapatan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvapatan exposure. There is not adequate experience to define the dose adjustment that would be needed to safely use tolvapatan with strong CYP 3A inhibitors such as dolutegravir, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, and telithromycin.

- **4.5 Anuric patients**
  
  In patients unable to make urine, no clinical benefit can be expected.

- **4.6 Hyperosmolality [see BOXED WARNING]**
  
  Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L in 24 hours). Osmotic demyelination results in dysartria, mutism, dysphagia, lethargy, affective changes, spas tic quadriparesis, seizures, coma or death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which tolvapatan was administered in titrated dosages starting at 15 mg once daily, 7% of tolvapatan-treated subjects with a serum sodium <130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium <130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L. Osmotic demyelination syndrome has been reported in association with SAMSCA therapy [see Adverse Reactions (6.2)]. Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline sodium concentration should be at greater risk for too rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

- **5.2 Liver Injury**

  SAMSCA can cause serious and potentially fatal liver injury. In a placebo-controlled and open label extension study of chronically administered tolvapatan in patients with autosomal dominant polycystic kidney disease, cases of serious liver injury attributed to tolvapatan were observed. An increased incidence of ALT greater than three times the upper limit of normal was associated with tolvapatan (42/958 or 4.4%) compared to placebo (5/464 or 1.0%). Cases of serious liver injury were generally observed starting 3 months after initiation of tolvapatan although elevations of ALT occurred prior to 3 months.

  Patients with symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice should discontinue treatment with SAMSCA. Limit duration of therapy with SAMSCA to 30 days. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired [see Adverse Reactions (6.1)].

**5.3 Dehydration and Hypovolemia**

SAMSCA therapy induces copious aquareasis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving tolvapatan. Dehydration is more likely in those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hypertensive patients were treated with tolvapatan, the incidence of dehydration was 3.3% for tolvapatan and 1.5% for placebo-treated patients. In patients receiving SAMSCA who develop medically significant signs or symptoms of hypovolemia, interrupt or discontinue SAMSCA therapy and provide supportive care with careful management of vital signs, fluid balance and electrolytes. Fluid restriction during therapy with SAMSCA may increase the risk of dehydration and hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

**5.4 Co-administration with Hypertonic Saline**

Concomitant use with hypertonic saline is not recommended.

**5.5 Drug Interactions**

Other Drugs Affecting Exposure to Tolvapatan

**CYP 3A Inhibitors**

Tolvapatan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvapatan concentrations [see Dosage and Administration (2.3), Drug Interactions (7.1)]. Do not use SAMSCA with strong inhibitors of CYP 3A [see Contraindications (4.4) and avoid concomitant use with moderate CYP 3A inhibitors.

**5.6 Hyperkalemia or Drugs that Increase Serum Potassium**

Treatment with tolvapatan is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium. Serum potassium levels should be monitored after initiation of tolvapatan treatment in patients with a serum potassium >5 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 the 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 hypertensive patients (serum sodium <135 mEq/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 58% were Caucasian. One hundred eighty nine (189) tolvapatan-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 in over 16% of these patients. 223 were treated with the recommended dose titration (15 mg titrated to 60 mg over 24 hours).

Overall, over 4,000 patients have been treated with oral doses of tolvapatan in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with tolvapatan for 6 months or more. The most common adverse reactions (incidence ≥5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hypotension trials in which tolvapatan was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthma, constipation, polkauria or polyuria and hyperglycemia. In these trials, 103 (23/223) of tolvapatan-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of <1% in tolvapatan-treated patients.

Table 1 lists the adverse reactions reported in tolvapatan-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 tolvapatan 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 tolvapatan-treated patients and 6% in placebo-treated patients.

**Table 1. Adverse Reactions (>2% more than placebo) in Tolvapatan-Treated Patients in Double-Blind, Placebo-Controlled Hypotension Trials**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Tolvapatan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>28 (13)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (7)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thirst</td>
<td>35 (16)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>19 (9)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polkauria or polyuria</td>
<td>25 (11)</td>
<td>7 (3)</td>
</tr>
</tbody>
</table>

The following terms are subsumed under the referenced ADR in Table 1: ± polydipsia; ± diabetes mellitus; ± decreased appetite; ± urine output increased, micturition urgency, nocturia.

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 tolvapatan-treated patients at a rate at least 2% greater than placebo: mortality (42% tolvapatan, 38% placebo), nausea (21% tolvapatan, 16% placebo), thirst (12% tolvapatan, 2% placebo), dry mouth (7% tolvapatan, 2% placebo) and polyuria or polkauria (4% tolvapatan, 1% placebo).

**Gastrointestinal bleeding in patients with cirrhosis**

In patients with cirrhosis treated with tolvapatan in the hypersodometric trials, gastrointestinal bleeding was reported in 6 of 63 (10%) tolvapatan-treated patients and 1 out of 57 (2%) placebo-treated patients.
The following adverse reactions occurred in <2% of hypotensive patients treated with SAMSCA® and at a greater rate than placebo in double-blind placebo-controlled trials (N = 667 total; N = 518 placebo) or in <2% of patients in an uncontrolled trial of patients with hypertensive nephropaenia (N = 111 who were not randomized and elsewhere in the label).

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

Neuropsychiatric Disorders: Hypersomnia
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 hyperventilation is observed, management may include dose decreases or interruption of tolvaptan treatment, combined with modification of free-water intake or infusion. During clinical trials of hypotensive patients, hyperventilation was noted 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 hyperventilation of 1.7% in patients receiving tolvaptan vs. 0.6% in patients receiving placebo.

Immune System Disorders: Hypersensitivity reactions including anaphylactic shock and rash (generalized) [see Contraindications (4.6)].

7 DRUG INTERACTIONS

7.1 Effects of Drugs on Tolvaptan

Ketoconazole and Other Strong CYP 3A4 Inhibitors

SAMSCA® is metabolized primarily by CYP 3A. Ketoconazole is a strong inhibitor of CYP 3A and also an 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 or with other strong CYP 3A4 inhibitors (e.g., darifenacin, iraconazole, telithromycin, saquinavir, neflurin, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in tolvaptan exposure. Thus, SAMSCA® and strong CYP 3A inhibitors should not be co-administered [see Dosage and Administration (2.3) and Contraindications (4.4)].

Moderate CYP 3A Inhibitors

The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered tolvaptan has not been assessed. A substantial increase in the exposure to tolvaptan would be expected when SAMSCA® is co-administered with moderate CYP 3A inhibitors. Co-administration of SAMSCA® with moderate CYP 3A inhibitors should therefore generally be avoided [see Dosage and Administration (2.3) and Warnings and Precautions (5.5)].

Grapefruit Juice

Co-administration of grapefruit juice and SAMSCA® results in a 1.8-fold increase in exposure to tolvaptan [see Dose and Administration (2.3) and Warnings and Precautions (5.5)].

P-gp Inhibitors

Reduction in the dose of SAMSCA® may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response [see Dose and Administration (2.3) and Warnings and Precautions (5.5)].

Rifampin and Other CYP 3A Inducers

Rifampin is an inducer of CYP 3A and P-gp. Co-administration of rifampin and SAMSCA® reduces exposure to tolvaptan by 85%. Therefore, the expected clinical effects of SAMSCA® in the presence of rifampin and other inducers (e.g., rifabutin, rifapentine, barbiturates, phenytoin, carbamazepine and St. John’s Wort) may not be observed at the usual dose levels of SAMSCA®. The dose of SAMSCA® may have to be increased [Doseage and Administration (2.3) and Warnings and Precautions (5.5)].

Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide

Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with SAMSCA® has no clinically relevant impact on the exposure to tolvaptan.

7.2 Effects of Tolvaptan on Other Drugs

Digoxin

Digoxin is a P-gp substrate. Co-administration of SAMSCA® with digoxin increased digoxin AUC by 20% and Cmax by 30%.

Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide

Co-administration of Tolventan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethyiamiodarone) to a clinically significant degree.

Lovastatin

SAMSCA® is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA® increases the exposure to lovastatin and its active metabolite lovastatin-β-hydroxyacid 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 results in 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 1-2% higher when 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 concurrent drug therapy.

As a V2 receptor antagonist, tolvaptan may interfere with the V3 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand’s (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral tolvaptan did not produce the expected increases in vW Factor Antigen or Factor VIII activity. It is not recommended to administer SAMSCA® with a V3 agonist.

8 USE IN SPECIFIC POPULATIONS

There is no need to adjust dose based on age, gender, race, or cardiac function. Co-administration with digoxin and furosemide did not affect exposure to tolvaptan plasma concentrations.

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

Of the total number of hypotensive subjects treated with SAMSCA® in clinical studies, 42% were 65 and over, while 19% were 75 and over. No overall differences in safety or effectiveness were observed between older and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Increasing age has no effect on tolvaptan plasma concentrations.

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 (4.5) 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 relevant increased. No dose adjustment is necessary.

10 OVERDOSAGE

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 LD50 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 300 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

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 of an overdose should be supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged diuresis should be anticipated, which if not matched by oral fluid ingestion, should 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 range. Dialysis may not be effective in removing tolvaptan because of its high binding affinity for human plasma protein (>99%). Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

Tolvaptan is (S)-4-(3-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1,1-benazepain-1-yl) carbonyl)-2-(1H-tetrazol-5-yl)methanamine. The empirical formula is C16H18ClNO4. Molecular weight is 448.4. The chemical structure is:
SAMSCA® (tolvaptan)

14 CLINICAL STUDIES

14.1 Hypotension

In two double-blind, placebo-controlled, multi-center studies (SALT-1 and SALT-2), a total of 424 patients with euolemic or hypervolemic hypotension (serum sodium <135 mEq/L) resulting from a variety of underlying causes (heart failure, liver cirrhosis, misdiagnosed antidiuretic hormone [SIADH] and others) were treated for 30 days with tolvaptan or placebo, then followed for an additional 7 days after withdrawal. Symptomatic patients, patients likely to require saline therapy during the course of therapy, patients with acute and transient hypotension with head trauma or postoperative state and patients with hypotension due to primary polydipsia, uncontrolled adrenal insufficiency or uncontrolled hypothyroidism were excluded. Patients were randomized to receive either placebo (N = 220) or tolvaptan (N = 223) at an initial oral dose of 15 mg once daily. The mean serum sodium concentration at baseline entry was 129 mEq/L. Fluid restriction was to be avoided if possible during the first 24 hours of therapy to avoid overly rapid correction of serum sodium, and during the first 24 hours of therapy 87% of patients had no fluid restriction. Thereafter, patients could resume or initiate fluid restriction (defined as daily fluid intake of ≤ 1.0 L/day) as clinically indicated.

The dose of tolvaptan could be increased at 24 hour intervals to 30 mg once daily, then to 60 mg once daily, until either the maximum dose of 60 mg or normotension (serum sodium ≥135 mEq/L) was reached. Serum sodium concentrations were determined at 8 hours after study drug initiation and did not exceed 50 mEq/L. The clinical effects were maintained at 30 mg daily for 9 days with no evidence of drug accumulation. The dose was titrated up to 120 mg (40 mg b.i.d. for 2 days) in 18 of 120 patients in whom the dose titration was not fully completed. Tolvaptan was maintained for 30 days with additional serum sodium assessments on Days 11, 18, 25 and 30. On the day of study discontinuation, all patients resumed previous therapies for hypotension and were reevaluated 7 days later. The primary endpoint for these studies was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30 in patients with a serum sodium less than 135 mEq/L. Compared to placebo, tolvaptan caused a statistically greater increase in serum sodium (p < 0.0001) during both periods in both studies (see Table 2). For patients with a serum sodium of <130 mEq/L or ≥135 mEq/L, the effects at Day 4 and Day 30 remained significant (see Table 2). This effect was also seen across all disease etiology subsets (e.g., CHF, cirrhosis, SIAD/HoH).

Table 2. Effects of Treatment with Tolvaptan 15 mg/day to 60 mg/day

<table>
<thead>
<tr>
<th>Subject with Serum Sodium &lt;135 mEq/L (ITT population)</th>
<th>Tolvaptan</th>
<th>Placebo</th>
<th>Estimated Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L Mean SD)</td>
<td>4.0 (2.8)</td>
<td>0.4 (2.4)</td>
<td>3.7 (3.3–4.2)</td>
</tr>
<tr>
<td>N: 213</td>
<td>203</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L Mean SD)</td>
<td>6.2 (4.0)</td>
<td>1.8 (3.7)</td>
<td>4.6 (3.9–5.2)</td>
</tr>
<tr>
<td>N: 213</td>
<td>203</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Percent of Patients Needing Fluid Restriction*</td>
<td>14%</td>
<td>30/215</td>
<td>25%</td>
</tr>
<tr>
<td>Subgroup with Serum Sodium &lt;130 mEq/L</td>
<td>30/215</td>
<td>51/206</td>
<td></td>
</tr>
<tr>
<td>p = 0.0017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L Mean SD)</td>
<td>4.8 (3.0)</td>
<td>0.7 (2.5)</td>
<td>4.2 (3.5–5.0)</td>
</tr>
<tr>
<td>N: 110</td>
<td>105</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L Mean SD)</td>
<td>7.9 (4.1)</td>
<td>2.6 (4.2)</td>
<td>5.5 (4.4–6.5)</td>
</tr>
<tr>
<td>N: 110</td>
<td>105</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Percent of Patients Needing Fluid Restriction*</td>
<td>19%</td>
<td>21/110</td>
<td>36%</td>
</tr>
<tr>
<td>Subgroup with Serum Sodium &lt;125 mEq/L</td>
<td>38/106</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L Mean SD)</td>
<td>5.7 (3.8)</td>
<td>1.0 (1.8)</td>
<td>5.3 (3.8–6.9)</td>
</tr>
<tr>
<td>N: 26</td>
<td>30</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L Mean SD)</td>
<td>10.9 (4.8)</td>
<td>4.1 (4.5)</td>
<td>5.7 (3.1–8.3)</td>
</tr>
<tr>
<td>N: 26</td>
<td>30</td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Percent of Patients Needing Fluid Restriction*</td>
<td>35%</td>
<td>9/26</td>
<td>50%</td>
</tr>
<tr>
<td>Subgroup with Serum Sodium &lt;125 mEq/L</td>
<td>15/30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p = 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Fluid Restriction defined as ≤ 1L/day at any time during treatment period.

In patients with hypotension (defined as <135 mEq/L), serum sodium concentration increased to a significantly greater degree in tolvaptan-treated patients compared to placebo-treated patients. A similar trend (but without statistical significance) was observed for patients with euolemic or hypervolemic hypotension. The percentage of patients requiring fluid restriction (defined as ≤ 1L/day at any time during the treatment period) was also significantly less (p = 0.0017) in the tolvaptan-treated group (30/215, 14%) as compared with the placebo-treated group (51/206, 25%).

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 a steady state ratio of the S(+)- to the R(-)- enantiomer of about 3:1. The absolute bioavailability of tolvaptan is unknown. At least 40% of the dose is absorbed as tolvaptan or metabolites. Peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Food does not impact the bioavailability of tolvaptan. In vitro data indicate that tolvaptan is a substrate of P-glycoprotein and a highly plasma protein bound (50%) and distributed into an apparent volume of distribution of about 3 L/Kg. Tolvaptan is eliminated entirely by non-renal routes and mainly, if not exclusively, metabolized by CYP 3A. Oral dosing, clearance is about 4 mL/min/kg and the terminal half-life is about 12 hours. The accumulation rate constant (KA) is 0.128/h. The pharmacokinetics of tolvaptan was not changed by age, weight, or sex and was not significantly different in subjects with or without liver disease.

In a study in patients with creatinine clearances ranging from 10-124 mL/min administered a single dose of 60 mg of tolvaptan at any dose level, the response was comparable in patients with severe renal impairment relative to the controls. The peak increase in serum sodium was 5.6 mEq/L, regardless of renal function, but the onset and offset of tolvaptan's effect on serum sodium were slower in patients with severe renal impairment (see Use in Special Populations (8.7)).
Figure 1 shows the change from baseline in serum sodium by visit in patients with serum sodium <135 mEq/L. Within 7 days of tolvaptan discontinuation, serum sodium concentrations in tolvaptan-treated patients declined to levels similar to those of placebo-treated patients.

14.2 Heart Failure
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)].

16 HOW SUPPLIED/STORAGE AND HANDLING
How Supplied
SAMSCA® (tolvaptan) tablets are available in the following strengths and packages.
SAMSCA 15 mg tablets are non-scored, blue, triangular, shallow-convex, debossed with “OTSUKA” and “15” on one side.
Blister of 10 NDC 59148-020-50
SAMSCA 30 mg tablets are non-scored, blue, round, shallow-convex, debossed with “OTSUKA” and “30” on one side.
Blister of 10 NDC 59148-021-50

Storage and Handling
Store at 25°C (77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP controlled Room Temperature].
Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION
As a part of patient counseling, healthcare providers must review the SAMSCA Medication Guide with every patient [see FDA-Approved Medication Guidel (17.3)].

17.1 Concomitant Medication
Advise patients to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs since there is a potential for interactions.

Strong and Moderate CYP 3A inhibitors and P-gp inhibitors
Advise patients to inform their physician if they use strong (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, nefluramin, saquinavir, indinavir, ritonavir) or moderate CYP 3A inhibitors (e.g., aprepitant, erythromycin, diltiazem, verapamil, fluconazole) or P-gp inhibitors (e.g., cyclosporine) [see Dosage and Administration (2.3), Contraindications (4.4), Warnings and Precautions (5.5) and Drug Interactions (7.1)].

17.2 Nursing
Advise patients not to breastfeed an infant if they are taking SAMSCA [see Use In Specific Populations (8.3)].

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17.3 FDA-Approved Medication Guide 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 is too difficult 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 you 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 can not 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

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 can not 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 (Sporonox)
  - 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 can not make urine.
- have liver problems
- can not 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.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

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.
- 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. 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.

How should I store SAMSCA?
Store SAMSCA between 59 °F to 86 °F (15 °C to 30 °C).

Keep SAMSCA and all medicines out of the reach of children.

General Information about SAMSCA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SAMSCA for a condition for which it was not prescribed. Do not give SAMSCA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about SAMSCA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about SAMSCA that is written for healthcare professionals. For more information about SAMSCA, call 1-877-726-7220 or go to www.samcsa.com.

What are the ingredients in SAMSCA?
Active ingredient: tolvaptan.

Inactive ingredients: corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose, and FD&C Blue No. 2 Aluminum Lake as colorant.

SAMSCA is a registered trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

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This Medication Guide has been approved by the U.S. Food and Drug Administration.
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