

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: 05/2009

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 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.

-----INDICATIONS AND USAGE-----

SAMSCA is a selective vasopressin V₂-receptor antagonist indicated for the treatment of clinically significant hypovolemic 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, cirrhosis, 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).

-----DOSAGE AND ADMINISTRATION-----

- SAMSCA should be initiated and re-initiated in a hospital (2.1).
- The recommended starting dose is 15 mg once daily. Dosage may be increased at intervals ≥ 24 hr to 30 mg once daily, and to a maximum of 60 mg once daily as needed to raise serum sodium. Monitor serum sodium and volume status (2.1).

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FULL PRESCRIBING INFORMATION

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1 INDICATIONS AND USAGE

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Important Limitations

Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA.

-----DOSAGE FORMS AND STRENGTHS-----

- Tablets: 15 mg and 30 mg (3)

-----CONTRAINDICATIONS-----

- Do not administer to patients requiring urgent intervention to raise serum sodium acutely (4.1).
- Do not use in patients who are unable to sense or to respond appropriately to thirst (4.2).
- Do not use in patients with hypovolemic hyponatremia (4.3).
- Do not use with strong CYP 3A inhibitors (4.4).
- Do not administer to patients who are anuric as no benefit is expected (4.5)

-----WARNINGS/PRECAUTIONS-----

- Monitor serum sodium and neurologic status as serious neurologic sequelae can result from over rapid correction of sodium (5.1).
- Because of the potential increased risk of gastrointestinal bleeding in patients with cirrhosis, use in patients with cirrhosis only when the need to treat outweighs this risk (5.2).
- Dehydration and hypovolemia may require intervention (5.3).
- Avoid use with hypertonic saline (5.4).
- Avoid use with CYP 3A inducers and moderate CYP 3A inhibitors (5.5).
- Consider dose reduction if co-administered with P-gp inhibitors (5.5).
- Monitor serum potassium in patients with potassium > 5 mEq/L or on drugs known to increase potassium (5.6).

-----ADVERSE REACTIONS-----

Most common adverse reactions (≥ 5% placebo) are thirst, dry mouth, asthenia, constipation, pollakiuria or 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).

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Nursing mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3).
- Pediatric Use: There are no studies (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

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. 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 Special Populations

There is no need to adjust dose based on age, gender, race, cardiac or hepatic function [see Use In Specific Populations (8) and Clinical Pharmacology (12.3)].

Renal Impairment

There is no need to adjust the dose in patients with mild to severe renal impairment (creatinine clearance 10-79 mL/min) as there is no increase in exposure to tolvaptan; tolvaptan has not been evaluated in patients with creatinine clearance < 10 mL/min or in patients undergoing dialysis. No benefit can be expected in patients who are anuric [see *Contraindications (4.5) and Clinical Pharmacology (12.3)*].

2.4 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 (4.4)*]. 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 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

Tolvaptan is a substrate of P-gp. Co-administration of SAMSCA with inhibitors of P-gp (e.g., cyclosporine) may necessitate 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)*].

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 hypovolemia.

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

Ketoconazole 200 mg administered with tolvaptan increased tolvaptan exposure by 5-fold. Larger doses would be expected to produce larger increases in tolvaptan exposure. There is not adequate experience to define the dose adjustment that would be needed to allow safe use of tolvaptan with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.

4.5 Anuric patients

In patients unable to make urine, no clinical benefit can be expected.

5 WARNINGS AND PRECAUTIONS**5.1 Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae (see BOXED WARNING)**

Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic 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 tolvaptan was administered in titrated doses starting at 15 mg once daily, 7% of tolvaptan-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/24 hours. None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium. 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 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 of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

5.2 Gastrointestinal Bleeding in Patients with Cirrhosis

In patients with cirrhosis treated with tolvaptan in hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo-treated patients. SAMSCA should be used in cirrhotic patients only when the need to treat outweighs this risk.

5.3 Dehydration and Hypovolemia

SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with tolvaptan, the incidence of dehydration was 3.3% for tolvaptan 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

There is no experience with concomitant use of SAMSCA and hypertonic saline. Concomitant use with hypertonic saline is not recommended.

5.5 Drug Interactions**Other Drugs Affecting Exposure to Tolvaptan****CYP 3A Inhibitors**

Tolvaptan is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in tolvaptan concentrations [see *Dosage and Administration (2.4), 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.

CYP 3A Inducers

Avoid co-administration of CYP 3A inducers (e.g., rifampin, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, St. John's Wort) with SAMSCA, as this can lead to a reduction in the plasma concentration of tolvaptan and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inducers, the dose of SAMSCA may need to be increased [see *Dosage and Administration (2.4), Drug Interactions (7.1)*].

P-gp Inhibitors

The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine [see *Dosage and Administration (2.4), Drug Interactions (7.1)*].

5.6 Hyperkalemia or Drugs that Increase Serum Potassium

Treatment with tolvaptan 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 tolvaptan 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 hyponatremic 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 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 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 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more.

The most common adverse reactions (incidence \geq 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% (23/223) of tolvaptan-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 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

System Organ Class MedDRA Preferred Term	Tolvaptan 15 mg/day-60 mg/day (N = 223) n (%)	Placebo (N = 220) n (%)
Gastrointestinal Disorders		
Dry mouth	28 (13)	9 (4)
Constipation	16 (7)	4 (2)
General Disorders and Administration Site Conditions		
Thirst ^a	35 (16)	11 (5)
Asthenia	19 (9)	9 (4)
Pyrexia	9 (4)	2 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia ^b	14 (6)	2 (1)
Anorexia ^c	8 (4)	2 (1)
Renal and Urinary Disorders		
Pollakiuria or polyuria ^d	25 (11)	7 (3)

The following terms are subsumed under the referenced ADR in Table 1:

^a polydipsia; ^b diabetes mellitus; ^c decreased appetite; ^d 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 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 pollakiuria (4% tolvaptan, 1% placebo).

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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 = 607 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: 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: Urethral hemorrhage

Reproductive System and Breast Disorders (female): Vaginal hemorrhage

Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary embolism, respiratory failure

Vascular disorder: Deep vein thrombosis

7 DRUG INTERACTIONS

7.1 Effects of Drugs on Tolvaptan

Ketoconazole and Other Strong CYP 3A 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 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, 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 (2.4) 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 (2.4) 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 (2.4) 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 (2.4) 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, rifapentin, 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 [see *Dosage and Administration (2.4) 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 and SAMSCA is a P-gp inhibitor. Co-administration of SAMSCA and digoxin results in a 1.3-fold increase in the exposure to digoxin.

Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide

Co-administration of tolvaptan does not appear to alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone) 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 concomitant drug therapy.

8 USE IN SPECIFIC POPULATIONS

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, and embryo-fetal death occurred. SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of tolvaptan (on a body surface area basis). Reduced fetal weights and delayed fetal ossification occurred at 162 times the MRHD. Signs of maternal toxicity (reduction in body weight gain and

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food consumption) occurred at 16 and 162 times the MRHD. When pregnant rabbits received oral tolvaptan at 32 to 324 times the MRHD (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 97 and 324 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 (13.3)*].

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

Of the total number of hyponatremic 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 these subjects 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. No dose adjustment of tolvaptan is necessary.

8.7 Use in Patients with Renal Impairment

Exposure and response to tolvaptan are similar in patients with a creatinine clearance 10-79 mL/min and in patients without renal impairment. No dose adjustment is necessary. Exposure and response to tolvaptan in patients with a creatinine clearance < 10 mL/min or in patients on chronic dialysis have not been studied. No benefit can be expected in patients who are anuric [see *Contraindications (4.5)*].

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 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 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

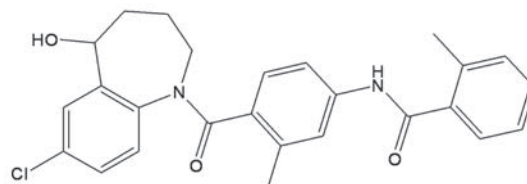
If overdose occurs, estimation of the severity of poisoning is an important first step. A thorough history and details of overdose should be obtained, and a physical examination should be performed. The possibility of multiple drug involvement should be considered.

Treatment 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 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 ranges. 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 (±)-4'-[[7-(chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]-o-tolu-m-toluidide. The empirical formula is C₂₆H₂₅C₁N₂O₃. Molecular weight is 448.94. The chemical structure is:



SAMSCA tablets for oral use contain 15 mg or 30 mg of tolvaptan. Inactive ingredients include 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.

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 V_{1a}-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 V₂-receptors compared with tolvaptan.

Plasma concentrations of native AVP may increase (avg. 2-9 pg/mL) with tolvaptan administration.

12.2 Pharmacodynamics

In healthy subjects receiving a single dose of SAMSCA 60 mg, the onset of the aquaretic 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 no longer elevated by this time. Doses above 60 mg tolvaptan do not increase aquaresis 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 aquaresis 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 and 300 mg doses, no significant effect of administering tolvaptan on the QTc interval was detected on Day 1 and Day 5. At the 300 mg dose, peak tolvaptan plasma concentrations were approximately 4-fold higher than the peak concentrations following a 30 mg dose. Moxifloxacin increased the QT interval by 12 ms at 2 hours after dosing on Day 1 and 17 ms at 1 hour after dosing on Day 5, indicating that the study was adequately designed and conducted to detect tolvaptan's effect on the QT interval, had an effect been present.

12.3 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, C_{max} 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. 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 and inhibitor of P-gp. Tolvaptan is highly plasma protein bound (99%) 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. After oral dosing, clearance is about 4 mL/min/kg and the terminal phase half-life is about 12 hours. The accumulation factor of tolvaptan with the once-daily regimen is 1.3 and the trough concentrations amount to $\leq 16\%$ of the peak concentrations, suggesting a dominant half-life somewhat shorter than 12 hours. There is marked inter-subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30 and 60%.

In patients with hyponatremia of any origin the clearance of tolvaptan is reduced to about 2 mL/min/kg. Moderate or severe hepatic impairment or congestive heart failure decrease the clearance and increase the volume of distribution of tolvaptan, but the respective changes are not clinically relevant. Exposure and response to tolvaptan in subjects with creatinine clearance ranging between 79 and 10 mL/min and patients with normal renal function are not different.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Up to two years of oral administration of tolvaptan to male and female rats at doses up to 1000 mg/kg/day (162 times the maximum recommended human dose [MRHD] on a body surface area basis), to male mice at doses up to 60 mg/kg/day (5 times the MRHD) and to female mice at doses up to 100 mg/kg/day (8 times the MRHD) did not increase the incidence of tumors.

Tolvaptan tested negative for genotoxicity in *in vitro* (bacterial reverse mutation assay and chromosomal aberration test in Chinese hamster lung fibroblast cells) and *in vivo* (rat micronucleus assay) test systems.

In a fertility study in which male and female rats were orally administered tolvaptan at 100, 300 or 1000 mg/kg/day, the highest dose level was associated with significantly fewer corpora lutea and implants than control.

13.3 Reproductive and Developmental Toxicology

In pregnant rats, oral administration of tolvaptan at 10, 100 and 1000 mg/kg/day during organogenesis was associated with a reduction in maternal body weight gain and food consumption at 100 and 1000 mg/kg/day, and reduced fetal weight and delayed ossification of fetuses at 1000 mg/kg/day (162 times the MRHD on a body surface area basis). Oral administration of tolvaptan at 100, 300 and 1000 mg/kg/day to pregnant rabbits during organogenesis was associated with reductions in maternal body weight gain and food consumption at all doses, and abortions at mid- and high-doses. At 1000 mg/kg/day (324 times the MRHD), increased incidences of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations were observed. There are no adequate and well-controlled studies of SAMSCA in pregnant women. SAMSCA should be used in pregnancy only if the potential benefit justifies the risk to the fetus.

14 CLINICAL STUDIES

14.1 Hyponatremia

In two double-blind, placebo-controlled, multi-center studies (SALT-1 and SALT-2), a total of 424 patients with euvolemic or hypervolemic hyponatremia (serum sodium < 135 mEq/L) resulting from a variety of underlying causes (heart failure, liver cirrhosis, syndrome of inappropriate 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 hyponatremia associated with head trauma or postoperative state and patients with hyponatremia 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 study 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 liter/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 normonatremia (serum sodium > 135 mEq/L) was reached. Serum sodium concentrations were determined at 8 hours after study drug initiation and daily up to 72 hours, within which time titration was typically completed. Treatment 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 hyponatremia 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 < 125 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, SIADH/other).

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

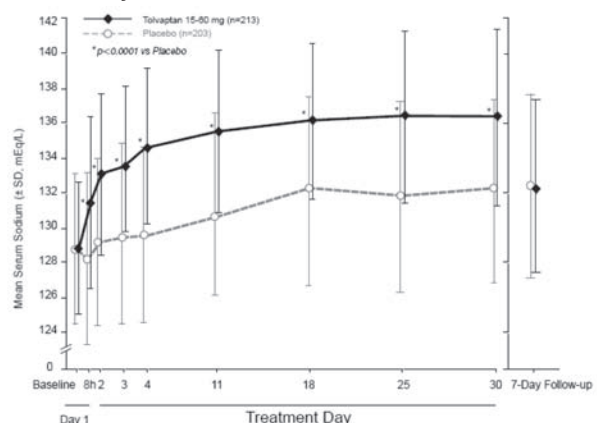
	Tolvaptan 15 mg/day- 60 mg/day	Placebo	Estimated Effect (95% CI)
Subjects with Serum Sodium < 135 mEq/L (ITT population)			
Change in average daily serum [Na ⁺] AUC baseline to Day 4 (mEq/L) Mean (SD) N	4.0 (2.8) 213	0.4 (2.4) 203	3.7 (3.3-4.2) $p < 0.0001$
Change in average daily serum [Na ⁺] AUC baseline to Day 30 (mEq/L) Mean (SD) N	6.2 (4.0) 213	1.8 (3.7) 203	4.6 (3.9-5.2) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	14% 30/215	25% 51/206	$p < 0.01$
Subgroup with Serum Sodium < 130 mEq/L			
Change in average daily serum [Na ⁺] AUC baseline to Day 4 (mEq/L) Mean (SD) N	4.8 (3.0) 110	0.7 (2.5) 105	4.2 (3.5-5.0) $p < 0.0001$
Change in average daily serum [Na ⁺] AUC baseline to Day 30 (mEq/L) Mean (SD) N	7.9 (4.1) 110	2.6 (4.2) 105	5.5 (4.4-6.5) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	19% 21/110	36% 38/106	$p < 0.01$
Subgroup with Serum Sodium < 125 mEq/L			
Change in average daily serum [Na ⁺] AUC baseline to Day 4 (mEq/L) Mean (SD) N	5.7 (3.8) 26	1.0 (1.8) 30	5.3 (3.8-6.9) $p < 0.0001$
Change in average daily serum [Na ⁺] AUC baseline to Day 30 (mEq/L) Mean (SD) N	10.0 (4.8) 26	4.1 (4.5) 30	5.7 (3.1-8.3) $p < 0.0001$
Percent of Patients Needing Fluid Restriction*	35% 9/26	50% 15/30	$p = 0.14$

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

In patients with hyponatremia (defined as < 135 mEq/L), serum sodium concentration increased to a significantly greater degree in tolvaptan-treated patients compared to placebo-treated patients as early as 8 hours after the first dose, and the change was maintained for 30 days. The percentage of patients requiring fluid restriction (defined as ≤ 1 L/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%).

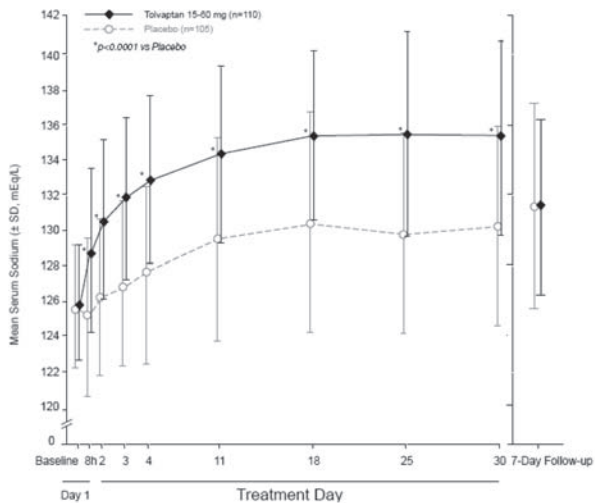
Figure 1 shows the change from baseline in serum sodium by visit in patients with serum sodium < 135 mEq/L. Within 7 days of tolvaptan discontinuation, serum sodium concentrations in tolvaptan-treated patients declined to levels similar to those of placebo-treated patients.

Figure 1: Pooled SALT Studies: Analysis of Mean Serum Sodium (\pm SD, mEq/L) by Visit - Patients with Baseline Serum Sodium < 135 mEq/L



*p-value < 0.0001 for all visits during tolvaptan treatment compared to placebo

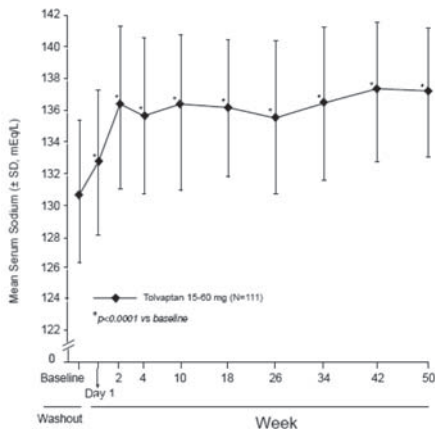
Figure 2: Pooled SALT Studies: Analysis of Mean Serum Sodium (\pm SD, mEq/L) by Visit - Patients with Baseline Serum Sodium < 130 mEq/L



*p-value < 0.0001 for all visits during tolvaptan treatment compared to placebo

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.

Figure 3: SALTWATER: Analysis of Mean Serum Sodium (\pm SD, mEq/L) by Visit



*p-value < 0.0001 for all visits during tolvaptan treatment compared to baseline

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 Guide (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 Pg-p inhibitors

Advise patients to inform their physician if they use strong (e.g., ketoconazole, itraconazole, clarithromycin, telithromycin, nelfinavir, 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 (2.4), 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)].

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850

US Patent Nos.: 5,258,510 and 5,753,677.

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



Otsuka America Pharmaceutical, Inc.

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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? 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 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.

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, liver disease, 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:

- the sodium level in your blood must be increased right away.
- you can not 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.
- 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.

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. 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.
- **Bleeding from the gastrointestinal tract in people with liver disease.** Tell your healthcare provider right away if you have any of these bleeding symptoms:

- you vomit bright red blood
- you vomit dark blood clots, or material that looks like coffee-grounds
- your stools are black or look like tar
- you pass blood or stool mixed with blood
- your stool is bright red or has maroon colored blood in it

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.samsca.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 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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