

PRODUCT MONOGRAPH

^{Pr}SAMSCA[®]

(tolvaptan)

Tablets, 15 mg, 30 mg and 60 mg

Vasopressin V₂-receptor Antagonist

Otsuka Pharmaceutical Company, Ltd.
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SAMSCA[®]

(tolvaptan tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablets, 15 mg, 30 mg and 60 mg	Corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, and FD&C Blue No. 2 Aluminum Lake as colorant

INDICATIONS AND CLINICAL USE

SAMSCA[®] (tolvaptan) is indicated for the treatment of clinically important, non-hypovolemic-hyponatremia (e.g., serum sodium < 130 mEq/L, or symptomatic hyponatremia).

SAMSCA[®] should be limited to use by physicians experienced in the management of clinically important hyponatremia.

SAMSCA[®] has not been studied in patients with serious neurological symptoms requiring urgent correction of serum sodium. Patients requiring urgent intervention to raise serum sodium to treat serious neurological symptoms associated with hyponatremia should not be treated with SAMSCA[®].

It has not been established that raising serum sodium with SAMSCA[®] provides symptomatic benefit to patients or improvement in clinical outcomes.

Geriatrics (> 65 years of age): To date, no overall differences have been identified in the safety or efficacy of SAMSCA[®] in patients over the age of 65 years, compared to younger patients.

Pediatrics (< 18 years of age): The safety and effectiveness of SAMSCA[®] in pediatric patients has not been established.

CONTRAINDICATIONS

SAMSCA[®] (tolvaptan) is contraindicated in the following conditions:

- hypovolemic hyponatremia
- urgent need to raise serum sodium acutely
- inability of the patient to sense or appropriately respond to thirst
- concomitant use of strong CYP 3A inhibitors, e.g., ketoconazole, clarithromycin, ritonavir, saquinavir, nefazodone (see DRUG INTERACTIONS, Drug-Drug Interactions)
- anuric patients
- in patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

SAMSCA[®] (tolvaptan) should be initiated, or re-initiated, only in hospital where serum sodium can be monitored closely by physicians experienced in the management of clinically important hyponatremia.

Too rapid correction of hyponatremia, e.g., > 12 mEq/L over 24 hours, can cause osmotic demyelination which may result 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.

Close monitoring of serum sodium during tolvaptan treatment is required, especially in patients with very low sodium (< 120 mEq/L) at baseline, or in those at high risk of demyelination syndromes, as described just above. Very careful management of these patients is required.

Tolvaptan treatment should be interrupted or discontinued, and followed by administration of hypotonic fluid, if the increase in serum sodium is too rapid, i.e., > 12 mEq/L over 24 hours, or > 18 mEq/L over 48 hours.

Co-administration of tolvaptan with drugs having a high sodium content, or with other drug treatments for hyponatremia, or with hypertonic saline, is not recommended, due to risk of developing hypernatremia.

General

Patients with hyponatremia whose serum sodium concentration is increased too rapidly, e.g., > 6 mEq/L over the first 6 hours, may be at risk for serious neurologic sequelae. In controlled clinical trials, this rapid rate of sodium correction has been observed in approximately 3% of patients treated with tolvaptan (N = 223) and 0% of placebo-treated patients (N = 220), in titrated doses of SAMSCA[®] between 15 mg/day and 60 mg/day. Patients treated with tolvaptan should be monitored to assess serum sodium concentrations and neurologic status, especially

during initiation and after titration. Patients with syndrome of inappropriate anti-diuretic hormone (SIADH) or very low baseline serum sodium concentrations may be at greater risk for too rapid correction of serum sodium. 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.

Osmotic demyelination syndrome (ODS) is a condition associated with too rapid correction of hyponatremia (e.g., > 12 mEq/L/24 hours). Osmotic demyelination may result in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death. None of the patients in the controlled clinical trials with tolvaptan exhibited evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too rapid correction of serum sodium.

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

Carcinogenesis and Mutagenesis

See TOXICOLOGY

Dehydration

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.

Hepatotoxicity

In a large double-blind, three year, placebo-controlled trial, called TEMPO 3:4, conducted in about 1,400 patients with autosomal dominant polycystic kidney disease (ADPKD), and its open-label extension trial, three patients treated with tolvaptan developed significant (> 3x ULN) increases in serum alanine aminotransferase (ALT), along with clinically significant (> 2x ULN) increases in serum total bilirubin. Following discontinuation of treatment, all three patients improved. These findings indicate, however, that tolvaptan has the potential to cause irreversible and potentially fatal liver injury.

In the same study, tolvaptan was associated with an increased incidence of significant (> 3x ULN) elevations of ALT, compared to placebo. Specifically, 4.4% (42/958) of ADPKD patients on tolvaptan and 1.0% (5/484) of patients on placebo exhibited elevations greater than 3x ULN

of ALT. Most of the liver enzyme abnormalities were observed during the first 18 months of therapy. The elevations gradually improved after discontinuation of tolvaptan.

In the ADPKD trials, the maximum daily dose of tolvaptan administered (90 mg in the morning and 30 mg in the afternoon) was higher than the maximum 60 mg daily dose approved for use in the treatment of hyponatremia.

In other clinical trials of SAMSCA[®], including the trials supporting the approved indication of clinically significant non-hypovolemic hyponatremia, liver injury has not been reported.

Note that SAMSCA[®] is not approved for the treatment of ADPKD. Data and information available are not adequate to exclude the possibility that patients receiving SAMSCA[®] for its indicated use of clinically significant non-hypovolemic hyponatremia are potentially at increased risk for irreversible and fatal liver injury.

To mitigate the risk of significant or irreversible liver injury, prescribers should perform blood tests for hepatic transaminases and total bilirubin prior to administration of SAMSCA[®], and on a monthly basis for 18 months during administration of SAMSCA[®], and at regular intervals thereafter (see DOSING AND ADMINISTRATION).

Prescribers should also perform liver tests promptly in patients taking SAMSCA[®] who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If hepatic injury is suspected, for example, an observed increase of equal to or greater than three times baseline AST or ALT values, or two times the baseline for bilirubin, SAMSCA[®] should be promptly discontinued, appropriate treatment should be instituted, and investigations should be performed to determine probable cause. SAMSCA[®] should not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with SAMSCA[®].

Hypernatremia

During treatment initiation, patients should be frequently monitored for serum sodium and volume status. Cessation of treatment with tolvaptan should be considered as serum sodium reaches the normal range. If serum sodium increases above the normal range, tolvaptan treatment must be discontinued promptly, serum sodium should be carefully monitored and appropriate clinical measures should be taken, as necessary.

Hyperkalemia

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 carefully after initiation of tolvaptan in patients with a serum potassium > 5 mEq/L, as well as in those who are receiving drugs known to increase serum potassium levels.

Gastrointestinal

While the overall risk of hemorrhage was similar to placebo in the total population studied to date, in patients with cirrhosis studied in hyponatremia trials, gastrointestinal bleeding was

reported in 6 of 63 (10%) tolvaptan-treated patients and 1 of 57 (2%) placebo-treated patients.

Laboratory findings

Treatment with tolvaptan may be associated with a modest increase in serum potassium.

Special Populations

Pregnant Women:

There are no adequate and well controlled trials of SAMSCA[®] use in pregnant women. In animal trials, 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 trials, 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 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.

Nursing Women:

It is not known whether SAMSCA[®] is secreted into human milk. The presence of tolvaptan has been observed in the milk of lactating rats. Because many drugs are secreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA[®], a decision should be made whether to discontinue nursing or the administration of tolvaptan, taking into consideration the importance of SAMSCA[®] to the mother.

Pediatrics (< 18 years of age):

Safety and effectiveness of SAMSCA[®] in pediatric patients have not been established.

Geriatrics (> 65 years of age):

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

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.

Renal Impairment:

Based on available data, no dose adjustment is required in those with mild to moderate renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

The efficacy and safety of tolvaptan has not been studied in patients with severe renal failure.

There are no clinical trial data in patients with estimated creatinine clearance (eCrCL) <10 mL/min, therefore, use of tolvaptan in these patients is not recommended. Due to the mechanism of action of tolvaptan, no benefit can be expected in patients who are anuric.

Heart Failure:

The exposure to tolvaptan in patients with heart failure is not increased to a clinically relevant extent. No dose adjustment is necessary.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

Overall, over 4,000 patients have been treated with oral doses of SAMSCA[®] (tolvaptan) in placebo-controlled or open-label clinical trials. Approximately 650 of these patients had hyponatremia, and approximately 219 of these hyponatremic patients were treated with tolvaptan for 6 months or more. About 223 patients with hyponatremia received tolvaptan in pivotal trials dedicated to evaluate its effects in the treatment of hyponatremia. Other patients with hyponatremia were evaluated in chronic heart failure trials.

The most common adverse reactions, at an incidence >5% more than placebo, as seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which tolvaptan was administered in titrated doses of 15 mg to 60 mg once daily, were thirst, dry mouth, and pollakiuria or polyuria, consistent with the known mechanism of action of the drug. 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, with no individual adverse reactions resulting in discontinuation of trial medication at an incidence of > 1% in tolvaptan-treated patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium < 135 mEq/L) were treated with SAMSCA[®], whether in hyponatremic trials or in those that evaluated patients with heart failure. The mean age of these patients was 62 years, with 70% of

patients male, and 82% 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, i.e., 15 mg OD titrated to 60 mg as needed to raise serum sodium.

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 trials, 223 patients were exposed to tolvaptan, starting at a dose of 15 mg once daily, 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).

Less Common Clinical Trial Adverse Drug Reactions

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 ADVERSE REACTIONS.

Blood and Lymphatic System Disorders: disseminated intravascular coagulation
Cardiac Disorders: intracardiac thrombus, ventricular fibrillation
Gastrointestinal Disorders: ischemic colitis
Investigations: Prothrombin Time prolonged
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

Abnormal Hematologic and Clinical Chemistry Findings

Clinically significant laboratory test result abnormalities with a potential association with tolvaptan therapy include increased potassium, glucose, sodium, and uric acid. Among these, the only notable difference in change from baseline values was observed for sodium. Only modest differences in these laboratory results have been seen to date with tolvaptan treatment, compared to placebo.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported spontaneously during the post-marketing period. The exact incidence of the spontaneously reported adverse reactions is unknown.

The most common post-marketing events reported with SAMSCA treatment include blood sodium increased, fluid retention, peripheral edema, ear pain, weight loss, dry throat, nasal congestion, cough, septic shock, cardiac failure, hypovolemic shock, and esophageal varices.

Angioedema, anaphylactic shock, and generalized rash, have been reported very rarely following administration of tolvaptan.

DRUG INTERACTIONS

Overview

SAMSCA[®] (tolvaptan) is a CYP 3A4 substrate and does not appear to have clinically meaningful inhibitory activity. *In vitro* trials indicated that tolvaptan was extensively metabolized by the cytochrome P450 isoenzyme CYP 3A4/5 and formed many metabolites. The metabolism of most tolvaptan metabolites is also mediated by CYP 3A4/5.

There have been no trials performed to determine the potential interaction of tolvaptan with alcohol.

Drug-Drug Interactions

Effects of Other 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. Therefore, co-administration of SAMSCA[®] with other strong CYP 3A inhibitors (e.g., some macrolides, azole antifungals, protease inhibitors, such as clarithromycin, telithromycin, itraconazole, ritonavir, saquinavir, nelfinavir, nefazodone) would significantly increase urine output and could produce a greater than expected increase in serum sodium. Thus, SAMSCA[®] and strong CYP 3A inhibitors should not be co-administered (see CONTRAINDICATIONS).

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.

P-gp Inhibitors

Reduction in the dose of SAMSCA[®] may be required in patients concomitantly treated with P-glycoprotein (P-gp) inhibitors, such as cyclosporine, based on clinical response.

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, if such co-administration is to be pursued.

Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide

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

Effects of Tolvaptan on Other Drugs

Digoxin

Digoxin is a P-gp substrate, while tolvaptan 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 does not appear to be a clinically relevant change.

Vasopressin Analogues

As a V₂ receptor antagonist, tolvaptan is capable of interfering with the release coagulation factors, e.g., von Willebrand factor, from endothelial cells, as well as producing the expected aquaretic effects. Accordingly, the effect of vasopressin analogues such as desmopressin (dDAVP) may be attenuated when co-administered with SAMSCA to prevent or control bleeding. Thus, it is generally not recommended to administer SAMSCA[®] with a V₂ agonist.

Drug-Food Interactions

Grapefruit Juice

Co-administration of grapefruit juice and SAMSCA[®] results in a 1.8-fold increase in exposure to tolvaptan. Concomitant use should be avoided.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Pharmacodynamic Interactions

Tolvaptan use produces a greater 24-hour urine volume than does furosemide or hydrochlorothiazide. However, concomitant administration of tolvaptan with furosemide or hydrochlorothiazide results in a 24-hour volume that is similar to that after tolvaptan administration alone.

Furosemide co-administered with tolvaptan produces a similar maximal rate of urine excretion compared to furosemide alone and 70% higher than tolvaptan alone. HCTZ co-administered with tolvaptan produces a slightly higher maximal excretion rate compared to tolvaptan alone and 66% higher compared to HCTZ alone.

Although specific interaction trials were not performed, in clinical trials tolvaptan was used concomitantly with beta-blockers, angiotensin-receptor blockers (ARB), angiotensin-converting-enzyme inhibitors (ACEI) and/or potassium-sparing diuretics. Adverse reactions of hyperkalemia were approximately 1-2% higher when tolvaptan was administered with ARB, ACEI, and/or potassium-sparing diuretics, compared to administration of these medications with placebo. Serum potassium levels should be monitored during concomitant drug therapy.

Drug-Lifestyle Interactions

Interactions with lifestyle parameters have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

SAMSCA[®] (tolvaptan) should be initiated, or re-initiated, only in hospital where serum sodium can be monitored closely by physicians experienced in the management of clinically important hyponatremia.

To mitigate the risk of significant or irreversible liver injury, laboratory testing for hepatic transaminases and bilirubin is required prior to initiation of tolvaptan, and continuing monthly for 18 months, and at regular intervals thereafter, e.g., every 3-6 months (see WARNINGS AND PRECAUTIONS, Hepatotoxicity).

In order to minimise risk of hepatotoxicity with SAMSCA[®], consideration should be given to limiting duration and exposure to tolvaptan, especially at 60 mg daily (see WARNINGS AND PRECAUTIONS, Hepatotoxicity).

Too rapid correction of hyponatremia, e.g., > 12 mEq/L over 24 hours, can cause osmotic demyelination syndrome (ODS) (see WARNINGS AND PRECAUTIONS). Caution is required.

There is no need to adjust dose based on age, gender, race, cardiac or hepatic function.

No dose adjustment is required in patients with mild to moderate renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

The efficacy and safety of tolvaptan has not been studied in patients with severe renal failure. Tolvaptan exposure in subjects with estimated creatinine clearance (eCrCL) < 30 mL/min was increased approximately 1.9 times over that seen in those with eCrCL > 60 mL/min, although no correlation between plasma levels and pharmacodynamic endpoints was seen (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

There are no clinical trial data in patients with eCrCL < 10 mL/min, therefore, use of tolvaptan in these patients is not recommended. Due to the mechanism of action of tolvaptan, no benefit can be expected in patients who are anuric.

Recommended Dose and Dosage Adjustment

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, and then 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.

The following table outlines the dosing considerations with reference to serum sodium levels:

Table 2: Dosing Regimen

Serum sodium (Na⁺) concentration while on SAMSCA[®]	Starting Dose (reference)	Day 2 (24 hours after starting dose)	Day 3 to treatment discontinuation
Change <5 mEq/L in 24 hours and serum sodium < 130 mEq/L	15 mg	Consider titration to 30 mg	Consider titration to 60 mg
Change ≥ 5 mEq/L in 24 hours	15 mg	Consider maintenance at 15 mg	Consider maintenance of prior current dose
Change > 8 mEq/L in 8hr or > 12 mEq/L in 24 hours	15 mg	Monitor sodium frequently, consider withholding dose and/or increasing hypotonic fluid intake	Consider withholding dose and/or increasing hypotonic fluid intake
≥ 140 mEq/L at any time	N/A	Discontinue SAMSCA and consider increasing hypotonic fluid intake	Discontinue SAMSCA [®] and consider increasing hypotonic fluid intake

Following discontinuation of SAMSCA[®], patients whose cause of hyponatremia has not been determined should be evaluated for maintenance of acceptable serum sodium levels. Appropriate therapy should be instituted, if needed.

Missed Dose

If a dose is missed, it should be taken as soon as possible. However, if it is near the time of the next dose, only the prescribed dose should be taken. A double dose should not be taken.

Administration

Tolvaptan can be taken without regard to food or the timing of food. It should not be taken with grapefruit juice, or after eating grapefruit, as this may cause a significant increase in tolvaptan concentrations (see DRUG INTERACTIONS, Drug-Food Interactions).

OVERDOSAGE

In healthy subjects, single oral doses of SAMSCA[®] (tolvaptan) of up to 480 mg, and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials. 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, that is, a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

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 must 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.

For management of suspected drug overdose, consult the regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

SAMSCA[®] (tolvaptan) is a racemate. Both enantiomers are selective vasopressin V₂-receptor antagonists with equal 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.

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/L increase in serum sodium and about 9 mL/min increase in urine excretion rate may be observed between 4 and 8 hours post-dose. 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 serum 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 msec at 2 hours after dosing on Day 1, and 17 msec 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.

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. For single doses, area under the curve (AUC) increases proportionally with dose. After administration of doses ≥ 60 mg, however, C_{max} increases less than proportionally with dose. For multiple administration of 300 mg doses compared to 30 mg doses, C_{max} and AUC were only 4.2- and 6.4-fold higher. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S(-) to the R(+) enantiomer of about 3.

Following oral administration of tolvaptan, peak concentrations are observed between 2 and 4 hours post-dose.

Moderate or severe hepatic impairment or congestive heart failure decrease the clearance and increase the volume of distribution of tolvaptan, but the respective changes do not appear to be clinically relevant.

Absorption:

The absolute bioavailability of tolvaptan is 56% (range 42-80%). Food does not impact the bioavailability of tolvaptan. *In vitro* data indicate that tolvaptan is a substrate and inhibitor of P-gp.

Distribution:

Tolvaptan is highly plasma protein bound (99%).

Metabolism:

Tolvaptan is extensively metabolized with less than 1% of the dose excreted unchanged in the urine. Under steady-state conditions, concentrations of the hydroxybutyric acid and oxobutyric acid metabolite are 28% lower and 12-fold higher than tolvaptan concentrations, respectively. Neither of these metabolites has shown measurable affinity for the V_2 receptor *in vitro*.

Tolvaptan is a CYP 3A4 substrate and does not appear to have clinically meaningful inhibitory activity. *In vitro* trials indicated that tolvaptan was extensively metabolized by the cytochrome P450 isoenzyme CYP 3A4/5 and formed many metabolites, with fourteen identified in plasma, urine and feces, to date. The metabolism of most tolvaptan metabolites was also mediated by CYP 3A4/5.

Excretion:

Tolvaptan itself is eliminated almost entirely by non-renal routes, with about 19% of the administered dose excreted unchanged in the feces. The rest is metabolized mainly, if not exclusively, by CYP 3A. The metabolites are excreted in both urine (40% of dose) and feces (40% of dose). The hydroxybutyric acid metabolite is excreted in both urine (9% of dose) and feces (12% of dose). Having a half-life of about 180 hours, excretion of the oxobutyric metabolite in the urine has been observed to be less than 1% of the total dose of tolvaptan administered and less than 3% in feces.

After oral dosing, clearance of tolvaptan is about 4 mL/min/kg and the terminal phase half-life is about 9 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 9 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.

Special Populations and Conditions**Pediatrics:**

The pharmacokinetics of tolvaptan in patients under the age of 18 years have not been studied.

Geriatrics:

Age did not substantially influence the pharmacokinetic characteristics of tolvaptan following single-dose or multiple-dose administration of 60 mg tablets.

Gender:

Gender was found to have no significant effect on tolvaptan pharmacokinetics.

Race:

In an open-label crossover trial, 24 Japanese and 25 Caucasian men were administered a single 30 mg oral dose of tolvaptan. The mean tolvaptan C_{max} and AUC_{∞} values were only 5-15% higher in Japanese subjects compared to Caucasian subjects. Decreases in mean fluid balance were greater for Japanese men than Caucasian men.

Hepatic Insufficiency:

In subjects with hyponatremia secondary to liver disease, tolvaptan concentrations appeared to accumulate 1.7- to 1.8-fold after multiple dosing. Clearance following a single dose is about half that of healthy subjects and following multiple dosing is about a third that of healthy subjects.

Renal Insufficiency:

Tolvaptan exposure, as measured by AUC, in subjects with $eCrCL < 30$ mL/min was increased approximately 1.9 times over that seen in those with $eCrCL > 60$ mL/min.

In subjects with preserved renal function, i.e., CrCL > 60 mL/min, increases in urine output and free water clearance occurred more quickly and were larger in amount, but then returned to baseline more quickly, compared to subjects with compromised renal function, see Table 3, below.

Table 3:- Mean (SD) Pharmacodynamic Parameters Following a Single 60-mg Dose of Tolvaptan to Subjects with Different Degrees of Renal Function as Determined by Creatinine Clearance

Time	Parameter	CrCL < 30 mL/min (n=12)	CrCL 30 to 60 mL/min (n=12)	CrCL > 60 mL/min (n=12)
Baseline	24-hour Urine Volume (mL)	2098 (805)	1949 (585)	2644 (897)
Chg for 0-24 h		1089 (785)	2704 (1375)	4247 (1673)
Chg for 24-48 h		537 (731)	512 (789)	-385 (754)
Baseline	24- hour Fluid Intake (mL)	2254 (662)	2162 (374)	2332 (753)
Chg for 0-24 h		560 (800)	836 (416)	2393 (1137)
Chg for 24-48 h		300 (769)	304 (452)	296 (1031)
Baseline	24-hour Fluid Balance (mL)	156 (908)	213 (526)	-311 (484)
Chg for 0-24 h		-529 (1141)	-1868 (1382)	-1853 (1530)
Chg for 24-48 h		-236 (1021)	-208 (701)	681 (721)

Following a single 60 mg dose of tolvaptan, 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 was slower in patients with CrCL < 30 mL/min.

Tolvaptan has not been evaluated in patients with CrCL < 10 mL/min or in patients on chronic dialysis.

STORAGE AND STABILITY

Store SAMSCA[®] at 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SAMSCA[®] (tolvaptan) tablets are available in the following strengths and packages:

SAMSCA[®] 15 mg tablets are non-scored, beveled-edge, blue, triangular, shallow-convex, debossed with "OTSUKA" and "15" on one side, and are packaged in blister packs of 10 tablets or in 10, 30, 90 or 500 count bottles.

SAMSCA[®] 30 mg tablets are non-scored, beveled-edge, blue, round, shallow-convex, debossed with "OTSUKA" and "30" on one side, and are packaged in blister packs of 10 tablets or in 10, 30, 90 or 500 count bottles.

SAMSCA[®] 60 mg tablets are non-scored, beveled-edge, blue, modified rectangular, shallow-convex, beveled-edge tablet, debossed with "OTSUKA" and "60" on one side, and packaged in blister packs of 10 tablets or in 10, 30, 90 or 500 count bottles.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

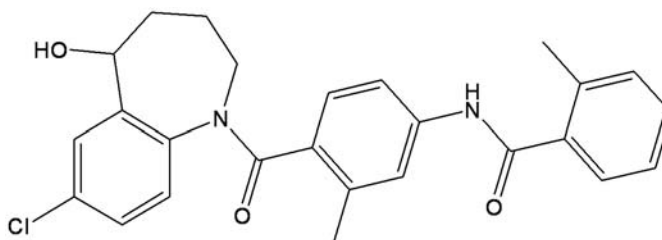
Drug Substance

Proper name: Tolvaptan

Chemical name: (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide

Molecular formula and molecular mass: C₂₆H₂₅ClN₂O₃ 448.94

Structural formula:



Physicochemical properties: Tolvaptan is a white crystalline powder. It is practically insoluble in water (0.00005 w/v% at 25°C), and no pH dependence of solubility was observed. Tolvaptan is stable to light.

CLINICAL TRIALS

In two 30-day, double-blind, placebo-controlled, multi-center trials (SALT-1 and SALT-2), a total of 424 patients with euvolemic or hypervolemic hyponatremia (serum sodium < 135 mEq/L) due to a variety of underlying causes (heart failure, liver cirrhosis, syndrome of inappropriate anti-diuretic hormone [SIADH], and others) were treated for 30 days with SAMSCA[®] (tolvaptan) or placebo, then followed for an additional 7 days after withdrawal. Patients were stratified by hyponatremia status (serum sodium 130-134 mEq/L for mild or < 130 mEq/L for severe), and received either tolvaptan (N = 223) at an initial oral dose of 15 mg/day, or placebo (N = 220). The mean serum sodium concentration at trial entry was 129 mEq/L overall (133 mEq/L for mild and 126 mEq/L for severe patients).

Fluid restriction was generally not used during the first 24 hours of therapy to avoid overly rapid correction rates (> 12 mEq/L/day). Thereafter, all 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 to 30 mg/day, then 60 mg/day until either the maximum dose or normonatremia (serum sodium > 135 mEq/L) was reached. Serum sodium concentrations were determined daily up to 72 hours after initiation of tolvaptan therapy, within which time titration was typically completed. Treatment was maintained for 30 days with serum sodium assessments on Days 11, 18, 25 and 30. On the day of trial discontinuation, all patients resumed previous therapies for hyponatremia and were re-evaluated on Day 37. As a precaution, those with severe hyponatremia were monitored more frequently. Post-baseline efficacy data were available for 213 tolvaptan-treated and 203 placebo-treated patients.

The primary endpoint for these trials was the change in average 24-hour AUC in serum sodium from baseline to that obtained on Day 4, and from baseline to that obtained on Day 30. Tolvaptan was superior to placebo ($p < 0.0001$) for both periods in both trials. This effect was seen in all patients, in both severe and mild subsets, and for all disease etiology subsets (i.e., CHF, cirrhosis, SIADH/other).

Following 3 days of oral treatment, a greater percentage of patients given tolvaptan, compared to placebo, had a categorical improvement (64% vs. 23%), or achieved normal serum sodium concentration (49% vs. 11%). On Day 30, more tolvaptan-treated patients had a categorical improvement (74% versus 46%), or had normal serum sodium concentrations (60% versus 27%) than placebo. However, 7 days after discontinuing trial drug, only 51% of tolvaptan and 49% of placebo patients maintained categorical improvement, with only 26% of these patients, in both treatment groups, maintaining eunatremic status.

Serum sodium concentrations 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 were maintained for up to 30 days, see Table 4.

The percentage of patients whose serum sodium concentration category worsened was significantly greater for placebo-treated patients, the maximum percentage for placebo being 49% versus a maximum of 16% for tolvaptan.

Table 4: Efficacy of Tolvaptan in Placebo-Controlled Hyponatremia Studies, Pooled data

	Treatment Group ^a	N	Mean (SD)	P-value	Estimated Treatment Effect	95% CI
Primary endpoints: Patients with Serum Sodium < 135 mEq/L (ITT), at baseline						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	213	4.01 (2.80)	< 0.0001	3.73	3.25 - 4.21
	Placebo	203	0.35 (2.36)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	213	6.21 (3.99)	< 0.0001	4.57	3.91 - 5.22
	Placebo	203	1.77 (3.72)			
Subgroup analysis of primary endpoints: Patients with Serum Sodium < 130 mEq/L (ITT), at baseline						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	110	4.83 (3.03)	< 0.0001	4.22	3.48 - 4.96
	Placebo	105	0.73 (2.51)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	110	7.90 (4.09)	< 0.0001	5.45	4.40 - 6.50
	Placebo	105	2.64 (4.21)			
Subgroup analysis of primary endpoints: Patients with Serum Sodium 130-134 mEq/L (ITT), at baseline						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	103	3.14 (2.24)	< 0.0001	3.18	2.59- 3.77
	Placebo	98	-0.06 (2.13)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	103	4.40 (2.97)	< 0.0001	3.59	2.83- 4.34
	Placebo	98	0.83 (2.83)			
Subgroup analysis of primary endpoints, by Hyponatremia Etiology						
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH)/Other						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	85	4.76 (2.81)	< 0.0001	4.70	3.93 - 5.47
	Placebo	88	0.19 (2.62)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	85	7.42 (3.75)	< 0.0001	6.15	5.19 - 7.11
	Placebo	88	1.53 (3.55)			
Congestive Heart Failure (CHF)						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	65	3.52 (2.97)	< 0.0001	2.98	2.12 - 3.85
	Placebo	61	0.51 (1.99)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	65	6.58 (4.12)	< 0.0001	4.05	2.75 - 5.35
	Placebo	61	2.38 (4.21)			

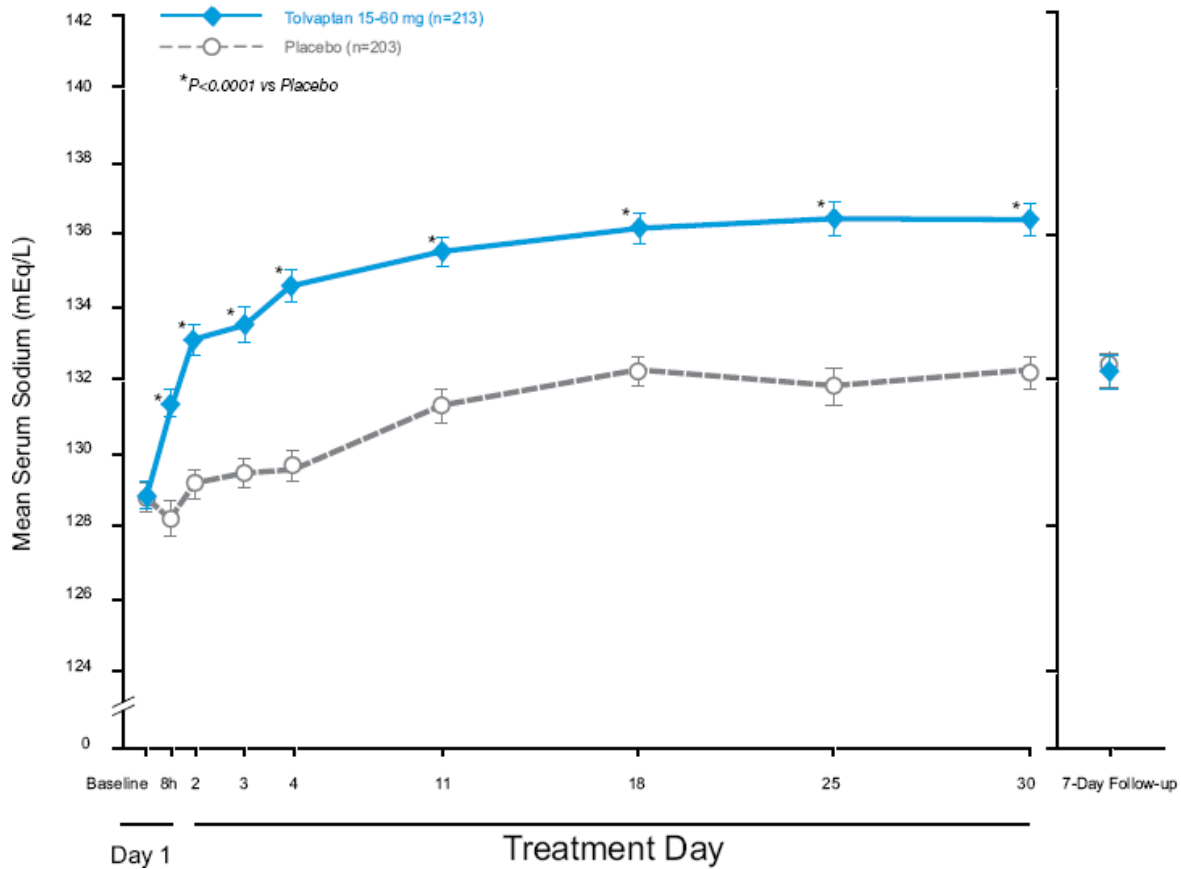
	Treatment Group	N	Mean (SD)	P-value	Estimated Treatment Effect	95% CI
Cirrhosis						
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 4 (mEq/L)	Tolvaptan	63	3.50 (2.41)	< 0.0001	3.15	2.32 - 3.99
	Placebo	54	0.42 (2.32)			
Change in average 24-hr serum [Na ⁺] AUC baseline to Day 30 (mEq/L)	Tolvaptan	63	4.18 (3.40)	< 0.0001	2.83	1.65 - 4.01
	Placebo	54	1.46 (3.37)			
Secondary efficacy endpoints						
	Tolvaptan		Placebo		Estimated Effect (95% CI)	
% Patients with normal serum sodium by Day 4 # (normal N/total N)	48.4 % (103/213)		11.8 % (24/203)		p < 0.0001	
% Patients with normal serum sodium by Day 30 # (normal N/total N)	55.9 % (119/213)		24.6 % (50/203)		p < 0.0001	
% Patients Needing Strict Fluid Restriction ^b	14% 30/215		24.8% 51/206		p < 0.0017	
% Patients with worsening (shift from mild to severe) # (worse N/total N)	15.5 % (16/103)		49.0 % (48/98)		0.3173 (0.19, 0.52) p < 0.0001	

^a Tolvaptan-treated patients were titrated from 15 to 60 mg per day, as required, to maintain optimal serum sodium status.

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

Figure 1 shows the change from baseline in serum sodium by visit in patients with serum sodium < 135 mEq/L. The entry criterion for hypernatremia in the SALT trials was < 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.

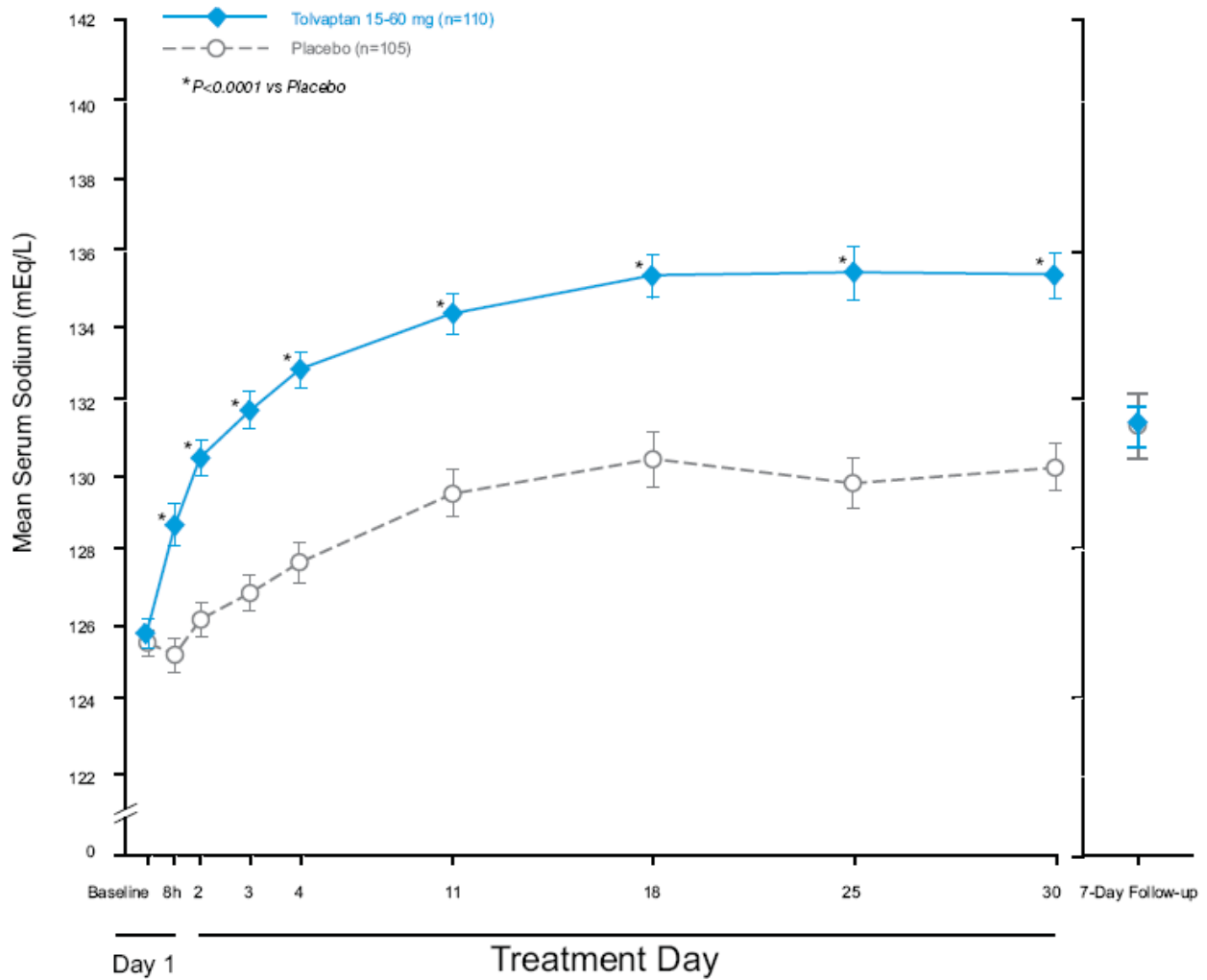
Figure 1: Pooled SALT Trials: Analysis of Mean Serum Sodium (\pm SE, mEq/L) by Visit, in Patients with Baseline Serum Sodium $<$ 135 mEq/L (All Patients)



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

Figure 2 shows the change from baseline in serum sodium by visit in patients with serum sodium $<$ 130 mEq/L. Of the 424 patients randomized in the SALT trials, 217 patients had serum sodium levels $<$ 130 mEq/L at baseline. Within 7 days of discontinuation, serum sodium concentrations in tolvaptan-treated patients declined to levels similar to those of placebo-treated patients.

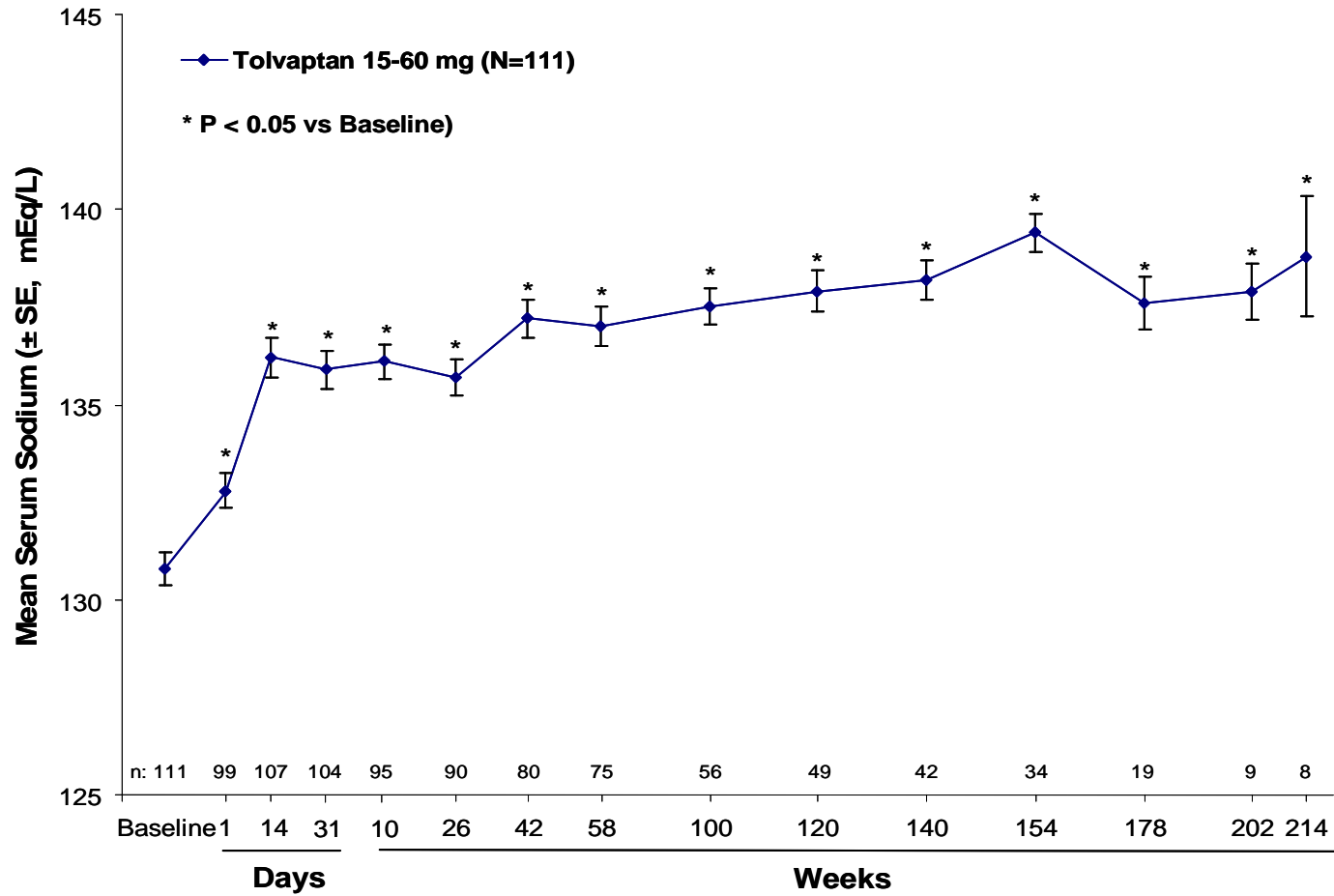
Figure 2: Pooled SALT Trials: Analysis of Mean Serum Sodium (\pm SE, mEq/L) by Visit, in Patients with Baseline Serum Sodium < 130 mEq/L



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

In the SALTWATER trial, an open-label trial of 111 patients previously on tol vaptan or placebo therapy for treatment of hyponatremia, the average serum sodium concentrations were increased significantly for up to 214 weeks (Figure 3). Upon commencement of tol vaptan treatment initially, all patients had serum sodium < 135 mEq/L.

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



Note: P-values denoted by an asterisk represent analysis of change in serum sodium from baseline of current trial.

Long-Term Exposure to Tolvaptan

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. In this trial, most patients were not hyponatremic at baseline. 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 cardiovascular mortality or subsequent hospitalization for worsening heart failure [HR (95% CI): 1.0 (0.9, 1.1)].

DETAILED PHARMACOLOGY

Arginine vasopressin (AVP) is a neuropeptide hormone which causes vasoconstriction via V_{1a} -receptors and promotes water reabsorption in the kidneys via V_2 -receptors, both of which are G-protein-coupled transmembrane receptors. The V_2 -receptors are primarily responsible for the anti-diuretic effects of AVP. Patients with various disorders, including congestive heart failure, liver cirrhosis, and syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), are at risk of experiencing excess water retention or inadequate water disposal due to increased vasopressin secretion. Tolvaptan is a competitive, non-peptide vasopressin antagonist drug that blocks the binding of arginine vasopressin at the V_2 -receptors of the distal nephron, thereby inducing water diuresis (aquaresis), but notably without the depletion of electrolytes.

Pharmacodynamics

In vitro antagonistic effects of tolvaptan were investigated in binding experiments using a human endocervical carcinoma cell line (HeLa cells) expressing human AVP receptor subtypes (V_{1a} , V_{1b} , and V_2). Tolvaptan inhibited [3 H]AVP binding to the V_2 -receptors in a concentration-dependent manner, with an inhibition constant (K_i) of 0.43 ± 0.06 nM, which was approximately 1.8 times higher than that of AVP ($K_i = 0.78 \pm 0.08$ nM). Tolvaptan also inhibited [3 H]AVP binding to the V_{1a} -receptors with a K_i of 12.3 ± 0.8 nM, but the affinity is approximately 29 times weaker than that for V_2 -receptors. On the other hand, tolvaptan did not inhibit [3 H]AVP binding to the V_{1b} -receptors even at 100 nM.

The affinities of tolvaptan for rat and canine AVP receptors were investigated by measuring the inhibition of [3 H]AVP binding to membrane preparations prepared from rat liver (V_{1a}), canine platelet (V_{1a}), and rat and canine kidney (V_2). Tolvaptan concentration-dependently inhibited [3 H]AVP binding to rat AVP V_{1a} - and V_2 -receptors with K_i of 345 ± 54 nM and 1.33 ± 0.26 nM, and to canine AVP V_{1a} - and V_2 -receptors with K_i of 40.3 ± 12.0 nM and 0.66 ± 0.09 nM, respectively. Thus tolvaptan was approximately 259- and 61-times more selective for V_2 -receptors than for V_{1a} -receptors in rats and dogs.

TOXICOLOGY

Single-Dose Toxicity

Single-dose toxicity trials of tolvaptan were conducted by the oral route at doses of up to 2000 mg/kg in Sprague-Dawley rats and Beagle dogs. No mortality or clinical signs indicative of toxicity were observed in rats or dogs. The minimum lethal dose was not determined in the single-dose trials in rats or dogs. There were no apparent gender differences in sensitivity to the acute effects of tolvaptan in either rats or dogs. There was no macroscopic evidence of target organ toxicity at any dose level.

Repeat-Dose Toxicity

Repeat-dose oral toxicity trials were conducted in Sprague-Dawley rats and Beagle dogs for up to 26 weeks and 52 weeks, respectively. In rats, the No Observed Adverse Effect Level (NOAEL) was 1000 mg/kg/day in both sexes in the 4-week and 13-week repeated oral dose toxicity trials. In the 26-week trial at doses of 30, 100 and 1000 mg/kg/day, the results showed neither overt toxicity nor target organ toxicity even at 1000 mg/kg/day. However, 3 females given 1000 mg/kg/day were euthanized in a moribund state (dehydration). Therefore, the NOAEL in this trial was estimated to be 1000 mg/kg/day in the males and 100 mg/kg/day in the females (serum drug concentration at the fourth week of administration: C_{\max} was 1.37 and 3.42 $\mu\text{g/mL}$ and $\text{AUC}_{0-24\text{h}}$ was 12.72 and 20.76 $\mu\text{g}\cdot\text{h/mL}$ in the males and females, respectively). In dogs, the NOAEL was 1000 mg/kg/day in both sexes in the 4-week and 13-week administration. In the 52-week administration trial at doses of 30, 100 and 1000 mg/kg/day, the results showed no notable target organ toxicity even at 1000 mg/kg/day. However, one male and 2 females given 1000 mg/kg/day were sacrificed in a moribund state because of decreases in body weight and food consumption. Therefore, the NOAEL in this trial was estimated to be 100 mg/kg/day in both sexes (serum drug concentration at 52nd week of administration: C_{\max} was 5.46 and 6.05 $\mu\text{g/mL}$ and $\text{AUC}_{0-24\text{h}}$ was 31.45 and 42.35 $\mu\text{g}\cdot\text{h/mL}$ in the males and females, respectively).

Genotoxicity

The genotoxic potential of tolvaptan was assessed in a battery of *in vitro* and *in vivo* test systems. Tolvaptan exhibited no genotoxic potential at concentrations up to 5000 $\mu\text{g/plate}$ in the bacterial (*Salmonella typhimurium* and *Escherichia coli*) reverse-mutation test, up to 200 $\mu\text{g/mL}$ in the forward gene mutation test in mouse lymphoma cells, following pulse treatment at up to 100 $\mu\text{g/mL}$ (in the presence or absence of metabolic activation) or with continuous treatment at up to 40 $\mu\text{g/mL}$ (in the presence or absence of metabolic activation) in the chromosomal aberration test using Chinese hamster lung fibroblast cell line (CHL) or at doses up to 2000 mg/kg in rat micronucleus test using bone marrow cells from male and female rats administered tolvaptan.

Carcinogenicity

The carcinogenic potential of tolvaptan was evaluated in one 104-week oral carcinogenicity trial in mice and one 104-week oral carcinogenicity trial in rats. Dose levels for the mouse carcinogenicity trial were 0, 10, 30 and 60 mg/kg/day in males and 0, 10, 30 and 100 mg/kg/day in females. The dose levels for the rat carcinogenicity trial were 0, 100, 300 and 1000 mg/kg/day in males and 0, 30, 100, 300 and 1000 mg/kg/day in females. Oral (gavage) administration of tolvaptan to B6C3F₁ mice or Sprague-Dawley rats for 104 weeks was not associated with a decrease in survival or an increase in the incidence of neoplastic or non-neoplastic drug-related findings in males or females. The highest doses tested in mice resulted in exposures (AUC_{0-24h}) that were just above (females; 4.3317 µg·h/mL) and just below (males; 2.8595 µg·h/mL) the exposure in humans at the MRHD (60 mg). The highest dose tested in rats resulted in exposures (AUC_{0-24h}) that were approximately 4-times (males; 12.716 µg·h/mL) and 10-times (females; 33.449 µg·h/mL) greater than the exposure in humans at steady state at the MRHD of 60 mg.

Reproductive and Developmental Toxicity Trials

In trials of effects on fertility and reproductive performance in Sprague-Dawley rats, tolvaptan did not impair reproductive performance at doses up to 1000 mg/kg/day in males and 100 mg/kg/day in females (approximately 162- and 16-times the MRHD on a mg/m² basis, respectively). Fertility was not affected at 1000 mg/kg/day in males and females. The drug-related effect of altered estrous cycles due to prolongation of diestrus was observed in females given 300 and 1000 mg/kg/day. The NOAEL was less than 100 mg/kg/day for general toxicologic effects in males and females, 100 mg/kg/day for reproductive performance in females and 1000 mg/kg/day for reproductive performance in males and for fetal development.

In trials of embryo-fetal development, tolvaptan did not cause any developmental toxicity in rats at maternal doses up to 100 mg/kg/day (16-times the MRHD on a mg/m² basis) or in New Zealand White rabbits at maternal doses up to 300 mg/kg/day (97-times the MRHD on a mg/m² basis). Dose-dependent maternal toxicity was evident in rats at 100 mg/kg/day and higher and in rabbits at 30 mg/kg/day and higher. The NOAEL in rats was 10 mg/kg/day for general toxicologic effects in the parental generation (F₀) dams, 1000 mg/kg/day for reproductive performance in F₀ dams and 100 mg/kg/day for embryo-fetal development in first generation (F₁) fetuses. Maternal toxicity in female rats consisted of decreased food consumption and body weight (100 mg/kg/day and higher) and developmental toxicity of the F₁ fetuses consisted of decreased body weight and delayed ossification (1000 mg/kg/day).

In rabbits, the NOAEL was 10 mg/kg/day for general toxicologic effects in F₀ dams, and 100 mg/kg/day for reproductive performance in F₀ dams and 300 mg/kg/day for embryo-fetal development in F₁ fetuses. Maternal toxicity in female rabbits consisted of decreased food consumption and body weight (30 mg/kg and higher). In addition, maternal changes in physiology were examined in dams given 1000 mg/kg and the changes included increased urine volume, decreased urine osmolality, increased water consumption and increased plasma sodium and chloride concentration as well as plasma osmolality and plasma AVP levels. Maternal reproductive performance, as assessed by the ability to maintain pregnancy, was altered at dose levels of 300 mg/kg and higher where a dose-dependent incidence of abortion was observed. There was also evidence of developmental toxicity in rabbits at the maternally toxic dose of 1000 mg/kg (324-times the MRHD on a mg/m² basis). This developmental toxicity consisted of increased incidences of embryo-fetal death, microphthalmia, open eyelids, cleft palate, brachymelia (zygopodium malformations) and fused phalanx.

Teratogenicity of tolvaptan was further investigated in rabbits. The sensitive period of teratogenicity was

during gestation Days 6 to 11, and the maximum sensitivity was shown to be during gestation Days 9 to 11. A toxicokinetics trial in pregnant rabbits showed that 13-day repetitive administration of tolvaptan caused a decrease in exposure level (AUC) of unchanged compound to approximately 1/10 of that at the first administration.

In the prenatal and postnatal trial in pregnant rats, tolvaptan had no effect on offspring development at doses up to 100 mg/kg/day following oral administration to pregnant rats from gestation Day 7 through lactation Day 21. Increased perinatal death and decreased body weight of F₁ generation animals during the lactation period and after weaning were observed in the 1000 mg/kg/day group. The NOAEL was less than 10 mg/kg/day for general toxicologic effects in F₀ dams, and 1000 mg/kg/day for reproductive performance in F₀ dams and 100 mg/kg/day in terms of effects on offspring development.

REFERENCES

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PART III: CONSUMER INFORMATIONPrSAMSCA[®]**Tolvaptan Tablets**

This leaflet is part III of a three-part "Product Monograph" published when SAMSCA[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SAMSCA[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

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.

What it does:

SAMSCA[®] helps raise salt levels in your blood by removing extra body water as urine.

When it should not be used:

Do not take SAMSCA[®] if:

- you are allergic or hypersensitive to tolvaptan or any of the ingredients in SAMSCA[®].
- 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 or telithromycin
 - the antifungal medicines, ketoconazole or itraconazole
 - the anti-HIV medicines, ritonavir, indinavir, nelfinavir, and saquinavir
 - the antidepressant medicine, nefazodone hydrochloride
- your body is not able to make any urine. SAMSCA[®] will not help your condition.

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

What the medicinal ingredient is:

tolvaptan

What the non-medicinal ingredients are:

Corn starch, hydroxypropyl cellulose, lactose monohydrate,

low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, , and FD&C Blue No. 2 Aluminum Lake as colorant.

What dosage forms it comes in:

Tablets: 15 mg, 30 mg, and 60 mg

WARNINGS AND PRECAUTIONS

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

SAMSCA[®] use may cause liver injury when used at much higher doses (twice as high) than those recommended for treatment of low sodium levels in the blood. SAMSCA[®] should not be used at higher doses than those recommended, or longer than necessary. Your physician will perform blood tests regularly while you are taking this medication.

BEFORE you use SAMSCA[®] talk to your doctor or pharmacist if you:

- have kidney problems and your body can not make any urine
- cannot sense thirst properly
- have any allergies
- 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.
- have liver disease
- have not eaten enough for a long period of time (malnourished)
- have very low sodium level in your blood (e.g., symptoms like excessive sweating, diarrhea, vomiting)
- have been drinking large amounts of alcohol for a long period of time (chronic alcoholism)

INTERACTIONS WITH THIS MEDICATION

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 great of a drug effect with SAMSCA[®] in your blood.

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.

SAMSCA[®] should not be taken by patients who are also taking clarithromycin, telithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, consuming grapefruit juice, or vasopressin drugs, such as desmopressin, used to control bleeding.

PROPER USE OF THIS MEDICATION

Usual dose:

- Take SAMSCA[®] once daily as directed by your doctor.
- You can take SAMSCA[®] with or without food.
- Do not drink grapefruit juice during treatment with SAMSCA[®]. This could cause you to have too great of a drug effect, while taking SAMSCA[®].
- 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.
- 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.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects of SAMSCA[®] are:

- thirst
- dry mouth
- weakness
- constipation

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Large amounts of urine and more frequent urination	√		
	High levels of sugar in blood	√		
Uncommon	Signs of dehydration including vomiting, dizziness, diarrhea, or cannot drink normally			√
	Bleeding from the gastrointestinal tract (symptoms such as blood in stool or vomit, black stool)			√
Unknown	Liver Injury (symptoms like fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice)			√

This is not a complete list of side effects. For any unexpected effects while taking SAMSCA[®], contact your doctor or pharmacist.

HOW TO STORE IT

Store SAMSCA[®] between 15°C to 30°C.

Keep SAMSCA[®] out of sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at**
www.healthcanada.gc.ca/medeffect
 - **Call toll-free at 1-866-234-2345**
 - **Complete a Canada Vigilance Reporting Form**
- and:**

- **Fax toll-free to 1-866-678-6789, or**
- **Mail to:**

**Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.samsca.ca>

or by contacting the marketer, Otsuka Canada Pharmaceutical Inc. (OCPI) at: 1-877-341-9245.

If you have any questions about this product, please contact OCPI at: 1-877-341-9245.

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