SAMSCA® (tolvaptan)

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

SAMSCA® (tolvaptan) tablets for oral use
Initial U.S. Approval: 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 quadriaparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

**RECENT MAJOR CHANGES**

Contraindications
Hypersensitivity (4.6)
02/2014

Warnings and Precautions
Liver Injury (5.2)
04/2013

**INDICATIONS AND USAGE**

SAMSCA is a selective vasopressin V2-receptor antagonist indicated for the treatment of clinically significant hyponatremia [serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has not responded to fluid restriction], including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

Important Limitations:
- Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA (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 2-24 hr to 30 mg once daily, and to a maximum of 60 mg once daily as needed to raise serum sodium (2.1)

**Dosage Forms and Strengths**

- Tablets: 15 mg and 30 mg (3)

**CONTRAINDICATIONS**

- Need to raise serum sodium acutely (4.2)
- Patients who are unable to respond appropriately to thirst (4.2)
- Hypovolemic hyponatremia (4.3)
- Concomitant use of strong CYP 3A inhibitors (4.4)
- Anuria (4.5)
- Hypersensitivity (4.6)

**WARNINGS/PRECAUTIONS**

- Liver injury: Limit treatment duration to 30 days. If hepatic injury is suspected, discontinue SAMSCA. Avoid use in patients with underlying liver disease (5.2)
- Dehydration and hypovolemia may require intervention (5.3)
- Avoid use with 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.

Revised: 02/2014

**FULL PRESCRIBING INFORMATION: CONTENTS**

**WARNING: INITIATE AND RE-INITIATE IN A HOSPITAL AND MONITOR SERUM SODIUM**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 OVERDOSE
10 DESCRIPTION
11 CLINICAL PHARMACOLOGY
12 NONCLINICAL TOXICOLOGY
13 CLINICAL STUDIES
14 HOW SUPPLIED/STORAGE AND HANDLING
15 PATIENT COUNSELING INFORMATION
16 PATIENT SAFETY INFORMATION
17 PATIENT COUNSELING INFORMATION

**1 INDICATIONS AND USAGE**

SAMSCA is indicated for the treatment of clinically significant hyponatremic and euclidean hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has not responded to fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

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

**2 DOSAGE AND ADMINISTRATION**

2.1 Usual Dosage in Adults
Patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriaparesis, seizures, coma and death.

The usual starting dose for SAMSCA is 15 mg administered once daily without regard to meals.

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

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

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

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 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:

- **Urgent need to raise serum sodium acutely**
- **Inability of the patient to sense or appropriately respond to thirst**
- **Patients who are unable to auto-regulate fluid balance**
- **Auric patients**
- **Hypersensitivity**

**DOSAGE FORMS AND STRENGTHS**

- **DOSAGE FORMS AND STRENGTHS**
- **4.1 Urgent need to raise serum sodium acutely**
- **4.2 Inability of the patient to sense or appropriately respond to thirst**
- **4.3 Patients who are unable to auto-regulate fluid balance**
- **4.4 Concomitant use of strong CYP 3A inhibitors**
- **4.5 Auric patients**
- **4.6 Hypersensitivity**

**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)].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae**

Drug metabolism in the liver is essential. SAMSCA is metabolized by the cytochrome P450 (CYP) 3A system and therefore may increase serum concentrations of tolvaptan in patients co-administered with drugs that inhibit this enzyme system. The co-administration of potent CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, rifampin, and bedaquiline may increase serum tolvaptan concentrations and decreased effectiveness of SAMSCA treatment. If co-administered with CYP 3A inhibitors, the dose of SAMSCA may need to be increased [see Dosage and Administration (2.3), Drug Interactions (7.1)].

**5.2 Liver Injury**

There were 16 cases of serious liver injury reported in the open-label, placebo-controlled trials of tolvaptan. These included hepatic failure, cholestasis, and jaundice. All cases occurred in patients with an underlying liver disease, including cirrhosis. Patients with a history of cirrhosis are at increased risk of liver injury. In patients with cirrhosis 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.

**5.3 Dehydration and Hypovolemia**

SAMSCA therapy induces copious diuresis, which is normally partially offset by fluid intake. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics. Dehydration can be avoided in multiple-dose, placebo-controlled trials of tolvaptan in which 607 hypertonic 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**

Concomitant use with hypertonic saline is not recommended.

**5.5 Drug Interactions**

**5.5.1 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 Warnings and Precautions (5.3), Drug Interactions (7.1)]. Do not use SAMSCA with strong inhibitors of CYP 3A [see Contraindications (4.4)] and avoid concomitant use with moderate CYP 3A inhibitors.

**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 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 (2.3), 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 such as cyclosporine [see Dosage and Administration (2.3), 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, 667 hypertonic 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.

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

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

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

In a subgroup of patients with hyponatremia (N = 475, serum sodium <135 mEq/L) enrolled in a double-blind, placebo-controlled trial (mean duration of treatment was 9 months) of patients with worsening heart failure, the following adverse reactions occurred in tolvaptan-treated patients at a rate at least 2% greater than placebo-treated patients: dry mouth (7% tolvaptan, 2% placebo), thirst (12% tolvaptan, 2% placebo), nausea (12% tolvaptan, 0% placebo), and polyuria or polydipsia (4% tolvaptan, 1% placebo).

**Gastrointestinal bleeding in patients with cirrhosis**

In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo-treated patients.

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

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**Gastrointestinal bleeding in patients with cirrhosis**

In patients with cirrhosis treated with tolvaptan in the hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) tolvaptan-treated patients and 1 out of 57 (2%) placebo-treated patients.
The following adverse reactions occurred in <2% of hyponatremic patients treated with SAMSCA and at a rate greater than placebo in double-blind placebo-controlled trials (N = 667 tolvaptan; N = 516 placebo) or in >2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and not mentioned elsewhere in the label.

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 elderly 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 plasma concentrations.

8.6 Use in Patients with Hepatic Impairment
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 2060 mg/kg (maximum feasible dose). A single oral dose of 400 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 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.

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 (S)-1-(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzenep-1-yl) carbonyl-[3H]-1-benzazepin-1-yl) carbonyl]-

The chemical structure is:
SAMSCA® (tolvaptan)

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 approximately 50 times greater than for the V₁a-receptor. When taken orally, 15 to 60 mg doses of tolvaptan antagonize the effect of vasopressin and cause an increase in urine water excretion that results in an increase in free water clearance (A), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations. Urinary excretion of sodium and potassium concentrations are not significantly changed. Tolvaptan metabolites have no or weak antidiuretic activity for human V₂-receptors compared with tolvaptan.

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

12.2 Pharmacodynamics

In healthy subjects receiving a single dose of SAMSCA 60 mg, the onset of the aquarectic and sodium increasing effects occurs within 2 to 4 hours post-dose. A peak effect of about 6 mEq increase in serum sodium concentration 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 of tolvaptan increase aquaresis or 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, 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, Cmax increases less than proportionally with dose. The pharmacokinetic properties of tolvaptan are stereospecific, with an enantiomeric ratio of the S-(+) to the R-(−) enantiomer of about 3:1. The absolute bioavailability of tolvaptan is unknown. At least 40% of the dose is absorbed as tolvaptan or metabolites. Peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Food does not impact the bioavailability of tolvaptan. In vitro data indicate that tolvaptan is a substrate of P-glycoprotein and is a high P-glycoprotein inhibitor. Tolvaptan is 88% bound to plasma protein 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 regimen is 1.3 and the trough concentrations amount to ≤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 results in a significantly lower 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. In a study in patients with creatinine clearances ranging from 10-124 mL/min administered a single dose of 30 mg tolvaptan and 15 mg of placebo, plasma tolvaptan levels were less than double in patients with severe renal impairment relative to the controls. The peak increase in serum sodium was 5-6 mEq/L, regardless of renal function, but the onset and offset of tolvaptan’s effect on serum sodium were slower in patients with severe renal impairment [see Use in Special Populations (8.7)].

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 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.

13.2 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 all doses, and about 9 mL/min increase in urine excretion rate was observed at 1000 mg/kg/day (254 times the MRHD), reduced incidences of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations were observed. There were 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 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 poldyposis, 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. Therapeutically, 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 dosing was adjusted to achieve a serum sodium concentration of 100 to 125 mEq/L. Tolvaptan was maintained for 30 days with additional serum sodium assessments on Days 11, 18, 25 and 30. On the day of study discontinuation, all patients resumed previous therapies for hyponatremia and were reevaluated 7 days later. The primary endpoint for these studies was the average daily AUC 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

<table>
<thead>
<tr>
<th>Subjects with Serum Sodium &lt;135 mEq/L (ITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N %</td>
</tr>
<tr>
<td>Placebo Estimated Effect</td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N</td>
</tr>
<tr>
<td>Placebo Estimated Effect</td>
</tr>
<tr>
<td>Percent of Patients Needing Fluid Restriction*</td>
</tr>
<tr>
<td>Subgroup with Serum Sodium &lt;130 mEq/L</td>
</tr>
<tr>
<td>Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N</td>
</tr>
<tr>
<td>Placebo Estimated Effect</td>
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<tr>
<td>Percent of Patients Needing Fluid Restriction*</td>
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</table>

* Fluid Restriction defined as ≤1L/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 9 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 (± 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*

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 (± 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

**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.
- SAMSCA 30 mg tablets are non-scored, blue, round, shallow-convex, debossed with “OTSUKA” and “30” on one side.

**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 P-gp inhibitors**

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

#### 17.2 Nursing

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

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17.3 FDA-Approved Medication Guide

**MEDICATION GUIDE**

SAMSCA® (sam-sca) tolvaptan Tablets

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

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

1) SAMSCA may make the salt (sodium) level in your blood rise too fast.

This can increase your risk of a serious condition called osmotic demyelination syndrome (ODS). ODS can lead to coma or death. ODS can also cause new symptoms such as:

- trouble speaking
- swallowing 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 you healthcare provider about any other new symptoms while taking SAMSCA.

You may be more at risk for ODS if you have:

- liver disease
- not eaten enough for a long period of time (mynamourished)
- 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.

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**SAMSCA® (tolvaptan)**

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What should I tell my healthcare provider before taking SAMSCA?

Tell your healthcare provider about all your medical conditions, including if you:
- Have kidney problems and your body cannot make urine.
- Have liver problems
- 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 complete list of ingredients in SAMSCA.
- Are pregnant or plan to become pregnant. It is not known if SAMSCA will harm your unborn baby.
- Are breast-feeding. It is not known if SAMSCA passes into your breast milk. You and your healthcare provider should decide if you will take SAMSCA or breast-feed. You should not do both.
- Are taking desmopressin (dDAVP).

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using SAMSCA with certain medicines could cause you to have too much SAMSCA in your blood. See “Who should not take SAMSCA?”

SAMSCA may affect the way other medicines work, and other medicines may affect how SAMSCA works.

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

How should I take SAMSCA?
- See “What is the most important information I should know about SAMSCA?”
- Take SAMSCA exactly as prescribed by your healthcare provider.
- Take SAMSCA one time each day.
- You can take SAMSCA with or without food.
- Do not drink grapefruit juice during treatment with SAMSCA. This could cause you to have too much SAMSCA in your blood.
- Certain medicines or illnesses may keep you from drinking fluids or may cause you to lose too much body fluid, such as vomiting or diarrhea. If you have these problems, call your healthcare provider right away.
- Do not miss or skip doses of SAMSCA. If you miss a dose, take it as soon as you remember. If it is near the time of the next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time.
- If you take too much SAMSCA, call your healthcare provider right away. If you take an overdose of SAMSCA, you may need to go to a hospital.
- If your healthcare provider tells you to stop taking SAMSCA, follow their instructions about limiting the amount of fluid you should drink.

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

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

The most common side effects of SAMSCA are:
- Thirst
- Dry mouth
- Weakness
- Constipation
- Making large amounts of urine and urinating often
- Increased blood sugar levels

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

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

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.sam sca.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.

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