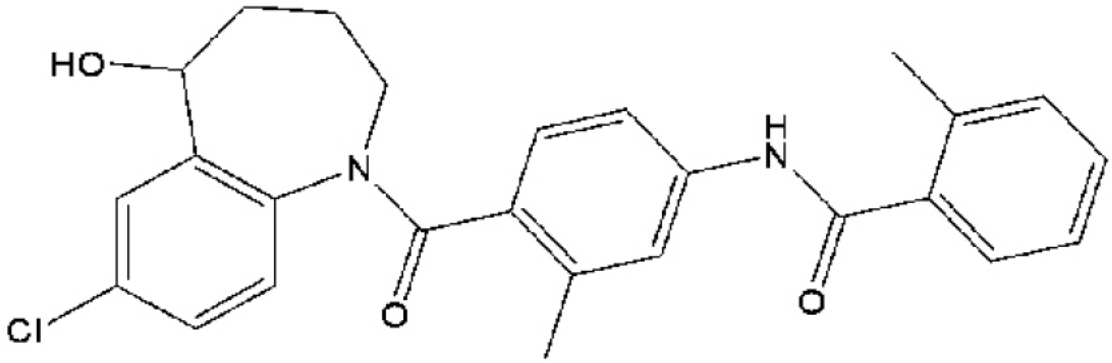
Samsca® Tablets 15 mg
(Tolvaptan)

[DESCRIPTION]

Tolvaptan is (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*tolu-*m*-toluidide. The empirical formula is $C_{26}H_{25}ClN_2O_3$. Molecular weight is 448.94. The chemical structure is:



[COMPOSITION]

Samsca Tablet 15mg: In 1 tablet,

*API: Tolvaptan (in-house)..... 15mg
*Excipient (Tar Colorant): FD&C Blue No. 2 Aluminum Lake
*Excipient (Animal source): Lactose monohydrate (Cow, milk)
*Other excipients: Microcrystalline cellulose, Magnesium stearate, Corn starch, Low Substituted Hydroxypropylcellulose, Hydroxypropylcellulose

[PHARMACEUTICAL FORM]

Samsca Tablet 15mg: Blue round tablets debossed with “SAMSCA”, “15” and cleavage line on one side. The cleavage line can be used to facilitate the halving of the tablet.

[INDICATIONS]

1. Hyponatremia

The treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

2. Adjunct Treatment of Volume Overload in Heart Failure

Volume overload in heart failure when adequate response is not obtained with other diuretics (e.g., loop diuretics).

Limitations of Use:
When conditions or symptoms due to volume overload are resolved, administration of SAMSCA should be discontinued. The efficacy and safety of SAMSCA for maintenance treatment following resolution have not been established. In a clinical study, 15 mg tolvaptan has been associated with worse clinical outcomes vs placebo when rated at 6 months (last visit).

[DOSAGE & ADMINISTRATION]

1. Usual Dosage in Adults

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

During initiation and titration, frequently monitor for change in serum electrolytes and volume.

In order to avoid nocturnal urination, SAMSCA is recommended to be administered in the morning and swallowed whole with water regardless of meal. Fluid restriction during the first 24 hours of therapy with SAMSCA should generally be avoided. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

1) Hyponatremia

The usual starting dose for SAMSCA is 15 mg administered once daily in adult. Increase the dose to 30 mg once daily, after at least 24 hours, to a maximum of 60 mg once daily, as needed to achieve the desired level of serum sodium. Do not administer SAMSCA for more than 30 days to minimize the risk of liver injury.

2) Adjunct treatment of volume overload in heart failure

SAMSCA should be used in combination with other diuretics, such as loop diuretics, thiazides, and aldosterone antagonists, since SAMSCA increases aquaresis but not natriuresis. There is no clinical experience of co-administration of SAMSCA with human atrial natriuretic peptide (hANP).

The usual adult dose is 15 mg once daily but it is recommended to start from 7.5 mg/day for patients whose serum sodium is less than 125 mEq/L, patients in whom rapid plasma volume

decrease is undesirable, elderly patients or patients with serum sodium concentration higher than 140 mEq/L.

The starting dose of 7.5mg/day is recommended based on safety considerations. If clinical symptoms such as persistent thirst and dehydration are observed, dosage of SAMSCA should be reduced and appropriate measures such as fluid replenishment, including fluid therapy, should be taken in accordance with the symptoms. If there is no improvement in symptoms, SAMSCA should be discontinued.

Administration of SAMSCA should not be continued after body weight has returned to the target level (body weight at which volume overload is appropriately controlled) or when conditions or symptoms due to volume overload are resolved.

Administration of SAMSCA should not be continued if volume overload or body fluid retention is not improved.

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.

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

CYP 3A Inhibitors

SAMSCA is metabolized by CYP 3A, and use with strong CYP 3A inhibitors causes a marked (5-fold) increase in exposure. The effect of moderate CYP 3A inhibitors on SAMSCA exposure has not been assessed. Avoid co-administration of SAMSCA and moderate CYP 3A inhibitors.

CYP 3A Inducers

Co-administration of SAMSCA with potent CYP 3A inducers (e.g., rifampin) reduces SAMSCA 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.

P-gp Inhibitors

SAMSCA 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.

[PRECAUTIONS]

1. Warnings

1) Too rapid correction of serum sodium can cause serious neurologic sequelae

SAMSCA should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely.

Patients should be frequently monitored for their serum sodium and volume status after administration of SAMSCA because SAMSCA can cause too rapid increase of serum sodium.

Osmotic demyelination syndrome is a risk associated with too rapid correction of hyponatremia (e.g., > 12 mEq/L/24 hours). Osmotic demyelination results in dysarthria, mutism, dysphagia, lethargy, affective changes or spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with hypoxia, severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.

Sodium correction that exceeds 6 mEq/L during the first 6 hours of administration or 8 mEq/L during the first 6 – 12 hours may be too rapid; in such patients close monitoring of serum sodium and administration of hypotonic fluid are recommended. SAMSCA treatment should be interrupted or discontinued and followed by administration of hypotonic fluid if the increase in serum sodium is too rapid (i.e. if it exceeds 12 mEq/L in 24 hours, or 18 mEq/L in 48 hours).

In controlled clinical trials in which SAMSCA was administered in titrated doses starting at 15 mg once daily, 7% of SAMSCA treated subjects with a serum sodium < 130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2% had an increase greater than 12 mEq/L at 24 hours. Approximately 1% of placebo-treated subjects with a serum sodium < 130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours.

Patients treated with SAMSCA should be monitored to assess serum sodium concentrations and neurologic status, especially during initiation and after titration. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA who develop too rapid a rise in serum sodium (>12 mEq/L/24 hours), discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours of therapy with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided. Co-administration of diuretics also increases the risk of too rapid correction of serum sodium and such patients should undergo close monitoring of serum sodium.

Co-administration of SAMSCA with any other treatment for hyponatremia, and medications that increase serum sodium concentration is not recommended. These patients may be at higher risk for developing rapid correction of serum sodium during the first 1-2 days of treatment due to potential additive effects. Therefore, if co-administration is essential then these patients should be managed very cautiously.

2) Liver Injury

SAMSCA can cause serious and potentially fatal liver injury. In placebo-controlled studies and an open-label extension study of chronically administered tolvaptan in patients with ADPKD, cases of serious liver injury attributed to tolvaptan, generally occurring during the first 18 months of therapy, were observed. In postmarketing experience with tolvaptan in ADPKD, acute injury resulting in liver failure requiring liver transplantation has been reported. SAMSCA should not be used to treat ADPKD.

Limit duration of therapy with SAMSCA to 30 days for treatment of hyponatremia. Avoid use in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired.
Liver function tests must be promptly performed in patients taking SAMSCA who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If liver injury is suspected, SAMSCA must be promptly discontinued, appropriate treatment has to be instituted, and investigations have to be performed to determine the probable cause. SAMSCA must not be re-initiated in patients unless the cause for the observed liver injury is definitively established to be unrelated to treatment with SAMSCA.

For the treatment of volume overload in heart failure, liver function tests should be performed prior to initiation of SAMSCA and frequently at least for the first 2 weeks of treatment.

3) Hypernatremia

Hemoconcentration associated with rapid diuresis may induce hypernatremia, possibly accompanied by consciousness disturbance. In patients being treated with SAMSCA, fluid intake, urine volume, serum sodium level, and the occurrence of clinical symptoms such as thirst and dehydration should be carefully monitored. If clinical symptoms such as persistent thirst and dehydration are observed, SAMSCA should be discontinued or the dosage reduced and appropriate measures such as fluid replenishment, including fluid therapy, should be taken in accordance with the symptoms. If serum sodium level is increased above the normal range, administration of SAMSCA should be discontinued immediately and appropriate measures such as fluid replenishment, including fluid therapy, should be taken.

2. Contraindications

1) Patients with known or suspected hypersensitivity (e.g. anaphylactic shock, rash generalized) to SAMSCA, benzazepine or benzazepine delivatives or to any ingredient of the drug.

2) Patients requiring urgent intervention to raise serum sodium acutely.

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

3) Inability of the patient to sense or appropriately respond to thirst.

Patients who are unable to auto-regulate fluid balance are at substantially increased risk of incurring an overly rapid correction of serum sodium, hypernatremia and hypovolemia.

4) Hypovolemic hyponatremia

Risks associated with worsening hypovolemia, including complications such as hypotension and renal failure, outweigh possible benefits.

5) Anuric patients

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

6) Volume depletion patients

7) Hypernatremia patients

8) Concomitant use of strong CYP3A inhibitors

Ketoconazole 200 mg administered with SAMSCA increased SAMSCA exposure by 5-fold. Larger doses would be expected to produce larger increases in SAMSCA exposure. There is no adequate experience to define the dose adjustment that would be needed to allow safe use of SAMSCA with strong CYP 3A inhibitors such as clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin.

9) SAMSCA contains lactose as an excipient. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take SAMSCA.

10) Use in Patients with Autosomal Dominant Polycystic Kidney Disease

Samsca can cause serious and potentially fatal liver injury. SAMSCA should not be prescribed or used outside of the approved indications.

11) Use during pregnancy

3. Careful Administration

1) Dehydration

SAMSCA therapy induces copious aquaresis, which is normally partially offset by fluid intake. Dehydration can occur, especially in patients receiving diuretics or those who are fluid restricted. In multiple-dose, placebo-controlled trials in which 607 hyponatremic patients were treated with SAMSCA, the incidence of dehydration was 3.3% for SAMSCA and 1.5% for placebo-treated patients. Patients' condition, such as thirst, should be monitored and body weight, blood pressure, pulse rate, and urine volume should be frequently measured. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst. If sensation of thirst persists, dose reduction should be considered.

2) Hypovolemia patients

Hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted. 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 hypovolemia. Patients receiving SAMSCA should continue ingestion of fluid in response to thirst.

3) **Diabetes mellitus**

Diabetic patients with an elevated glucose concentration (e.g. in excess of 300mg/dl) may present with pseudohyponatremia. This condition should be excluded prior and during treatment with SAMSCA.

SAMSCA may cause hyperglycemia. Therefore, diabetic patients treated with SAMSCA should be managed cautiously. In particular this applies to patients with inadequately controlled type II diabetes.

4) Patients with serious coronary artery disease or cerebrovascular disease and elderly patients.

Rapid volume decrease or hemoconcentration associated with rapid diuresis may induce thromboembolism.

5) Patients with Hyperkalemia or Drugs that Increase Serum Potassium

Treatment with SAMSCA is associated with an acute reduction of the extracellular fluid volume which could result in increased serum potassium and may lead to ventricular fibrillation and ventricular tachycardia. Serum potassium levels should be monitored after initiation of SAMSCA 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) Urinary outflow obstruction

Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.

7) Patients with renal impairment

Dose adjustment of SAMSCA is not required in patients with renal impairment. No clinical trials in hyponatremic subjects with a creatinine clearance <10 mL/min or in patients undergoing dialysis have been conducted.

8) Co-administration with hypertonic saline

Concomitant use with hypertonic saline is not recommended

9) Other drugs affecting exposure to SAMSCA

CYP 3A Inhibitors

SAMSCA is a substrate of CYP 3A. CYP 3A inhibitors can lead to a marked increase in SAMSCA concentrations. Do not use SAMSCA with strong inhibitors of CYP3A and avoid concomitant use with moderate CYP 3A inhibitors.

CYP 3A Inducers

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

P-gp Inhibitors

The dose of SAMSCA may have to be reduced when SAMSCA is co-administered with P-gp inhibitors, e.g., cyclosporine.

4. Adverse reactions

1) Clinical Trials Experience

1.1) Hyponatremia

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

In multiple-dose, placebo-controlled trials, 607 hyponatremic patients (serum sodium < 135 mEq/L) were treated with SAMSCA. The mean age of these patients was 62 years; 70% of patients were male and 82% were Caucasian. One hundred eighty nine (189) SAMSCA-treated patients had a serum sodium < 130 mEq/L, and 52 patients had a serum sodium < 125 mEq/L. Hyponatremia was attributed to cirrhosis in 17% of patients, heart failure in 68% and SIADH/other in 16%. Of these patients, 223 were treated with the recommended dose titration (15 mg titrated to 60 mg as needed to raise serum sodium).

Overall, over 4,000 patients have been treated with oral doses of SAMSCA in open-label or placebo-controlled clinical trials. Approximately 650 of these patients had hyponatremia; approximately 219 of these hyponatremic patients were treated with SAMSCA for 6 months or more.

The most common adverse reactions (incidence ≥ 5% more than placebo) seen in two 30-day, double-blind, placebo-controlled hyponatremia trials in which SAMSCA was administered in titrated doses (15 mg to 60 mg once daily) were thirst, dry mouth, asthenia, constipation, pollakiuria or polyuria and hyperglycemia. In these trials, 10% (23/223) of SAMSCA-treated patients discontinued treatment because of an adverse event, compared to 12% (26/220) of placebo-treated patients; no adverse reaction resulting in discontinuation of trial medication occurred at an incidence of > 1% in SAMSCA-treated patients.

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

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

System Organ Class MedDRA Preferred Term	SAMSCA 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 SAMSCA-treated patients at a rate at least 2% greater than placebo: mortality (42% SAMSCA, 38% placebo), nausea (21% SAMSCA, 16% placebo), thirst (12% SAMSCA, 2% placebo), dry mouth (7% SAMSCA, 2% placebo) and polyuria or pollakiuria (4% SAMSCA, 1% placebo).

Gastrointestinal bleeding in patients with cirrhosis

In patients with cirrhosis treated with SAMSCA in hyponatremia trials, gastrointestinal bleeding was reported in 6 out of 63 (10%) SAMSCA-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 = 607 SAMSCA; N = 518 placebo) or in < 2% of patients in an uncontrolled trial of patients with hyponatremia (N = 111) and are not mentioned elsewhere in the label.

* *Blood and Lymphatic System Disorders:* Disseminated intravascular coagulation

* *Cardiac Disorders: Intracardiac* thrombus, ventricular fibrillation

* *Investigations:* Prothrombin time prolonged

* *Gastrointestinal Disorders:* Ischemic colitis
* *Metabolism and Nutrition Disorders:* Diabetic ketoacidosis

* *Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis

* *Nervous System:* Cerebrovascular accident

* *Renal and Urinary Disorders:* Urethral hemorrhage

* *Reproductive System and Breast Disorders (female):* Vaginal hemorrhage

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

* *Vascular disorder:* Deep vein thrombosis

1.2) Adjunct treatment of volume overload in heart failure (Japanese data)

Table 2 shows the adverse reactions reported in Japanese clinical trials of tolvaptan in patients with volume overload in heart failure (N= 213). Included are adverse events that were reported in ≥2% of patients who received any oral tolvaptan dose and assessed as reasonably associated with tolvaptan use.

Table 2. Adverse Reactions in SAMSCA-Treated Patients in Japanese Clinical Trials for Volume Overload in Heart Failure

Gastrointestinal Disorders	
Very common (≥10%)	Constipation
Common (≥2% and <10%)	Diarrhea
General Disorders and Administration Site Conditions	
Very common (≥10%)	Thirst
Common (≥2% and <10%)	Malaise
Investigations	
Very common (≥10%)	Blood creatinine increased, Blood urea increased, Blood uric acid increased
Common (≥2% and <10%)	Blood glucose increased, Blood potassium increased, Blood pressure decreased, Blood urine present
Nervous system disorders	
Common (≥2% and <10%)	Dizziness[a], Headache
Renal and Urinary Disorders	
Common (≥2% and <10%)	**Pollakiuria**

The following term is subsumed under the referenced ADR in Table 2: [a] Dizziness postural

2) Postmarketing Experience

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

drug exposure.

Neurologic: Osmotic demyelination syndrome

Investigations: Hypernatremia

Removal of excess free body water increases serum osmolality and serum sodium concentrations. All patients treated with SAMSCA, especially those whose serum sodium levels become normal, should continue to be monitored to ensure serum sodium remains within normal limits. If hypernatremia is observed, management may include dose decreases or interruption of SAMSCA treatment, combined with modification of free-water intake or infusion. During clinical trials of hyponatremia patients, hypernatremia was reported as an adverse event in 0.7% of patients receiving SAMSCA vs. 0.6% of patients receiving placebo; analysis of laboratory values demonstrated an incidence of hypernatremia of 1.7% in patients receiving SAMSCA vs. 0.8% in patients receiving placebo.

Immune system disorders: hypersensitivity reactions including anaphylactic shock and rash generalized

In post-marketing experience, anaphylaxis (including anaphylactic shock and rash generalised) has been reported very rarely following administration of SAMSCA. This type of reaction occurred after the first administration of SAMSCA. If an anaphylactic reaction or other serious allergic reactions occur, administration of SAMSCA must be discontinued immediately and appropriate therapy initiated. Since hypersensitivity is a contraindication, treatment must never be restarted after an anaphylactic reaction or other serious allergic reactions.

5. General Precautions

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

2) It has not been established that SAMSCA provides a symptomatic benefit to hyponatremia patients.

3) When driving vehicles or using machines it should be taken into account that occasionally dizziness, asthenia or syncope may occur.

4) Fluid and electrolyte balance

Fluid and electrolyte status must be monitored in all patients. Administration of SAMSCA induces copious aquaresis and may cause dehydration and increases in serum sodium and is contraindicated in hypernatraemic patients. Serum creatinine, electrolytes and symptoms of electrolyte imbalances (e.g. dizziness, fainting, palpitations, confusion, weakness, gait instability, hyper-reflexia, seizures, coma) have to be assessed prior to and after starting SAMSCA to monitor for dehydration.

Adjunct treatment of volume overload in heart failure

As the aquaretic effect of SAMSCA is most potent within 24 hours after initial administration, serum sodium concentration should be measured at least at 4 to 6 hours and 8 to 12 hours after administration on the first day of administration. From the second to around the seventh day of administration, serum sodium concentration should be measured every day, and if administration is continued further, serum sodium concentration should be measured at appropriate intervals.

6. Drug Interactions

1) Effects of drugs on SAMSCA

Ketoconazole and other strong CYP3A 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 SAMSCA. Co-administration of SAMSCA with 400 mg ketoconazole daily or with other strong CYP 3A inhibitors (e.g., clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir and nefazodone) at the highest labeled dose would be expected to cause an even greater increase in SAMSCA exposure. Thus, SAMSCA and strong CYP 3A inhibitors should not be co-administered.

Moderate CYP3A Inhibitors

The impact of moderate CYP 3A inhibitors (e.g., erythromycin, fluconazole, aprepitant, diltiazem and verapamil) on the exposure to co-administered SAMSCA has not been assessed. A substantial increase in the exposure to SAMSCA would be expected when SAMSCA is co-administered with moderate CYP 3A inhibitors. Co-administration of moderate CYP3A inhibitors with SAMSCA should generally be avoided.

Grapefruit Juice

Co-administration of grapefruit juice and SAMSCA results in a 1.9-fold increase in exposure to SAMSCA. Patients taking SAMSCA should avoid ingesting grapefruit juice.

P-gp Inhibitors

Reduction in the dose of SAMSCA may be required in patients concomitantly treated with P-gp inhibitors, such as e.g., cyclosporine, based on clinical response.

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 SAMSCA 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.

Lovastatin, Digoxin, Furosemide, and Hydrochlorothiazide

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

Medicinal products that increase serum sodium concentration

There is no experience from controlled clinical trials with concomitant use of SAMSCA and hypertonic saline, oral sodium formulations, and medicinal products that increase serum sodium concentration. Medicinal products with high sodium content such as effervescent analgesic preparations and certain sodium containing treatments for dyspepsia may also increase serum sodium concentration. Concomitant use of SAMSCA with medicinal products that increase serum sodium concentration may result in a higher risk for developing hypernatraemia and is therefore not recommended.

2) Effects of SAMSCA on Other Drugs

Digoxin

Digoxin is a P-gp substrate and SAMSCA is a P-gp inhibitor.
Steady state digoxin concentrations were increased (1.3-fold in maximum observed plasma concentration [Cmax] and 1.2-fold in area under the plasma concentration-time curve over the dosing interval [AUC_τ]) when co administered with multiple once daily 60 mg doses of SAMSCA. Concomitant use of SAMSCA with digoxin is not recommended.

Warfarin, Amiodarone, Furosemide, and Hydrochlorothiazide

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

Lovastatin

SAMSCA is a weak inhibitor of CYP 3A. Co-administration of lovastatin and SAMSCA increases the exposure to lovastatin and its active metabolite lovastatin-β hydroxyacid by factors of 1.4 and 1.3, respectively. This is not a clinically relevant change.

3) Pharmacodynamic Interactions

SAMSCA produces a greater 24 hour urine volume and 24 hour excretion rate than does furosemide or hydrochlorothiazide. Concomitant administration of SAMSCA with furosemide or hydrochlorothiazide results in a 24 hour urine volume and 24 hour excretion rate that is similar to the rate after SAMSCA administration alone.

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

As a V2 receptor antagonist, SAMSCA may interfere with the V2 agonist activity of desmopressin (dDAVP). In a male subject with mild Von Willebrand (vW) disease, intravenous infusion of dDAVP 2 hours after administration of oral SAMSCA did not produce the expected

increases in vW Factor Antigen or Factor Ⅷ activity. It is not recommended to administer SAMSCA with a V2 agonist.

4) Hypertonic saline

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

7. Use in specific populations

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

1) Pregnancy

There are no adequate and well controlled studies of SAMSCA use in pregnant women. In animal studies, cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryo-fetal death occurred. The potential risk for humans is unknown. SAMSCA is contraindicated during pregnancy. Women of childbearing potential have to use effective contraception during SAMSCA treatment.

In embryo-fetal development studies, pregnant rats and rabbits received oral SAMSCA during organogenesis. Rats received 2 to 162 times the maximum recommended human dose (MRHD) of SAMSCA (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 SAMSCA 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.

2) Nursing Mothers

It is not known whether SAMSCA is excreted into human milk. SAMSCA 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.

3) Labor and Delivery

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

4) Use in Pediatric population

Safety and effectiveness of SAMSCA in children and adolescents under the age of 18 years have not been established.

5) Use in Elderly population

A rapid decrease in circulating plasma volume or hemoconcentration associated with rapid diuresis may induce thromboembolism. SAMSCA should be administered with care and the patient's condition should be closely monitored. Elderly patients generally have reduced physiological function and are known to be susceptible to dehydration.

Hyponatremia

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

Adjunct treatment of volume overload in heart failure

In Japanese trials in cardiac edema, the age eligibility criteria were age 20 to < 80 years in one phase 2 trial and 20 to 85 years, inclusive, in three phase 3 trials, and the trials included many elderly subjects (generally defined in Japan as aged ≥ 65). There were no notable safety concerns observed in the elderly subjects when starting administration at a dose of 15 mg in those trials. However, in a Japanese post marketing safety survey comprising of 3349 patients, the results indicated an increased risk of hypernatremia-related adverse drug reactions in patients' age ≥ 85. The incidence of hypernatremia in elderly patients was 3.1% for a starting dose of 7.5 mg and 6.9% for a starting dose of 15 mg, indicating a significantly high incidence of hypernatremia for a starting dose of 15 mg.

Initiation of SAMSCA at half dose (7.5mg) is recommended in elderly patients with volume overload due to heart failure, because elderly patients were found to be at risk for hypernatremia.

6) Use in Patients with Hepatic Impairment

While moderate and severe hepatic impairment do not affect exposure to SAMSCA to a clinically relevant extent, there are limited data on the risk of hepatic injury in such pati ents. Therefore, one should avoid use of SAMSCA in patients with underlying liver disease.

7) Use in patients with Renal impairment

No dose adjustment is necessary based on renal function. There are no clinical trial data in patients with CrCl <10 mL/min, and, because drug effects on serum sodium levels are likely lost at very low levels of renal function, use in patients with a CrCl <10 mL/min is not recommended. No benefit can be expected in patients who are anuric.

8) Use in Patients with Congestive Heart Failure

Heart failure increases the bioavailability of SAMSCA and increases the volume of distribution of SAMSCA but not clinically relevant. No dose adjustment is necessary.

8. Overdose

Single oral doses up to 480 mg and multiple doses up to 300 mg once daily for 5 days have been well tolerated in studies in healthy subjects. There is no specific antidote for SAMSCA 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 SAMSCA in rats and dogs is > 2000 mg/kg. No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

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

Treatment should involve symptomatic and supportive care, with respiratory, ECG and blood pressure monitoring and water/electrolyte supplements as needed. A profuse and prolonged aquaresis should be anticipated, which, if not matched by oral fluid ingestion, should be replaced with intravenous hypotonic fluids, while closely monitoring electrolytes and fluid balance.

ECG monitoring should begin immediately and continue until ECG parameters are within normal ranges. Dialysis may not be effective in removing SAMSCA because of its high binding affinity for human plasma protein (> 98 %). Close medical supervision and monitoring should continue until the patient recovers.

[CLINICAL PHARMACOLOGY]

WHO ATC Code: C03XA01

1. Mechanism of action

SAMSCA 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). SAMSCA affinity for the V2-receptor is 29 times greater than for the V1a-receptor. When taken orally, 15 to 60 mg doses of SAMSCA 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. SAMSCA metabolites have no or weak antagonist activity for human V2-receptors compared with SAMSCA.

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

2. Pharmacodynamics

In healthy subjects receiving a single dose of SAMSCA 60 mg, the onset of the aquaretic and sodium increasing effects occurs within 2 to 4 hours post-dose. A peak effect of about a 6 mEq increase in serum sodium and about 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose; thus, the pharmacological activity lags behind the plasma concentrations of SAMSCA. 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 SAMSCA do not increase aquaresis or serum sodium further. The effects of SAMSCA 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 SAMSCA and placebo), placebo-and positive-controlled, multiple dose study of the effect of SAMSCA on the QTc interval, 172 healthy subjects were randomized to SAMSCA 30 mg, SAMSCA 300 mg, placebo, or moxifloxacin 400 mg once daily. At both the 30 mg and 300 mg doses, no significant effect of administering SAMSCA on the QTc interval was detected on Day 1 and Day 5. At the 300 mg dose, peak SAMSCA 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 SAMSCA's effect on the QT interval, had an effect been present.

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 a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3. The absolute bioavailability of SAMSCA is 56%. Peak concentrations of SAMSCA are observed between 2 and 4 hours post-dose. Food does not impact the bioavailability of SAMSCA. *In vitro* data indicate that SAMSCA is a substrate and inhibitor of P-gp. SAMSCA is highly plasma protein bound (99%) and distributed into an apparent volume of distribution of about 3 L/kg. SAMSCA is eliminated entirely by non-renal routes and mainly, if not exclusively, metabolized by CYP 3A. After oral dosing, clearance is about 4 mL/min/kg and the terminal phase half-life is about 12 hours. The accumulation factor of SAMSCA with the once-daily 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 SAMSCA with a percent coefficient of variation ranging between 30 and 60%.
In patients with hyponatremia of any origin the clearance of SAMSCA is reduced to about 2 mL/min/kg. Moderate or severe hepatic impairment or congestive heart failure decrease the clearance and increase the volume of distribution of SAMSCA, but the respective changes are not clinically relevant. Exposure and response to SAMSCA 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 60 mg SAMSCA, AUC and Cmax of plasma SAMSCA were less than doubled 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 SAMSCA's

effect on serum sodium were slower in patients with severe renal impairment.

[NONCLINICAL TOXICOLOGY]

1. Carcinogenesis, mutagenesis, impairment of fertility

Up to two years of oral administration of SAMSCA to male and female rats at doses up to 1000 mg/kg/day (162 times the maximum recommended human dose [MRHD] on a body surface area basis), to male mice at doses up to 60 mg/kg/day (5 times the MRHD) and to female mice at doses up to 100 mg/kg/day (8 times the MRHD) did not increase the incidence of tumors. SAMSCA 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 SAMSCA at 100, 300 or 1000 mg/kg/day, the highest dose level was associated with significantly fewer corpora lutea and implants than control.

2. Reproductive and developmental toxicology

In pregnant rats, oral administration of SAMSCA at 10, 100 and 1000 mg/kg/day during organogenesis was associated with a reduction in maternal body weight gain and food consumption at 100 and 1000 mg/kg/day (16 and 162 times the MRHD), and reduced fetal weight and delayed ossification of fetuses at 1000 mg/kg/day (162 times the MRHD on a body surface area basis). Oral administration of SAMSCA at 100, 300 and 1000 mg/kg/day to pregnant rabbits during organogenesis was associated with reductions in maternal body weight gain and food consumption at all doses (32 to 324 times the MRHD), and abortions at mid- and high-doses (97 to 324 times the MRHD). At 1000 mg/kg/day (324 times the MRHD), increased incidences of embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations were observed. There are no adequate and well-controlled studies of SAMSCA in pregnant women. SAMSCA is contraindicated during pregnancy.

[CLINICAL STUDIES]

1. Hyponatremia

In two double-blind, placebo-controlled, multi-center studies (SALT-1 and SALT-2), a total of 424 patients with euvolemic or hypervolemic hyponatremia (serum sodium <135 mEq/L) resulting from a variety of underlying causes (heart failure, liver cirrhosis, syndrome of inappropriate antidiuretic hormone [SIADH] and others) were treated for 30 days with SAMSCA or placebo, then followed for an additional 7 days after withdrawal. Symptomatic patients, patients likely to require saline therapy during the course of therapy, patients with acute and transient hyponatremia associated with head trauma or postoperative state and patients with hyponatremia due to primary polydipsia, uncontrolled adrenal insufficiency or uncontrolled hypothyroidism were excluded. Patients were randomized to receive either

placebo (N = 220) or SAMSCA (N = 223) at an initial oral dose of 15 mg once daily. The mean serum sodium concentration at study entry was 129 mEq/L. Fluid restriction was to be avoided if possible during the first 24 hours of therapy to avoid overly rapid correction of serum sodium, and during the first 24 hours of therapy 87% of patients had no fluid restriction. Thereafter, patients could resume or initiate fluid restriction (defined as daily fluid intake of ≤1.0 liter/day) as clinically indicated.

The dose of SAMSCA could be increased at 24 hour intervals to 30 mg once daily, then to 60 mg once daily, until either the maximum dose of 60 mg or normonatremia (serum sodium >135 mEq/L) was reached. Serum sodium concentrations were determined at 8 hours after study drug initiation and daily up to 72 hours, within which time titration was typically completed. Treatment was maintained for 30 days with additional serum sodium assessments on Days 11, 18, 25 and 30. On the day of study discontinuation, all patients resumed previous therapies for hyponatremia and were reevaluated 7 days later. The primary endpoint for these studies was the average daily AUC for change in serum sodium from baseline to Day 4 and baseline to Day 30 in patients with a serum sodium less than 135 mEq/L. Compared to placebo, SAMSCA caused a statistically greater increase in serum sodium (p <0.0001) during both periods in both studies (see Table 3). 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 3). This effect was also seen across all disease etiology subsets (e.g., CHF, SIADH/other).

Table 3. Effects of Treatment with SAMSCA 15 mg/day to 60 mg/day

	SAMSCA 15 mg/day - 60 mg/day	**Placebo**	**Estimated Effect (95% CI)**
Subjects with Serum Sodium <135 mEq/L (ITT population)			
Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N	4.0 (2.8) 213	0.4 (2.4) 203	3.7 (3.3-4.2) p <0.0001
Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L) Mean (SD) N	6.2 (4.0) 213	1.8 (3.7) 203	4.6 (3.9-5.2) p <0.0001
Percent of Patients Needing Fluid Restriction*	14% 30/215	25% 51/206	*p =0.0017*
Subgroup with Serum Sodium <130 mEq/L			
Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N	4.8 (3.0) 110	0.7 (2.5) 105	4.2 (3.5-5.0) p <0.0001
Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L) Mean (SD) N	7.9 (4.1) 110	2.6 (4.2) 105	5.5 (4.4-6.5) p <0.0001
Percent of Patients Needing Fluid Restriction*	19% 21/110	36% 38/106	*p <0.01*
Subgroup with Serum Sodium <125 mEq/L			
Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N	5.7 (3.8) 26	1.0 (1.8) 30	5.3 (3.8-6.9) p <0.0001
Change in average daily serum	10.0 (4.8)	4.1 (4.5)	5.7 (3.1-8.3)

[Na+] AUC baseline to Day 30 (mEq/L) Mean (SD) N	26	30	*p* <0.0001
Percent of Patients Needing Fluid Restriction*	35% 9/26	50% 15/30	*p* = 0.14

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

SIADH/Other

For SIADH subjects in the pooled analysis, an average daily AUC of mean change from baseline in serum sodium concentration of 4.8 mEq/L for SAMSCA and 0.2 mEq/L for placebo (an estimated treatment effect of 4.7 mEq/L for SAMSCA over placebo) up to Day 4 ($p < 0.0001$); and of 7.4 mEq/L for SAMSCA and 1.5 mEq/L for placebo (an estimated treatment effect of 6.2 mEq/L for SAMSCA over placebo) up to Day 30 ($p < 0.0001$) was observed.

Congestive Heart Failure (CHF)

For subjects with CHF, an average daily AUC of mean change from baseline in serum sodium concentration of 3.5 mEq/L for SAMSCA and 0.5 mEq/L for placebo (an estimated treatment effect of 3.0 mEq/L for SAMSCA over placebo) up to Day 4 ($p < 0.0001$); and of 6.6 mEq/L for SAMSCA and 2.4 mEq/L for placebo (an estimated treatment effect of 4.1 mEq/L for SAMSCA over placebo) up to Day 30 ($p < 0.0001$) was observed.

Table 4 represents the pooled analysis result of the average daily AUC of mean change from baseline in serum sodium concentration by hyponatremia etiology (SIADH/other and CHF).

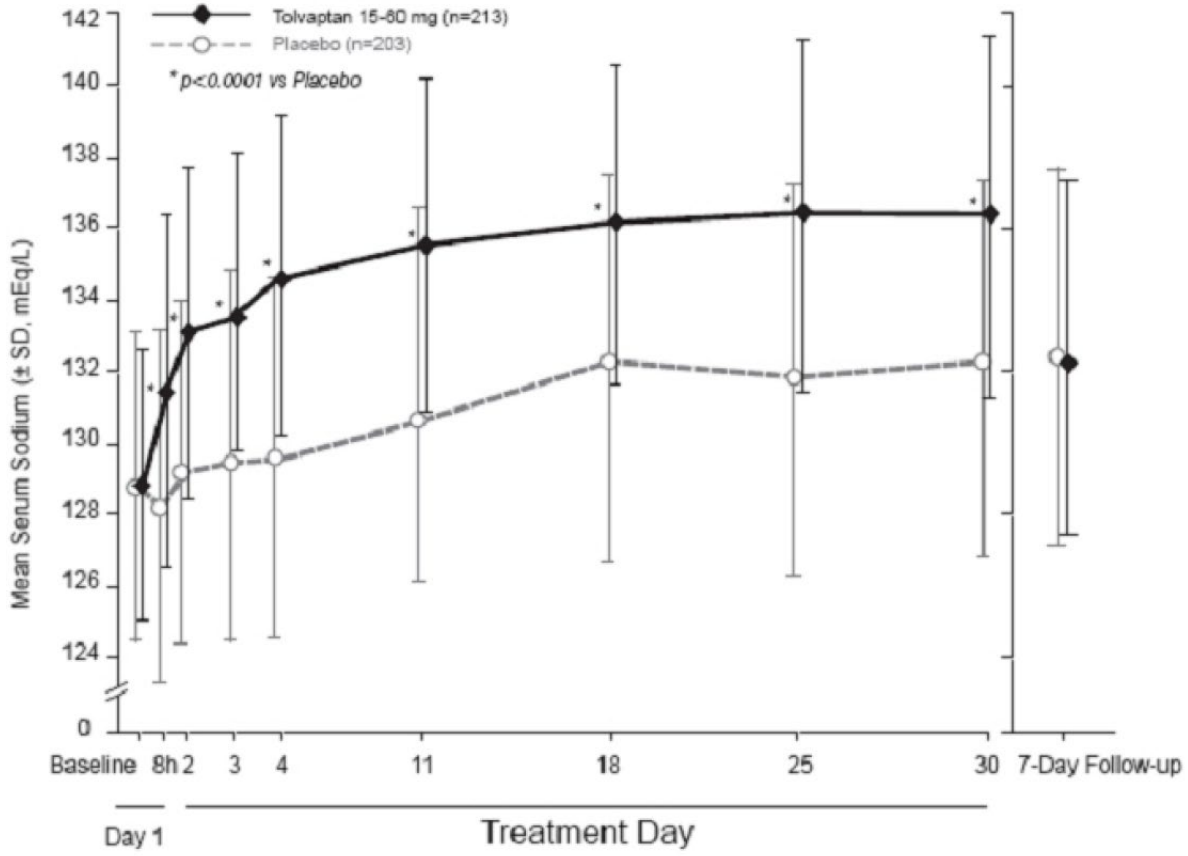
Table 4: Average Daily AUC up to Day 4 and Day 30 of Mean Change From Baseline in Serum Sodium Concentration (mEq/L) by Hyponatremia Etiology (SIADH/other and CHF) in the Pooled Placebo-controlled Phase 3 Hyponatremia Trials

	SAMSCA	**Placebo**	**Estimated Effect (95% CI)**
SIADH/Other			
Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N	4.76 (2.81) 85	0.19 (2.62) 88	4.7 (3.93-5.47) *p* <0.0001
Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L) Mean (SD) N	7.42 (3.75) 85	1.53 (3.55) 88	6.15 (5.19-7.11) *p* <0.0001
CHF			
Change in average daily serum [Na+] AUC baseline to Day 4 (mEq/L) Mean (SD) N	3.52 (2.97) 65	0.51 (1.99) 61	2.98 (2.12-3.85) *p* <0.0001
Change in average daily serum [Na+] AUC baseline to Day 30 (mEq/L) Mean (SD) N	6.58 (4.12) 65	2.38 (4.21) 61	4.05 (2.75-5.35) *p* <0.0001

In patients with hyponatremia (defined as <135 mEq/L), serum sodium concentration increased to a significantly greater degree in SAMSCA-treated patients compared to placebo-treated patients as early as 8 hours after the first dose, and the change was maintained for 30 days. The percentage of patients requiring fluid restriction (defined as ≤1 L/day at any time during the treatment period) was also significantly less (p =0.0017) in the SAMSCA-treated group (30/215, 14%) as compared with the placebo-treated group (51/206, 25%).

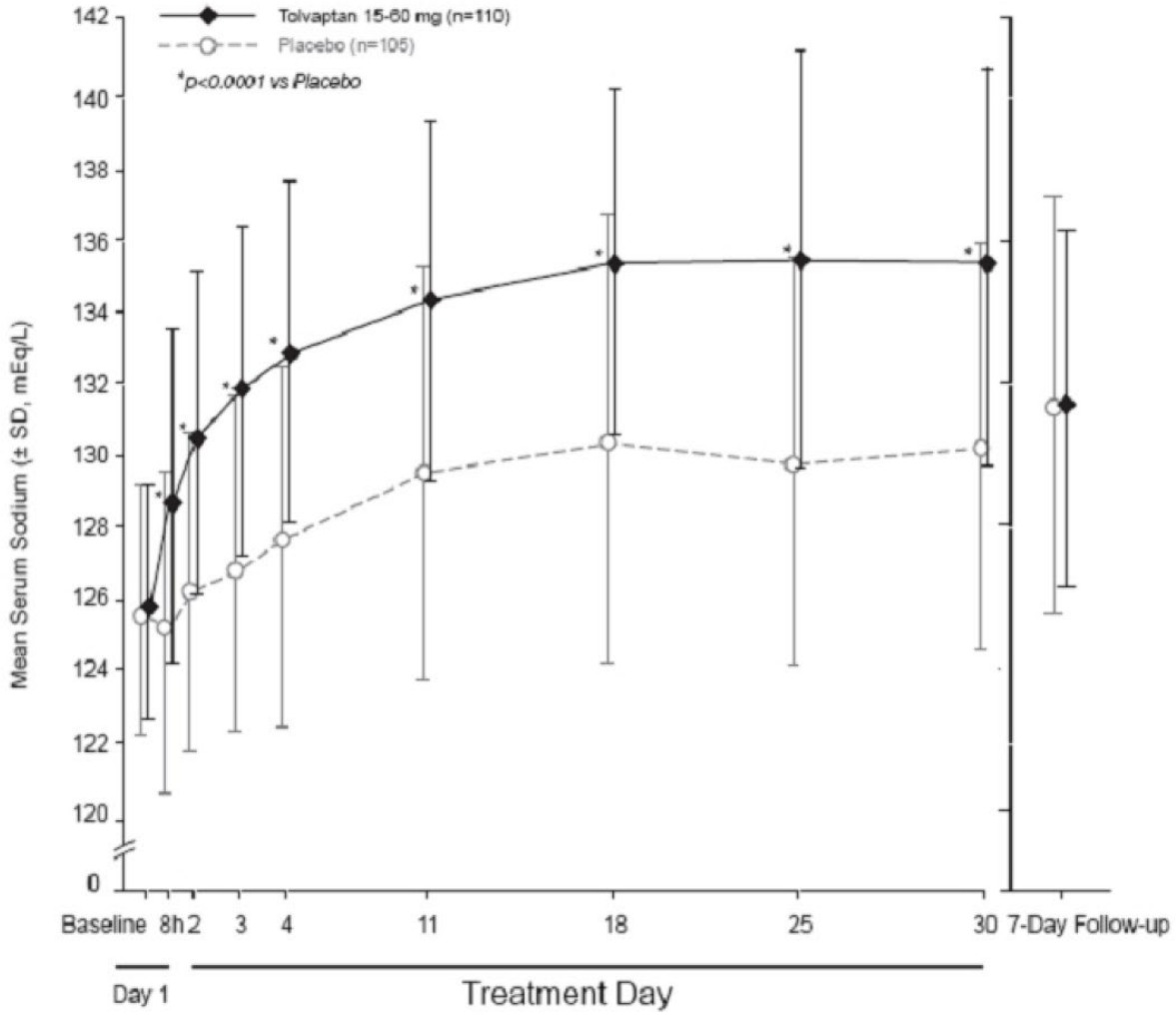
Figure 1 shows the change from baseline in serum sodium by visit in patients with serum sodium <135 mEq/L. Within 7 days of SAMSCA discontinuation, serum sodium concentrations in SAMSCA-treated patients declined to levels similar to those of placebo-treated patients.

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 SAMSCA treatment compared to placebo

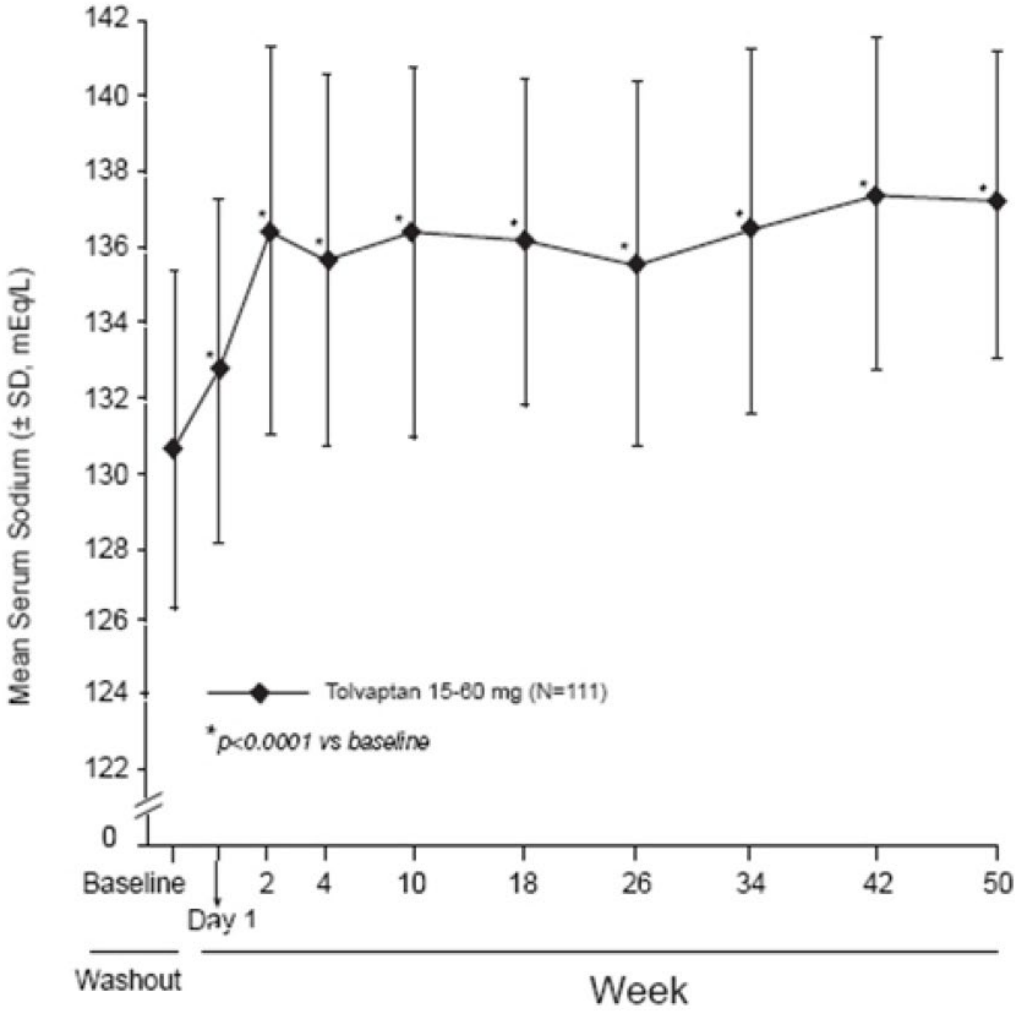
Figure 2: Pooled SALT Studies: Analysis of Mean Serum Sodium (± SD, mEq/L) by Visit Patients with Baseline Serum Sodium <130 mEq/L



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

In the open-label study SALTWATER, 111 patients, 94 of them hyponatremic (serum sodium <135 mEq/L), previously on SAMSCA or placebo therapy were given SAMSCA 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 SAMSCA, 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 SAMSCA treatment compared to baseline

2. Adjunct treatment of volume overload in heart failure

Japanese Data

The efficacy of oral administration of SAMSCA at 15 mg or placebo once daily for 7 days in congestive heart failure patients with volume overload despite the use of a conventional diuretic was evaluated in a double-blind, placebo-controlled phase 3 study. Patients with acute heart failure were excluded. Changes in body weight from baseline at the end of treatment, the primary efficacy endpoint, were -1.54 ± 1.61 kg (mean ± SD) in the SAMSCA 15-mg group (baseline: 59.42 ± 12.30 kg, n=53) and -0.45 ± 0.93 kg in the placebo group (baseline: 55.68 ± 12.60 kg, n=57), showing that SAMSCA 15 mg significantly decreased body weight compared with placebo (p<0.0001, t-test). A marked reduction in body weight was observed in the SAMSCA 15-mg group on Day 1, with subsequent decrease during the treatment period (Figure 4). Signs and symptoms associated with cardiac edema, including jugular venous distention, hepatomegaly, and lower limb edema, were also improved at the end of treatment (Table 5).

Figure 4: Change in Body Weight from Baseline in Patients with Cardiac Edema in a Placebo-controlled Double-blind Study

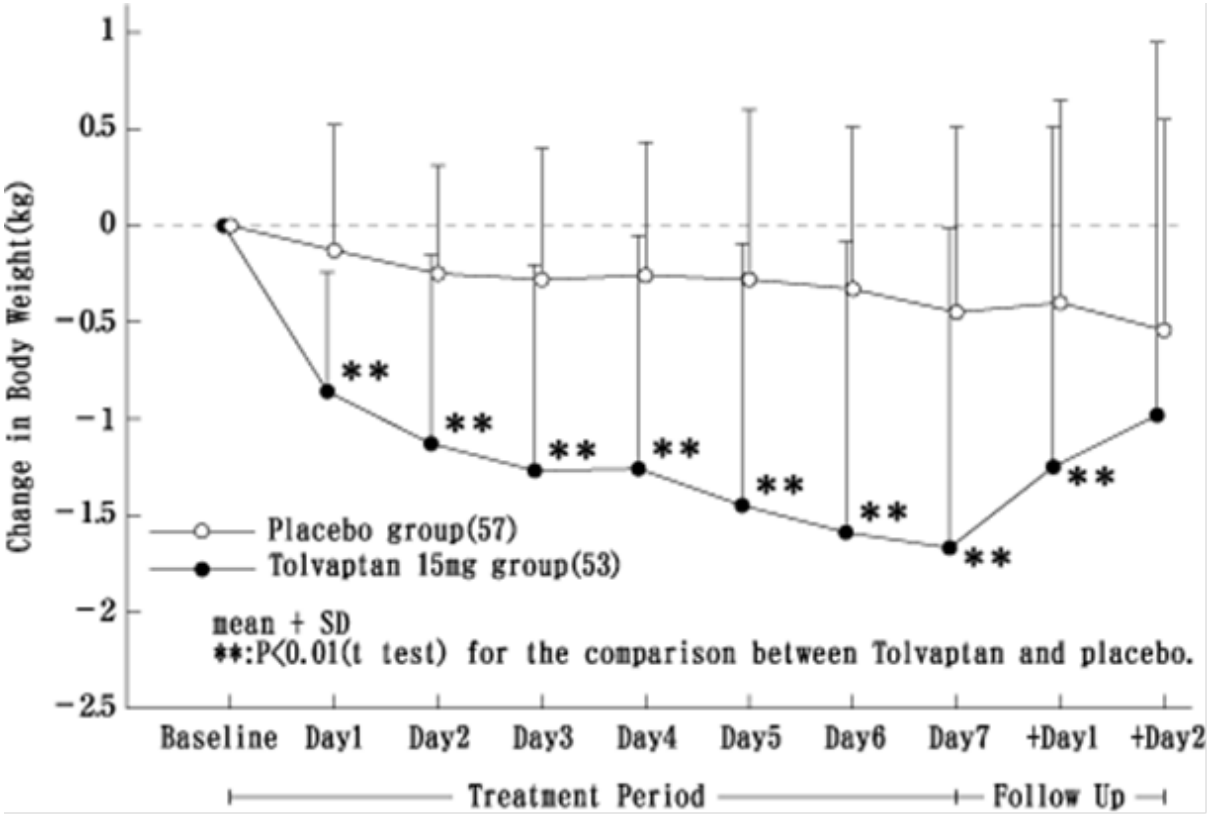


Table 5: Signs and Symptoms due to Cardiac Edema in a Placebo-controlled Double-blind Study

Signs and Symptoms Due to Cardiac Edema	SAMSCA 15 mg Group	Placebo Group
Change in jugular venous distention (cm) [n]	-2.03±2.81 [27]	-0.51±1.18 [19]
Change in hepatomegaly (cm) [n]	-1.07±0.89 [18]	-0.35±1.00 [17]
Improvement of lower limb edema (%) [n]	63.9 [23/36]	42.1 [16/38]

(Mean ± SD)

Other data

The efficacy and safety of SAMSCA as adjunct treatment of volume overload in heart failure was evaluated in one other phase 2 study and two other phase 3 studies.

In a multicenter, randomized, double-blind, placebo-controlled phase 2 study, the effect and safety of oral administration of SAMSCA at 15 mg, 30 mg, 60 mg or placebo once daily in conjunction with conventional therapy for up to 6 months on the chronic outcomes of patients with congestive heart failure (CHF) was evaluated. Of the 330 subjects receiving either 15 mg, 30 mg or 60 mg of SAMSCA, or placebo for up to 6 months, the study suggests that patients with stable CHF (NYHA Class II and III) on standard optimal background therapy did not demonstrate an improvement in outcomes when exposed to once daily dosing of SAMSCA for up to six months. However, possible additional symptomatic and outcome benefit (i.e. improvements in NYHA class and CHF symptoms such as pedal edema, jugular venous pressure (JVP), hepatomegaly, orthopnea and patent-assessed overall treatment effect) may be present in the subset of patients with evidence of congestion (edema at baseline). SAMSCA at 15mg showed some early improvement in NYHA score as early as Week 1. SAMSCA given at doses of 15 mg, 30 mg, and 60 mg once daily for up to six months was well tolerated and safe in this population.

In a randomized, double-blind, multicenter, placebo-controlled, parallel phase 3 study to evaluate the efficacy and safety of SAMSCA in the treatment of patients with cardiac edema based on the conventional therapy, patients treated with SAMSCA 15 mg once daily achieved a statistically significant greater reduction in body weight over placebo at the end of the treatment. Changes in body weight from baseline were -1.482 ± 1.947 kg (mean ± SD) in the SAMSCA 15 mg group (baseline: 67.379 ± 11.624 kg, n= 123) and -0.540 ± 1.506 kg in the placebo group (baseline: 65.480 ± 13.430 kg, n= 120), showing a statistically significant greater reduction in body weight in the SAMSCA 15 mg group compared with placebo ($p<0.0001$, t-test). There was a significant increase in both the improvement (SAMSCA: 85.71% vs placebo: 68.48%; $p = 0.0045$) and disappearance rate (SAMSCA: 68.37% vs placebo: 54.35%, $p = 0.0471$) of the lower extremity edema in the SAMSCA treatment group compared to the placebo group. There was also a significant difference in the disappearance rate of jugular vein engorgement in the SAMSCA group as compared to the placebo group (SAMSCA: 40.82% vs placebo: 14.89%, $p = 0.0047$). There was a general improvement in the other congestive symptoms such as hepatomegaly and pulmonary congestion in the SAMSCA group although the improvements did not reach statistical significance. Oral administration of SAMSCA 15 mg was safe as compared to placebo in the study.

In another multicenter, double-blind, randomized, placebo-controlled phase 3 study to evaluate the efficacy and safety of SAMSCA in the treatment of cardiac edema in patients with heart failure, the mean change in body weight from baseline were −1.36 ± 2.13 kg (mean ± SD) in the SAMSCA group and −0.59 ± 1.27 kg in the placebo group. The significant difference in the mean changes between the two groups was −0.78 kg ($p=0.0394$; 95% CI: −1.52 to −0.04 kg), showing a statistically significant reduction in body weight in the SAMSCA 15 mg group compared with placebo ($p < 0.0001$, t-test). Significant daily urine volume output was observed when compared with the placebo for the four days of treatment. Without fluid restriction, mean daily fluid intake/urine volume output balance revealed significant difference in two groups (mean daily intake/output balance: −97.5 mL in the SAMSCA group vs. 262.1 mL in the placebo group, $p = 0.0131$).

For pulmonary congestion, the improvement rate (SAMSCA:47.83% vs. placebo: 42.22%, $p = 0.6751$) and resolution rate (SAMSCA: 29.27% vs. placebo: 25.64%; $p = 0.8045$) in the SAMSCA group was numerically higher than that in placebo group although no significant difference was observed between the two groups. At the end of the study, pulmonary rales remained unchanged in most subjects (SAMSCA: 60.87% vs. placebo: 68.89%) but more subjects in the SAMSCA group achieved improvement ($p = 0.8386$). None of the subjects showed worsened lower limb edema at the end of the study. Overall, a total of 31 subjects

(67.39%) in the SAMSCA group experienced at least 1-level grade of improvement, while a total of 26 subjects in placebo showed improvement (57.78%) in the intention-to-treat (ITT) population (p = 0.3905). The severity of change from baseline in lower limb edema was compared between groups by the proportional odds model, no statistically significant difference was observed between treatment groups (OR 1.3297; p = 0.5164). For patient self-assessed dyspnea status, there was higher percentage of improvement in the dyspnea in the SAMSCA group (SAMSCA: 89.13% vs placebo: 80.00%), however this failed to meet statistical significance (OR 1.175; p = 0.7717). For physician-assessed dyspnea, 73.91% of subjects reached some grade of improvement vs. 66.67% in the placebo group, but there was no significant difference (p = 0.4971) in the mitigation of dyspnea between groups. SAMSCA was well tolerated in the study.

[STORAGE]

Store at or below 30°C.

[SHELF-LIFE]

36 months after the date of manufacture

[PACKAGING UNIT]

10 tablets (1 x 10's), Alu/Alu Blister

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Korea Otsuka Pharmaceutical Co., Ltd.
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, Republic of Korea

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