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U.S.  
Debra Kaufmann  
Otsuka America Pharmaceutical, Inc.  
240.683.3568  
[debra.kaufmann@otsuka-us.com](mailto:debra.kaufmann@otsuka-us.com)

JAPAN  
Masamitsu Kitada  
Otsuka Pharmaceutical Co., Ltd.  
[kitadams@otsuka.jp](mailto:kitadams@otsuka.jp)

**FDA APPROVES SAMSCA™ (tolvaptan), THE FIRST AND ONLY ORAL  
VASOPRESSIN ANTAGONIST TO TREAT PATIENTS WITH CLINICALLY  
SIGNIFICANT HYPERVOLEMIC AND EUVOLEMIC HYPONATREMIA**

***Once-Daily SAMSCA Increases Serum Sodium Levels Through Increase in Free Water  
Clearance***

Tokyo, Japan and Princeton, N.J. May 21, 2009 – Otsuka Pharmaceutical Co., Ltd. (OPC) and Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC) announced today that the U.S. Food and Drug Administration (FDA) has approved SAMSCA™ (tolvaptan) as the only oral selective vasopressin antagonist for the treatment of patients with clinically significant hypervolemic and euvolemic hyponatremia (serum sodium less than 125 mEq/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure, cirrhosis, and the syndrome of inappropriate anti-diuretic hormone (SIADH). Patients requiring urgent treatment to raise serum sodium to prevent or to treat serious neurological deficits should not be treated with SAMSCA. Additionally, it has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients. SAMSCA, an oral vasopressin V<sub>2</sub>-receptor antagonist, will be commercialized in the United States by Otsuka America Pharmaceutical, Inc. (OAPI).

Once-daily SAMSCA has been shown to significantly raise serum sodium concentrations in as early as 8 hours, and the change was maintained for 30 days. Exposure and response to SAMSCA are similar in patients with a creatinine clearance of 10-79 mL/min and in patients without renal impairment; thus no dosage adjustment is necessary. SAMSCA has not been evaluated in patients with creatinine clearance less than 10 mL/min or in patients undergoing dialysis.

“The approval of SAMSCA marks a significant milestone for Otsuka,” said Taro Iwamoto, Ph.D., President and Representative Director, Otsuka Pharmaceutical Co., Ltd. “Otsuka Pharmaceutical Co., Ltd. has continued its commitment to create innovative products for cardiovascular, respiratory, digestive and infectious diseases as well as in its core R&D areas of central nervous system and oncology to address unmet medical needs. We are delighted that with the approval of SAMSCA, Otsuka will deliver a selective and corrective treatment for hyponatremia to patients and physicians in the United States.”

The unique mechanism of action of SAMSCA™ (tolvaptan) selectively blocks the binding of vasopressin to the V<sub>2</sub>-receptors in the collecting duct of the kidney. If the V<sub>2</sub>-receptors are left unblocked, the binding of vasopressin with these receptors can cause water retention resulting in hyponatremia. By inhibiting the effects of vasopressin at the V<sub>2</sub>-receptor, SAMSCA increases the excretion of free water, while the excretion of sodium and other electrolytes is not directly affected (aquaresis).

“SAMSCA can help increase serum sodium concentrations without causing a significant change in urine excretion of electrolytes, which is good news for patients with hyponatremia,” said Robert W. Schrier, M.D., Professor of Medicine, University of Colorado School of Medicine. “In addition, patients receiving SAMSCA can and should continue drinking fluids in response to thirst.”

SAMSCA should be initiated and re-initiated in patients only in a hospital where their serum sodium can be monitored closely due to the risk of overly rapid correction of hyponatremia. Too rapid correction of hyponatremia (e.g., increase greater than 12 mEq/L/24 hours) can cause osmotic demyelination syndrome (ODS), resulting in dysarthria (difficulty speaking), mutism, dysphagia (trouble swallowing), lethargy, affective changes (mood changes), spastic quadraparesis (involuntary muscle weakness), seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. In controlled clinical trials in which SAMSCA was administered in titrated doses starting at 15 mg once daily, 7 percent of SAMSCA-treated subjects with a serum sodium less than 130 mEq/L had an increase in serum sodium greater than 8 mEq/L at approximately 8 hours and 2 percent had an increase greater than 12 mEq/L at 24 hours. Approximately 1 percent of placebo-treated subjects with a serum sodium less than 130 mEq/L had a rise greater than 8 mEq/L at 8 hours and no patient had a rise greater than 12 mEq/L/24 hours. None of the patients in these studies had evidence of osmotic demyelination syndrome or related neurological sequelae, but such complications have been reported following too-rapid correction of serum sodium.

### **Study Information**

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 less than 135 mEq/L) resulting from a variety of underlying causes (congestive heart failure [CHF], liver cirrhosis, syndrome of inappropriate anti-diuretic hormone [SIADH], and others) were treated for 30 days with SAMSCA or placebo, then followed for an additional 7 days after withdrawal.

The primary endpoint of these studies was the average daily area under the curve (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 less than 0.0001) during both periods in both studies. For patients with a serum sodium of less than 130 mEq/L or less than 125 mEq/L, the effects at Day 4 and Day 30 remained significant. This effect was also seen across all disease etiology subsets (e.g., CHF, cirrhosis, SIADH/other). Seven days after withdrawal of SAMSCA, serum sodium levels of patients decreased to levels approximately equivalent to those of patients treated with placebo.

In addition, serum sodium concentrations 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 less than 1L/day at any time during the treatment period) was also significantly less (p

less than 0.0017) in the SAMSCA™ (tolvaptan)-treated group (30/215, 14 percent) as compared with the placebo-treated group (51/206, 25 percent).

In an open-label study (SALTWATER), 111 patients, 94 of whom were hyponatremic, who had previously been treated with either placebo or SAMSCA (and who had returned to standard of care for at least 7 days), were administered SAMSCA. Upon initiation of therapy, average serum sodium concentrations increased to approximately the same levels as observed for those patients previously treated with SAMSCA and were sustained for at least a year.

The safety of SAMSCA has been evaluated in more than 4,000 patients, approximately 650 of which had hyponatremia. Of these 650 patients, approximately 219 received SAMSCA for six months or more. In the two 30-day, double-blind, placebo-controlled trials, the most common adverse reactions (greater than or equal to 5 percent more frequently than in patients receiving placebo) observed in patients receiving SAMSCA (n equals 223, placebo n equals 220) were thirst (16 percent vs. 5 percent in placebo patients), dry mouth (13 percent vs. 4 percent), asthenia (9 percent vs. 4 percent), constipation (7 percent vs. 2 percent), pollakiuria or polyuria (11 percent vs. 3 percent), and hyperglycemia (6 percent vs. 1 percent). In these studies, 10 percent of SAMSCA patients discontinued therapy due to adverse reactions compared to 12 percent of placebo-treated patients.

### **About Hyponatremia**

Hyponatremia, a common electrolyte disorder in hospitals, occurs in as many as 6 million people in the United States or 15-20 percent of hospitalized patients. The severity of symptomatology is associated with the rapidity of onset of hyponatremia: the quicker the onset, the more severe the symptoms. Hyponatremia that develops more slowly may show symptoms such as muscle cramps and headaches; however, more rapidly occurring hyponatremia may cause altered mental status with confusion, coma, and possibly seizures. Patients with chronic hyponatremia do have symptoms such as attention deficits, unsteadiness, gait imbalance, posture impairment and increased falls. Other hyponatremia symptoms may include nausea and vomiting, irritability and weakness. SAMSCA is indicated for the treatment of patients with clinically significant hypervolemic and euvolemic hyponatremia (serum sodium less than 125 mEq/L, or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure, cirrhosis, and the syndrome of inappropriate anti-diuretic hormone (SIADH). Patients requiring urgent treatment to raise serum sodium to prevent or to treat serious neurological deficits should not be treated with SAMSCA. Additionally, it has not been established that raising serum sodium with SAMSCA provides a symptomatic benefit to patients.

### **IMPORTANT SAFETY INFORMATION for SAMSCA**

**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., increase greater than 12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable.**

**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, hypovolemic hyponatremia, concomitant use of strong CYP 3A inhibitors, anuric patients

- **Too Rapid Correction of Serum Sodium Can Cause Serious Neurologic Sequelae** – During initiation and after titration monitor patients to assess serum sodium concentrations and

neurologic status. Subjects with SIADH or very low baseline serum sodium concentrations may be at greater risk for too-rapid correction of serum sodium. In patients receiving SAMSCA™ (tolvaptan) who develop too rapid a rise in serum sodium, discontinue or interrupt treatment with SAMSCA and consider administration of hypotonic fluid. Fluid restriction during the first 24 hours with SAMSCA may increase the likelihood of overly-rapid correction of serum sodium, and should generally be avoided.

- **Gastrointestinal Bleeding in Patients with Cirrhosis** – Used only when the need to treat outweighs this risk
- **Dehydration and Hypovolemia** – In patients who develop medically significant signs or symptoms of hypovolemia, discontinuation is recommended. Dehydration and hypovolemia can occur, especially in potentially volume-depleted patients receiving diuretics or those who are fluid restricted.
- **Co-administration with Hypertonic Saline** – Not recommended
- **Other Drugs Affecting Exposure to SAMSCA** –
  - **CYP 3A Inhibitors** – Do not use with strong inhibitors of CYP 3A; avoid concomitant use with moderate CYP 3A inhibitors
  - **CYP 3A Inducers** – Avoid concomitant use with CYP 3A inducers. If co-administered, the dose of SAMSCA may need to be increased
  - **P-gp Inhibitors** – The dose of SAMSCA may have to be reduced if co-administered with P-gp inhibitors
- **Hyperkalemia or Drugs that Increase Serum Potassium** – Monitor serum potassium levels in patients with a serum potassium less than 5 mEq/L and in patients receiving drugs known to increase serum potassium levels

**Pregnancy and Nursing Mothers** – SAMSCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from SAMSCA, a decision should be made to discontinue nursing or SAMSCA, taking into consideration the importance of SAMSCA to the mother.

**Commonly observed adverse reactions** – (incidence less than or equal to 5 percent more than placebo): thirst (16 percent vs 5 percent), dry mouth (13 percent vs 4 percent), asthenia (9 percent vs 4 percent), constipation (7 percent vs 2 percent), pollakiuria or polyuria (11 percent vs 3 percent) and hyperglycemia (6 percent vs 1 percent)

**Please see accompanying FULL PRESCRIBING INFORMATION, including Boxed WARNING, or visit [www.samsca.com](http://www.samsca.com).**

#### **About Otsuka Pharmaceutical Co., Ltd. (OPC)**

Founded in 1964, Otsuka Pharmaceutical Co., Ltd. is a global healthcare company with the corporate philosophy: 'Otsuka-people creating new products for better health worldwide.' Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and consumer products for the maintenance of everyday health. Otsuka is committed to being a corporation that creates global value, adhering to the high ethical standards required of a company involved in human health and life, maintaining a dynamic corporate culture, and working in harmony with local communities and the natural environment.

For additional information, please visit [www.otsuka-global.com](http://www.otsuka-global.com).

Otsuka Pharmaceutical Co., Ltd. is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group. The Otsuka Group comprises 153 companies and employs approximately 36,000 people in 23 countries and regions worldwide. Otsuka and its consolidated subsidiaries earned ¥955.9 billion (approx. US \$9.7 billion\*) in annual revenues in fiscal 2008.

\* Exchange rate as of March 31, 2009.

**About Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)**

Otsuka Pharmaceutical Development and Commercialization, Inc. is involved in conducting all phases of clinical research and development of innovative healthcare products to address unmet medical needs. OPDC is well established in the scientific community as a globally focused organization that plays a leadership role in the research and development of Otsuka's ethical healthcare products. The Company is dedicated to the improvement of the quality of human life and health of patients around the world with a strong commitment to research and development in the areas of cardiovascular, gastrointestinal, respiratory, renal and neuroscience systems, and to treat cancer and ophthalmic disorders. OPDC is part of the Otsuka Pharmaceutical Group of companies. For additional information, please visit [www.otsuka-us.com](http://www.otsuka-us.com).

**About Otsuka America Pharmaceutical, Inc.**

Otsuka America Pharmaceutical, Inc. (OAPI) is a successful, innovative, fast-growing healthcare company that commercializes Otsuka-discovered and other product opportunities in North America, with a strong focus on and commitment to neuroscience, cardiovascular, oncologic, and gastrointestinal therapeutic treatments. OAPI is dedicated to improving patients' health and the quality of human life. OAPI is part of the Otsuka Pharmaceutical Group, and was established in 1989 by Otsuka America, Inc. (OAI), which is wholly owned by Otsuka Pharmaceutical Co., Ltd. (OPC). For additional information, please visit [www.otsuka-us.com](http://www.otsuka-us.com)

OPDC and OAPI are subsidiaries of Otsuka America, Inc., which is wholly owned by OPC.

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