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News Release

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Study Shows VAPRISOL[®] is Effective in Increasing Serum Sodium Levels and Well-Tolerated in Patients With Euvolemic or Hypervolemic Hyponatremia

Deerfield, Illinois – October 25, 2007 – Astellas Pharma US, Inc. today announced data demonstrating that VAPRISOL[®] (conivaptan hydrochloride injection) effectively raises serum sodium concentration ($[Na^+]$) and is well-tolerated among hospitalized patients with euvolemic or hypervolemic hyponatremia, a potentially life-threatening condition that occurs when the body's sodium level falls below normal. The efficacy and safety profile of VAPRISOL was comparable under double-blind or open-label conditions. The study results were presented at the American College of Chest Physicians (CHEST) 2007 meeting.

“Hyponatremia is common in patients with congestive heart failure and in patients with the syndrome of inappropriate antidiuretic hormone (SIADH), which is seen in various pulmonary disorders and postsurgical settings,” said Joseph G. Verbalis, M.D., at the Georgetown University Hospital. “These data suggest that VAPRISOL can safely and effectively raise serum sodium levels in patients with underlying conditions such as pneumonia, chronic obstructive pulmonary disease and impaired heart function.”

VAPRISOL is the first in a new class of arginine vasopressin (AVP) receptor antagonists. VAPRISOL blocks both V_{1a} and V_2 vasopressin receptors, resulting in increased urine output without increased sodium loss. This effect, known as “aquaresis,” increases serum sodium levels and helps to restore salt and water balance in patients with hyponatremia due to increased body water (dilutional hyponatremia).

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VAPRISOL is approved by the U.S. Food and Drug Administration as a treatment for euvolemic and hypervolemic hyponatremia in hospitalized patients. VAPRISOL is not indicated for the treatment of congestive heart failure. It should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected benefit of raising serum sodium outweighs the increased risk of adverse events. The approved doses for VAPRISOL include 20 mg/day and 40 mg/day. The 80 mg/day dose used in this study is not an approved dose.

Study Findings

The post-hoc pooled analysis is based on results from a randomized controlled trial (RCT) of 84 patients and an open-label study (OLS) of 251 patients, all with euvolemic or hypervolemic hyponatremia.

After infusion of a 20 mg loading dose or placebo, VAPRISOL was given in a continuous 4-day infusion of 40 or 80 mg/d in the RCT and 20 or 40 mg/d in the OLS. Follow-up time after the 4-day treatment included serum $[Na^+]$ assessments at day 11 for both groups as well as day 34 for the OLS group only. The primary endpoint of both studies was the change from baseline in serum $[Na^+]$ over the entire course of treatment (expressed as the area under the curve, or AUC). Secondary endpoints included: time to reach a ≥ 4 mEq/L increase in serum $[Na^+]$; total time during which patients had a ≥ 4 mEq/L increase in serum $[Na^+]$; change in serum $[Na^+]$ at day four; and number of patients who achieved a ≥ 6 mEq/L increase in serum $[Na^+]$ or a normal serum $[Na^+]$ (≥ 135 mEq/L) over the course of the study.

Across both studies, patients receiving VAPRISOL showed significant increases in serum $[Na^+]$ starting on day one of treatment, with a sustained increase in serum $[Na^+]$ one to four weeks after the completion of the studies. In each VAPRISOL dosing group, mean time to a confirmed ≥ 4 -mEq/L increase was ~ 24 hours and the increase was maintained above baseline for most of the treatment period. By day four, VAPRISOL increased serum $[Na^+]$ above baseline (mean) from 6.8 to 9.7 mEq/L across the studies. Most VAPRISOL-treated patients achieved a confirmed ≥ 6 -mEq/L increase in serum $[Na^+]$ or normal serum $[Na^+]$ (69 to 88.5 percent in the RCT and 70.3 to 72 percent in the OLS).

In the RCT, VAPRISOL was significantly more effective than placebo in increasing baseline-adjusted serum $[Na^+]$ AUC during the four-day treatment ($P=.0001$). In the OLS, the increases in serum $[Na^+]$ were sustained at the post-treatment assessments. Mean increases in serum $[Na^+]$ above baseline with VAPRISOL on day 11 were 7.1 mEq/L with 20 mg/d and 8.0 mEq/L with 40 mg/d. On day 34, increases were 11.5 and 10.7 mEq/L with 20 and 40 mg/d, respectively.

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The most common adverse events included injection-site phlebitis, injection-site reaction and hypokalemia. An overly rapid serum $[\text{Na}^+]$ increase occurred in 15 patients treated with VAPRISOL, usually manifested by a $>12\text{-mEq/L}$ rise within 24 hours. Treatment was discontinued in 12 patients; the dose was lowered in the other three. No adverse events related to a rapid rise in serum $[\text{Na}^+]$ were reported.

About Hyponatremia

Hyponatremia often results from elevated levels of the hormone arginine vasopressin (AVP), which regulates water and salt balance in the body. It is the most common electrolyte disorder in clinical medicine.

Syndrome of inappropriate antidiuretic hormone (SIADH), advanced kidney failure, hypothyroidism, cancer and chronic high blood pressure are common causes of hyponatremia. Dilutional hyponatremia, which includes euvolemic and hypervolemic hyponatremia, is the most common form of the condition, and occurs when retained water dilutes serum sodium content. Patients with hyponatremia are classified as *hypervolemic* if swelling of body tissues (edema) is present or *euvolemic* if there is an increase in total body water content without edema.^{1,2}

About VAPRISOL

Discovered and developed by Astellas Pharma Inc. headquartered in Tokyo, Japan, VAPRISOL is a novel drug that blocks the activity of AVP, resulting in increased urine output without loss of valuable electrolytes such as sodium and potassium. This effect, known as “aquaresis,” helps to increase serum sodium levels in patients with hyponatremia, a condition of low serum sodium concentration, due to increased body water (dilutional hyponatremia). VAPRISOL is the first AVP receptor antagonist with a demonstrated safety profile and that effectively promotes aquaresis which helps to restore salt and water balance in patients with euvolemic and hypervolemic hyponatremia.

VAPRISOL is indicated for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients. VAPRISOL is not indicated for the treatment of congestive heart failure. It should only be used for the treatment of hyponatremia in patients with underlying heart failure when the expected benefit of raising serum sodium outweighs the increased risk of adverse events. VAPRISOL is contraindicated in patients with hypovolemic hyponatremia.

In addition, coadministration of VAPRISOL with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated.

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Serum sodium, volume, and neurological status must be monitored frequently because VAPRISOL potentially can cause overly rapid correction of sodium leading to serious sequelae.

The use of VAPRISOL in patients with hepatic impairment (including ascites, cirrhosis, or portal hypertension) or renal impairment has not been systematically evaluated. Use caution when administering VAPRISOL to these patients.

The most common adverse reactions reported were infusion site reactions (incidence of 73% and 63% for 20 mg/day and 40 mg/day respectively) which were also the most common type of adverse reaction leading to discontinuation of VAPRISOL.

Discontinuations from treatment due to infusion site reactions were more common among VAPRISOL-treated patients (3%) than among placebo-treated patients (0%). Other common adverse reactions were headaches (8%, 10%), hypokalemia (22%, 10%), orthostatic hypotension (14%, 6%), and pyrexia (11%, 5%) for VAPRISOL 20mg/day and 40mg/day, respectively.

Complete prescribing information for VAPRISOL can be accessed at www.VAPRISOL.com.

About Astellas

Astellas Pharma US, Inc., located in Deerfield, Illinois, is a U.S. affiliate of Tokyo-based Astellas Pharma Inc., Astellas is a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. The organization is committed to becoming a global category leader in focused areas by combining outstanding R&D and marketing capabilities. In the US, Astellas markets products in the areas of Immunology, Urology, Anti-Infectives, Cardiovascular and Dermatology. For more information about Astellas Pharma US, Inc., please visit our website at www.astellas.com/us.

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