



# Otsuka Pharmaceutical Development & Commercialization, Inc.

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## NEW DRUG APPLICATION FOR TOLVAPTAN, OTSUKA'S INVESTIGATIONAL NOVEL ORAL TREATMENT FOR WORSENING HEART FAILURE AND HYPONATREMIA, ACCEPTED BY THE U.S. FOOD AND DRUG ADMINISTRATION

PRINCETON, NJ, Dec. 21, 2007-- Otsuka Pharmaceutical Development & Commercialization, Inc. announced today that the U.S. Food and Drug Administration has accepted a new drug application (NDA) for the company's investigational oral once-daily medication tolvaptan, a selective  $V_2$ -vasopressin receptor antagonist, for two indications: treatment of adults with worsening heart failure and treatment of hyponatremia.<sup>1</sup> These indications are based on data from three phase 3 pivotal trials.<sup>2</sup>

OPDC was established in 2007 by Otsuka America, Inc. (OAI). OPDC is wholly owned by OAI, which is the holding company for Otsuka Pharmaceutical Co., Ltd. (OPC) interests in the U.S. OAI is wholly owned by OPC.

Tolvaptan is a novel, investigational small molecule designed to be an antagonist of the vasopressin  $V_2$  receptor, which plays a role in the kidney's regulation of fluid excretion. The majority of patients hospitalized for worsening heart failure have edema or excess body fluid, which is treated with diuretics to excrete the fluid. In contrast to diuretics, tolvaptan is designed to promote aquaresis, the excretion of

electrolyte-free water. In clinical trials, the most common adverse reactions in patients with worsening heart failure (incidence greater than or equal to 5% in patients treated with tolvaptan and double the incidence of patients treated with placebo) were thirst, dry mouth and polyuria. In patients with hyponatremia, the most common adverse reactions in clinical trials (incidence greater than or equal to 5% in patients treated with tolvaptan and double the incidence of patients treated with placebo) were thirst, dry mouth, asthenia, constipation, pollakiuria and hyperglycemia. The most serious adverse events were cardiogenic shock (1.7% in patients receiving tolvaptan vs. 1.2% of patients receiving placebo), pulmonary embolism (1.3% in patients receiving tolvaptan vs. 0.8% for patients receiving placebo,) and gout (4.7% in patients receiving tolvaptan vs. 3.9% in patients receiving placebo). For all of these, the number of patients that received tolvaptan was 2063 and for placebo was 2055 in addition to standard of care.

### **About Heart Failure**

More than 14 million people in Europe<sup>3</sup> and five million U.S. residents<sup>4</sup> have heart failure (HF), a serious chronic condition in which the heart cannot effectively pump blood. Hospitalizations in the United States related to HF account for 75 percent of the \$46 billion spent each year on the care of HF patients, according to the American Heart Association.<sup>5</sup> The majority of patients hospitalized for worsening HF, about 1 million U.S. residents annually, have edema or excess body fluid.

### **About Hyponatremia**

Hyponatremia, characterized by low concentrations of sodium in the blood, is a known predictor of death in patients with serious underlying illnesses.<sup>6</sup> Hyponatremia has long been associated with neurological symptoms including in its worst forms seizure and coma, and in its mildest forms slowed thoughts and reflexes.<sup>7</sup> Normal serum sodium is between 135 to 145 mEq/L, whereas patients diagnosed with hyponatremia have sodium levels of less than 135 mEq/L.<sup>8</sup>

### **About Otsuka Pharmaceutical Development & Commercialization, Inc.**

Otsuka Pharmaceutical Development & Commercialization (OPDC) 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, neuroscience, renal and respiratory diseases, as well as cancer and ophthalmic disorders. The Company is part of the Otsuka Pharmaceutical Group, which is comprised of 99 companies and approximately 31,000 people around the

world. Otsuka and its consolidated subsidiaries earned US \$7.2 billion in consolidated annual revenues in fiscal 2006. For additional information, please visit [www.otsuka.com](http://www.otsuka.com).

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<sup>1</sup> Current Proposed PLR, October 19, 2007. Page 1. Supplied by Otsuka.

<sup>2</sup> EVEREST, SALT-1, SALT-2

<sup>3</sup> SHAPE Survey Results to the General Public, Annual Congress of the European Society of Cardiology in Vienna, September 2003.

<sup>4</sup> ACC News Release, "American College of Cardiology / American Heart Association guidelines: New heart failure guidelines stress early diagnosis and treatment," August 16, 2005. Accessed at <http://www.acc.org/media/releases/highlights/2005/aug05/hf%5Fguideline%5Fupdate.htm> on March 1, 2007.

<sup>5</sup> American Heart Association. *Heart Disease and Stroke Statistics: 2005 Update*. Dallas, Tex: American Heart Association; 2005. as cited in Gheorghiade M, et al. *Circulation*. 2005;112:3958-3968.

<sup>6</sup> Schrier RW, Gheorghiade M, Gross P, et al. Results from the SALT 1 and 2 Trials. Multicenter, Randomized, Placebo-Controlled Trials in Patients with Euvolemic and Hypervolemic Hyponatremia. Being Presented at American Heart Association's Scientific Sessions in November 2006.

<sup>7</sup> Adroge HJ, Madias NE. Hyponatremia. *NEJM*. 2000; 342 (21):1581-1589.

<sup>8</sup> Gheorghiade M, Gottlieb SS, Udelson JE, et al. Vasopressin V2 Receptor Blockade With Tolvaptan Versus Fluid Restriction in the Treatment of Hyponatremia. *AmJCardiol* 2006;97:1064-1067.