DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Division of Cardiovascular and Renal Products is currently reviewing a New Drug Application (NDA) for tolvaptan, an orally administered selective vasopressin V2-receptor antagonist that has been developed for the treatment of euvolemic and hypervolemic hyponatremia, as well as worsening congestive heart failure.

The sponsor (Otsuka Pharmaceutical) is seeking efficacy claims based on the drug's ability to increase the serum sodium concentration in patients with hyponatremia (defined as a serum sodium <135 mEq/L). At this time, the Division is seeking guidance from the Cardiovascular and Renal Drugs Advisory Committee on how best to define efficacy for products such as tolvaptan, where there may be a clear demonstration of activity (increasing serum sodium concentration) without a clearly tangible clinical benefit. The goal of this meeting is to define a reasonable path forward for establishing the clinical benefit and efficacy of such products, and to determine a reasonable basis for their approval.

It is worth noting that the regulatory responsibility for the tolvaptan development program was switched with the Division of Metabolic and Endocrine Products to the Division of Cardiovascular and Renal Products in 2006. After the New Drug Application was submitted, with knowledge that the focus of the sponsor's development program was increasing serum sodium concentration, the Division asked Otsuka to perform post-hoc analyses in an effort to identify a possible clinical benefit associated with raising serum sodium in the studied population. In essence, we asked the sponsor to make their best case in favor of a clinical benefit, based on exploration of the database. Their analyses are included in the Otsuka's briefing document, although they have not been thoroughly reviewed by the FDA team. Though post-hoc analyses have well-recognized limitations, they nonetheless provide an opportunity to explore further possible clinical benefits associated with raising serum sodium with tolvaptan.

Of note, there is already an approved drug in this class. Conivaptan was approved in 2005 for the treatment of euvolemic hyponatremia (e.g., the syndrome of inappropriate secretion of antidiuretic hormone, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders, etc.) in hospitalized patients. Conivaptan is administered by the intravenous route, and the duration of treatment is not to exceed four days. Unlike conivaptan, tovaptan is an oral agent, and there is potential for much broader use in the outpatient setting, including patients with hyponatremia of milder severity, and long-term use.

Although the sponsor is seeking an indication for congestive heart failure, the focus of the discussion will be hyponatremia, and more specifically the clinical benefit associated with increasing serum sodium concentration.