Oral Agent for Hyponatremia Gets Panel's Nod

BY ELIZABETH MECHCATIE
Senior Writer

SILVER SPRING, MD. — The Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee voted 8 - 3 that tolvaptan, an oral selective arginine vasopressin (AVP) V_2-receptor antagonist administered once a day, be approved for use in the chronic treatment of hypervolemic or euvolemic hyponatremia.

Recommendations of those voting in favor of approval included limiting treatment to patients with very low serum sodium levels, hospitalizing patients at the start of treatment, and conducting postmarketing follow-up of patients on chronic treatment.

The panel also agreed in an 8 - 3 vote that there was adequate evidence that the drug could be expected to produce clinical benefits in the treatment of this group of patients. But several panelists said they were more convinced about the benefits in people whose serum levels were below 130 mEq/L, and that they would not be comfortable using tolvaptan to treat people with higher sodium levels until there was more evidence about whether treatment made a difference for this group.

Most of the panel agreed that there were no safety issues that would affect approvability, although several panelists were concerned about bleeding in cirrhosis patients, thirst, and the need for more long-term data, because it would be used chronically in many patients.

Tolvaptan, a product of Otsuka Pharmaceutical Development and Commercialization Inc., belongs to the "vaptan" class of compounds that blocks the action of AVP in the collecting ducts and induces free water clearance in the body (aquaresis), according to the company.

Because the company is pursuing approval of efficacy claims based on tolvaptan's ability to increase serum sodium levels in patients with hyponatremia, the agency said it held the meeting to obtain guidance from the panel on "how best to define efficacy for products such as tolvaptan, where there may be a clear demonstration of activity," which in this case is increasing serum sodium concentration, "without a clearly tangible clinical benefit."

In addition to the hyponatremia indication, the FDA is also reviewing tolvaptan as a treatment for worsening HF, regardless of baseline serum sodium. The panel was not asked to review or vote on the HF indication, which was studied in patients hospitalized for HF in the phase III study, Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST).

Most of the data presented by Otsuka were from two phase III studies of patients with hyponatremia due to all causes, with heart failure, antidiuretic hormone (SIADH), or cirrhosis; their mean age was 61-62 years, the mean serum sodium was 129 mEq/L, and about half had levels below 130 mEq/L.

The studies, SALT-1 and 2, compared daily treatment with 15 mg of tolvaptan a day to placebo and found that treatment improved hyponatremia, prevented worsening of hyponatremia, and maintained superior mean serum sodium concentrations from day 4 and at 30 days, when compared with those on placebo. More than 70% of patients completed the 30-day evaluation. The largest effects were seen in the SIADH patients.

The primary end point was the average daily area under the curve changes in serum sodium concentration from baseline to day 4 (short-term) and from baseline to day 30 (sustained), which were significant in both studies, and in a pooled analysis of the studies. In the pooled analysis, the average daily AUC of mean change from baseline in serum sodium levels was 4.0 mEq/L for those on tolvaptan, compared with 0. 4 mEq/L for those on placebo (from baseline to day 4), and 6.2 mEq/L for those on tolvaptan compared with 1.8 mEq/L for those on placebo (the sustained effect).

The most common adverse effects included excessive thirst and dry mouth. Serious adverse events included more cases of GI bleeding in cirrhotic patients on tolvaptan than those on placebo. Overly rapid correction of serum sodium was seen in some patients, but without neurologic sequelae, said Otsuka.

The company also used two patient-reported outcome scales to measure the clinical impact of changes in sodium level changes on treatment on quality of life measure. The mental component scores of one of the scales, the SF-12, improved and were positively correlated with changes in serum sodium in one of the two studies, but not the other.

Otsuka also presented supportive data on a subgroup of 475 patients with hyponatremia, who were in the EVEREST study of patients hospitalized for HF, who received 30 mg of tolvaptan daily or placebo. Their mean LVEF was 26%, most were male. Those on tolvaptan had a significantly greater rates of normalization of serum sodium on day 1 and at discharge, and significantly fewer treated patients went from mild to severe hyponatremia, said Otsuka. Patients with treated with tolvaptan also reported greater improvements in dyspnea than those on placebo.

Those voting against approval included Dr. Robert Harrington, professor of medicine, in the division of cardiology, Duke University, Durham, N.C., who cited as concerns the lack of data in the outpatient setting, the small amount of long-term data in those on chronic treatment; and bleeding in cirrhotic patients.

Tolvaptan should be studied in a phase III trial in outpatients, managed by clinicians other than renal and endocrine experts, to "mimic how it will be incorporated into practice," he said.

The FDA usually follows the recommendations of its advisory panels, which are not binding.

If approved, Otsuka plans to market tolvaptan under the trade name Samska. It would be the second drug approved in this class. In 2005, the FDA approved conivaptan for treating euvolemic hyponatremia in hospitalized patients, but it's administered intravenously. ■

Tissue Doppler Imaging May Help Flag Heart Failure Risk

BY MITCHEL L. ZOLER
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CHICAGO — Tissue Doppler imaging of the heart may be a way to safely and noninvasively screen asymptomatic people who are at risk of dying from heart failure, according to results from a pilot study.

Participants in the study who fell into the lowest tertile of left ventricular motion had a 2.6-fold increased risk of dying over the next 5 years, compared with patients who had the highest level of ventricular wall motion, in an analysis that controlled for age and gender, Dr. Rasmus Mogelvang said at the annual meeting of the American College of Cardiology.

The finding suggested tissue Doppler imaging (TDI) may be effective for early detection of heart failure and an increased risk of death from heart failure, but the data collected so far are preliminary and did not allow Dr. Mogelvang, a cardiologist at Gentofte Hospital in Copenhagen, and his associates to calculate a threshold value for increased risk.

"Before we can start to use this in daily practice, we need to set cut-off values," he said.

The investigators used TDI data collected on 1,100 apparently healthy people enrolled in the Copenhagen City Heart Study, with an average age of about 60 years. They all underwent ventricular assessment using both TDI and conventional echocardiography, and were then followed for an average of 5.1 years. During follow-up, 90 people died.

Three TDI measurements were made for each subject: s', which corresponds to left ventricular wall motion at peak systole; e', which is wall motion between systole and diastole; and a', wall speed at end diastole. In general, people with slower ventricular wall motion also had worse survival. Wall-motion speed is also linked with age; older people have reduced wall-motion speed.

In a series of multivariate analyses that adjusted for baseline differences in age and gender, a combined wall-speed assessment that included readings for s', e', and a' was the best correlate of survival, Dr. Mogelvang reported. In absolute terms, 5-year survival was about 96% in people in the tertile with the greatest wall motion, about 92% in those in the middle tertile, and about 85% in those in the tertile with the lowest level of wall motion.

The combined TDI value, which integrated s', e', and a', was a powerful predictor of survival even in people who had normal ventricular function based on their conventional echocardiogram, he said. ■

Exertnal Counterpulsation Ups Ejection Fraction, 1-Year Survival

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Enhanced external counterpulsation therapy results in significantly increased left ventricular ejection fraction and improved 1-year survival in patients with advanced ischemic heart disease, according to two studies presented by Dr. William E. Lawson at the annual meeting of the American College of Cardiology.

Enhanced external counterpulsation (EECP) already is covered by Medicare and other third-party payers for relief of refractory symptoms of angina pectoris or heart failure. These two new studies provide the first evidence of additional benefits in the key areas of mortality and ventricular function, noted Dr. Lawson, professor of medicine and director of preventive cardiology and heart center outcomes research at Stony Brook (N.Y.) University.

In one study, he analyzed the records of 4,597 patients with end-stage coronary disease enrolled in the prospective observational International EECP Patient Registry. He compared 1-year outcomes in the 3,962 patients who completed the standard course of 35 hours of EECP over 7 weeks with the 14% who completed fewer than 30 hours and a mean of 13 hours.

After censoring deaths within 60 days of starting EECP as a potential confounding variable, the 1-year mortality in EECP completers was 4.1%, compared with 14.1% in noncompleters. There were significant differences in other 1-year outcomes as well: 85% of EECP completers had improved by at least one Canadian Cardiovascular Society angina functional class, compared with 25% of noncompleters; and 4.1% in the completer group had an MI, vs. 7.7% of noncompleters.

Baseline characteristics of the two groups were similar: 89% had previously undergone a revascularization procedure, 70% had a prior MI, 92% had class III or IV angina, and only 15% were considered candidates for coronary revascularization.

In a separate study, 505 patients with ischemic heart disease underwent 2-D echocardiography 1 week prior to beginning a 35-hour, 7-week course of EECP and again within 1 week after completing therapy.

Among the 145 patients who had a baseline left ventricular (LV) ejection fraction (EF) of 35% or less, EF increased from a mean baseline of 29% to 45%, while stroke volume improved from 68 mL to 75 mL with no change in heart rate.

Dr. Lawson is on the speakers bureau for Vasomedical Inc., which markets a proprietary EECP system. ■