New Orleans — Conivaptan was safe and effective for treating hyponatremia in three phase III studies that together involved about 200 evaluable patients. Based on those findings, the Food and Drug Administration issued an approvable letter for conivaptan last December. According to Yamanouchi Pharma America, the company that developed the drug and sponsored the studies, the FDA said that will license conivaptan for the treatment of hyponatremia if the company provides additional safety data and meets certain conditions.

Currently, no agent has FDA approval for treating hyponatremia, which affects 2%-3% of all hospitalized patients and is more prevalent among patients with advanced heart failure and in the elderly. Hyponatremia is defined as a serum sodium concentration of less than 136 mEq/L, and is usually managed by restricting fluids.

Conivaptan is an antagonist for the argi- nine vasopressor receptor. The drug causes aquaresis and reduces vasomotor tone. Patients with heart failure often have abnormally high levels of arginine vasopressin, which promotes water reabsorption and helps produce the edema that often accompanies heart failure. Conivaptan can be given either orally or intravenous, however, Yamanouchi is only seeking approval for intravenous administration.

Results from the three studies were presented in posters at the annual scientific sessions of the American Heart Association. One study included 74 men and women at least 18 years old with a serum sodium level of 115-130 mEq/L who were either hypervolemic or euvolemic. About 43% of the patients had hyponatremia secondary to cardiac causes, with 20% having idiopathic or nonhypotonic hyponatremia, and in the rest it was due to other factors. About 74% of the patients were euvolemic.

Patients were randomized to treatment with 20 mg conivaptan orally b.i.d, 40 mg orally b.i.d, or placebo, and treatment continued for 5 days. Three patients dropped out during the study, one from each group.

During the 5 days of treatment, serum sodium levels increased in the conivaptan group in a dose-related manner and to levels that were significantly above those, found in the control group. During the study, Jala K. Ghali, M.D., director of clinical research at Cardiology Centers of Louisiana in Shreveport, reported that more than 5 million people in the U.S. have a low relative lymphocyte count, or RLC. About 58% of the patients were euvolemic at baseline, and 30% had heart failure as their cause of hyponatremia. Patients were randomly assigned to oral conivaptan b.i.d, 40 mg b.i.d, or placebo.

After 4 days of treatment, serum sodium levels had increased significantly in both treatment groups, compared with the control patients, reported Joseph G. Verbalis, M.D., professor of medicine and chief of the division of endocrinology and metabolism at Georgetown University, Washington. Once again, the increases were dose dependent, and were very similar to those seen with oral dosing. And conivaptan was effective whether patients were euvo- lemic or hypertensive, and regardless of the etiology of their hyponatremia.

Both dosages of the intravenous drug were well tolerated, and the increases in those seen in the two U.S. studies. The effects on sodium levels were similar regardless of renal status at baseline and hyponatremia etiology. Conivaptan was well tolerated, with a low rate of drug-related adverse effects and few discontinuations due to adverse effects.

In three phase III studies, conivaptan increased serum sodium levels significantly more than placebo after less than a week of treatment.

Conivaptan Reverses Hyponatremia, Studies Show

New Orleans — Conivaptan was effective regardless of whether patients were euvo-lemic or hypertensive, and regardless of the etiology of their hyponatremia. Both dosages were well tolerated; the rate of drug-related adverse events was similar in the three treatment groups, with those who received placebo being mild to moderate. Dr. Verbalis said Discontinuations due to adverse effects were similar in all treatment groups.

The third study resembled the first oral administration study, but was run in Europe. It enrolled 89 patients, of whom 72 completed the 5-day treatment. It included adult men and women with serum sodium levels of less than 130 mEq/L. About 58% of the patients were euvolemic at baseline, and 30% had heart failure as their cause of hyponatremia. Patients were randomly assigned to oral conivaptan b.i.d., 40 mg b.i.d., or placebo.

After 5 days of treatment, serum sodium levels were significantly higher in both treatment groups, compared with control patients, said Peter Gross, M.D., professor of medicine and nephrology at the Carl Gustav Carus University Clinic in Dresden, Germany. Sodium levels rose in a dose-de- pendent fashion, and the increases were similar to those seen in the two U.S. studies. The effects on sodium levels were similar regardless of renal status at baseline and hyponatremia etiology. Conivaptan was well tolerated, with a low rate of drug-related adverse effects and few discontinuations due to adverse effects.

Chronic Methamphetamine Use Appears to Be Cardiotoxic

New Orleans Chronic use of methamphetamine can lead to nonischemic, dilated cardiomyopathy and profound left-ventricular dysfunction, according to a study of 53 methamphetamine users seen at a single medical center in California.

“To our knowledge, this is the first study of its type to examine the relationship between chronic methamphetamine use and its effect on the heart,” Melissa R. Robinson, M.D., professor of medicine and chief of the department of internal medicine at the University of California, Davis. Although the number of chronic users of methamphetame- mine is not known, a 2001 survey estimat- ed that more than 5 million people in the U.S. are methamphetamine users. Methamphetamine use seems to have a di- stinct effect on the heart,” Melissa R. Robinson, M.D., professor of medicine and chief of the department of internal medicine at the University of California, Davis.

In contrast with cocaine, long-term methamphetamine use seems to have a direct, cardiotonic effect, and promotes the de- velopment of severe, nonischemic, dilated cardiomyopathy, said Dr. Robinson of the department of internal medicine at the Uni- versity of California, Davis. Although the number of chronic users of methamphetamine is not known, a 2001 survey estimat- ed that more than 5 million people in the United States had tried the drug, she said.

Her review started with 226 patients who were either hospitalized at the UC Davis Medical Center or seen in its emergency de- partment in 2002 and reported being treated using methamphetamine and were diag- nosed with either cardiomyopathy or heart failure. This list of patients was then pared to exclude those with another possible ex- planation for their heart disease, including a history of significant alcohol use (at least four drinks per day for at least 5 years), al- coholic cirrhosis, cocaine use, or severe coro- nary artery disease.

This left 53 methamphetamine-using pa- tients who had no clear etiology for their car- diomyopathy or heart failure. Their average age was 46 years, and 43% were younger than 45. Their average left-ventricular end-diastolic dimension was 66.3 mm, and 88% had an end-diastolic di- menion of more than 55 mm, indicating severe dilated cardiomyopathy. Echocardiography was done on 46 patients, who had an aver- age left-ventricular ejection fraction of 25%; 15 of 46 patients (32%) had an ejection fraction of less than 30%.

Several of the patients had severe com- plications while they were followed at UC Davis. Five patients had strokes, another five patients had severe ventricular arrhythmias that required implantation of a cardioverter de- fibrillator, and six had sudden deaths. Four patients had resolution of their cardiomy- opathy after ceasing methamphetamine use.

“Several of the patients had severe comp- lications while they were followed at UC Davis. Five patients had strokes, another five patients had severe ventricular arrhythmias that required implantation of a cardioverter defibrillator, and six had sudden deaths. Four patients had resolution of their cardiomyopathy after ceasing methamphetamine use.”

“Low Relative Lymphocyte Count Flags Cardiomyopathy Risk

New Orleans — A depressed relative lymphocyte count was associ- ated with an increased risk of death in patients with hypertrophic cardiomy- opathy in a study with 962 patients.

The relative lymphocyte count (RLC) is an inexpensive, universally available test “that may be helpful in identifying patients with hypertrophic cardiomyopathy who have a worse prognosis,” Steve R. Ommen, M.D., said while presenting a poster at the annual scientific sessions of the Ameri- can Heart Association.

“The relative lymphocyte count is part of the standard complete blood count, and involves no incremental cost,” added Dr. Ommen, a cardiol- ogist at the Mayo Clinic in Rochester, Minn. A depressed RLC is a marker of systemic stress, and the results from prior studies have linked the marker to adverse outcomes in patients with other chronic diseases.

Dr. Ommen and his associates re- viewed case records for patients with hypertrophic cardiomyopathy who were seen at Mayo Clinic in Rochester, Minn. Patients who had RLCs of less than 2.1%, compared with those with a normal RLC, had a statistically significant increase in risk of death: increased age; atrial fibrillation, which boosted the risk of death 1.4-fold; and a depressed RLC, which raised the relative risk of death 2.1-fold, Dr. Ommen said.

In a multivariate analysis that control- led for possible confounding clinical and demographic factors, three parameters had a statistically significant increase in risk of death: increased age; atrial fibrillation, which boosted the risk of death 1.4-fold; and a depressed RLC, which raised the relative risk of death 2.1-fold, Dr. Ommen said.