Expert Panel Calls for Limiting Nesiritide Use

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Use of nesiritide for patients with heart failure should be "strictly limited" to hospitalized patients with acute decompensated heart failure and dyspnea, said an expert panel that was assembled by the drug's manufacturer, Scios, a division of Johnson & Johnson.

The panel, which met on June 8 following two reports suggesting that nesiritide might boost patients' risk of death and worse renal function, also warned physicians not to give nesiritide (Natrecor) on a scheduled, repetitive basis or to outpatients. Although nesiritide's approval by the Food and Drug Administration 4 years ago was solely for treating hospitalized patients with acute decompensated heart failure and dyspnea, it has increasingly been used to treat outpatients, who come for regularly scheduled infusions.

The drug is also seen by some physicians to improve renal function and to replace diuretics, but the panel said that both of these perceptions are unfounded.

Scios assembled the group of 10 cardiologists, chaired by Eugene Braunwald, M.D., chairman of the TIMI Study Group at Brigham and Women's Hospital in Boston, after questions about nesiritide's safety arose in two metaanalyses. One study combined results from three randomized, double-blind trials that examined mortality in patients with acute decompensated heart failure during the 30 days after one nesiritide infusion, and found a trend toward more deaths in patients treated with nesiritide than in those who received comparator drugs (JAMA 2005;293:1900-5).

The second study compiled data from five randomized, double-blind studies and found that more patients who were treated with one dose of nesiritide had worsening kidney function than those treated with alternative drugs (Circulation 2005; 111:1487-91). In addition to initiating the panel's review, in April Scios expanded the section of nesiritide's label that discusses the potential effect on mortality.

The panel also reviewed the evidence that led to nesiritide's approval, from 10 clinical trials in a total of 1,456 patients. They concluded that the evidence was inadequate to establish definitively the effect of the drug on mortality and renal function, and endorsed Scios' plan to run a new study with several thousand patients to further assess the drug's impact on clinical outcomes.

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The expert panel also directed Scios to immediately start a "proactive educational program to inform physicians regarding the conditions and circumstances in which nesiritide should and should not be used."

"We accept all of the panel's recommendations," said Darlene Horton, M.D., senior vice president of clinical research and medical affairs at Scios.

A large, clinical outcomes trial similar to what the panel recommended was already planned, she said in an interview. The study will also try to expand the benefit claims on the drug, which is now labeled to improve symptoms and reduce pulmonary capillary wedge pressure. Dr. Horton also endorsed the panel's conclusion that nesiritide's current use should be limited to its labeled indication. "We absolutely believe that outpatient, intermittent use is not [in accordance with] the label," she said.

The panel's recommendations were, in general, praised by Jonathan D. Sackner-Bernstein, M.D., director of heart failure and preventative research at North Shore University Hospital in Manhasset, N.Y., and lead author of the two metaanalyses that suggested nesiritide's danger.

"The wording is fair, and the tone is fair," he said in an interview. "It could have been a stronger recommendation for caution, but given the drug's context you can't get a clearer warning than" what the panel said. In his JAMA article, Dr. Sackner-Bernstein recommended using nesiritide only when alternative treatments are ineffective.

Reshaping physician opinion on nesiritide will be challenging, he added. "Scios has allowed the perception that this drug can be safely used on outpatients. It will take an incredible effort by Scios and Johnson & Johnson to get the new message out." ■