Candesartan Approved For Heart Failure Tx

BY ELIZABETH MECHCATIE Senior Writer

The recent approval of candesartan for a heart failure indication reflects the key findings of one of the three international trials comparing candesartan with placebo in patients with heart failure.

In February, the Food and Drug Administration approved the angiotensin receptor blocker (ARB) for treating patients with heart failure (New York Heart Association class II or IV) and a left ventricular ejection fraction (LVEF) of 40% or less, "to reduce the risk of death from cardiovascular causes and to reduce hospitalizations for heart failure."

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial, the risk of cardiovascular death or hospitalization for heart failure, the primary end point, was reduced by 23% among those on candesartan after a median follow-up of 34 months, compared with those on placebo—a highly statistically significant effect.

There were 2,628 patients with symptomatic heart failure and an LVEF less than or equal to 40%, who were on standard heart failure treatments but were intolerant of ACE inhibitors. At baseline, 85% were on diuretics, 46% on digoxin, 53% on blockers, and 24% on spironolactone.

There were 334 events in the 1,013 patients on candesartan, vs. 406 events in the 1,015 on placebo. Supporting the approval of this indication, according to the FDA, were the results of CHARM-Added, which enrolled more than 2,500 patients with NYHA class II-IV heart failure and LVEFs at or below 40% who were on an ACE inhibitor. In this trial, adding candesartan to standard treatment, including a blocker, reduced the risk of cardiovascular mortality by 15%, compared with placebo, and significantly improved in heart failure symptoms, as assessed by NYHA functional class.

An approval for use in heart failure patients on ACE inhibitors is likely to follow. (See accompanying story.)

Candesartan, marketed as Atacand by AstraZeneca Pharmaceuticals LP, is the second ARB approved for heart failure; the first was Diwan (valsartan), approved in 2002 for a narrower indication, NYHA class II IV heart failure in people who cannot tolerate ACE inhibitors. Candesartan was approved for hypertension in 1998.

Using candesartan for these indications will provide an important new tool for treating heart failure, said Christopher Granger, M.D., CHARM-Alternative’s principal investigator, in an interview. In the Candesartan program, 4% of those on candesartan had stopped treatment with the drug because of hypotension, versus 2% of those on placebo. Hyperkalemia leading to discontinuation occurred in 2.4% of those on candesartan, versus 0.6% of those on placebo.

The recommended starting dosage for the drug was a targeted dose of 32 mg once daily, achieved by doubling the dose approximately every 2 weeks, as tolerated, according to the package insert.

Patients need to be monitored closely when the drug is being titrated—because some will develop renal insufficiency, hypokalemia, or hyperkalemia during titration, side effects expected with any drug that affects the renal angiotensin system, said Dr. Granger, who is director of the cardiac care unit at Duke University, Durham, N.C. In the CHARM trials, it was recommended that investigators check serum potassium and creatinine approximately 2 weeks after dose titration.

Dr. Granger was on the executive committee for CHARM and was a consultant to AstraZeneca for this FDA approval and for the meeting of the FDA’s cardiovascular and renal drugs advisory committee.

Poor Kidney Function Is a Harbinger of Anemia in Heart Failure Patients

New Orleans — Poor kidney function is the strongest indicator for anemia in heart failure patients, according to the results of a large study in HMO patients. A reduced glomerular filtration rate emerged as the strongest risk factor for developing anemia in 41,754 heart failure (HF) patients free of anemia at baseline, Alan S. Go, M.D., reported at the annual scientific sessions of the American Heart Association.

Anemia was a common occurrence in this HMO population with HF with an incidence of 9% per year, according to Dr. Go of Kaiser Permanente of Northern California, Oakland. The study featured nearly 83,000 person-years of follow-up.

The incidence of anemia was common among HF patients. Roughly 40% of patients had a baseline glomerular filtration rate of less than 60 mL/min per 1.73 m². The risk of developing anemia during follow-up was proportionate to their degree of baseline renal impairment. Heart failure patients with an estimated GFR of 45-59 mL/min per 1.73 m² were 34% more likely to become anemic than those with a GFR of 60 or more. Those with a GFR of 30-44 had a more than twofold increased incidence of anemia, while patients with a GFR of 15-29 were at more than fourfold increased risk.

Among those patients with a baseline GFR less than 60 mL/min per 1.73 m² who weren’t on dialysis, the incidence of anemia during follow-up was more than eight times greater than in patients with a GFR of at least 60. In those on dialysis, the rate increased nearly fivefold.

Other independent predictors of the development of anemia in a multivariate analysis included copathology, with an adjusted 2.3-fold relative risk, compared with noncirrhotic patients, and HIV infection, which conferred an 80% increase in risk. African descent and age greater than 70 years were each associated with a 40% increased risk of becoming anemic, he said.

—Bruce Jancin