Panel Backs Candesartan–ACE Inhibitor Combo

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ROCKVILLE, MD. — The angiotensin receptor blocker candesartan should be approved as a treatment for heart failure in patients who are on an ACE inhibitor, a Food and Drug Administration advisory panel has recommended.

At a meeting of the FDA's cardiovascular and renal drugs advisory committee, all eight panel members backed approval of such an indication for candesartan on the basis of results of one of the three Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials.

In CHARM–Added, candesartan (titrated to a target dose of 32 mg/day) was compared with placebo in 2,548 patients with New York Heart Association (NYHA) class II-IV heart failure and a left ventricular ejection fraction (LVEF) at or below 40% who were on an ACE inhibitor and standard therapy. The results showed that adding an ARB to standard treatment that included an ACE inhibitor added an incremental benefit in this population: The relative risk of cardiovascular mortality or heart failure (HF) hospitalization—the primary end point—was reduced by 15% among those on candesartan during a median follow-up of 41 months. The benefits were also seen in patients treated with -blockers, which suggested there were no adverse interactions among -blockers, candesartan, and ACE inhibitors, as noted in the Valsartan Heart Failure Trial (Val-HeFT), where the outcome for heart failure morbidity was worse among patients on an ACE inhibitor, -blocker, and valsartan, according to the FDA.

The purpose of the meeting was to determine, according to the agenda, "whether CHARM–Added provides compelling evidence that candesartan should, under some circumstances, be recommended for use in patients on an ACE inhibitor."

But a large portion of the meeting was spent discussing whether patients in the trial were on optimal ACE inhibitor doses and whether the same benefits might have been achieved by increasing the dose of the ACE inhibitor. What was missing in the study was a protocol-driven effort to ensure that investigators pushed ACE inhibitor doses to the best level possible, according to the agency.

Although panelists said a forced titration of ACE inhibitor therapy in the study protocol would have been ideal, they said they felt comfortable that the ACE inhibitor doses used fell into the ranges considered adequate or optimal. The "final doses of ACE inhibitor achieved were quite substantial" and in line with the doses seen in other trials of ACE inhibitor therapy, said Blasé Carabello, M.D., professor of medicine at Baylor University, Houston. In addition, an analysis of a subset of patients on high doses of ACE inhibitors "all go in the same direction" favoring the benefit.

The FDA usually follows the recommendations of its advisory panels, which are made up of outside experts. If approved, candesartan (marketed as Atacand by AstraZeneca Pharmaceuticals LP) will be the first ARB approved for use with an ACE inhibitor. Shortly before the panel meeting, the agency approved candesartan for patients with NYHA class II-IV heart failure, and an LVEF at or below 40%, who are not on an ACE inhibitor, to reduce the risk of death from cardiovascular causes and reduce HF hospitalization based on the CHARM–Alternative trial (FAMILY PRACTICE NEWS, Mar. 15, 2005, page 30).

James Hainer, M.D., senior director of clinical research at AstraZeneca, said that as expected, due to a greater degree of renin-angiotensin-aldosterone system inhibition, rates of hypotension, abnormal renal function, and hyperkalemia were greater with candesartan. However, these adverse events did not translate into any increases in all-cause hospitalization and/or mortality, sudden death, renal failure, or ventricular fibrillation. These risks will be addressed in warnings and precautions on the label, in recommendations for monitoring and reducing risk, and through interactions with major societies and guidelines committees.

Risks were "substantially" in favor of candesartan: An economic cost analysis found that over the course of the study, for every 1,000 patients treated with candesartan, there were 1,900 fewer days spent in the hospital for worsening heart failure, John McMurray, M.D., principal investigator of CHARM–Added and professor of medical cardiology, Western Infirmary, Glasgow, Scotland, told the panel. ■