FDA Approves Combo Drug for HF in Blacks

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — The fixed-dose combination of isosorbide dinitrate and hydralazine is the first product approved specifically for treating patients in a specific racial group—a development that has been lauded as a significant advance that could help save the lives of many African Americans and criticized as scientifically unjustified and generating a racial stigma.

The Food and Drug Administration's approval is "for the treatment of heart failure as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to hospitalization for heart failure, and to improve patient-reported functional status."

Those outcomes were evaluated in the African American Heart Failure Trial (A-HeFT), which compared the combination with placebo in self-identified African American patients with moderate to severe heart failure (HF) who were on standard HF treatments, and which was the basis for the approval. The label notes that most patients were on a loop diuretic, an ACE inhibitor or an angiotensin receptor blocker, and a β-blocker; many were also on a cardiac glycoside or an aldosterone antagonist.

The "approval of a drug to treat severe heart failure in a self-identified black population is a striking example of how a treatment can benefit some patients even if it does not help all patients," Robert Temple, M.D., director of the office of drug evaluation at FDA, Rockville, Md., said in a statement.

One week prior to the June 23 approval, the nine panel members of the FDA's Cardiovascular and Renal Drugs Advisory Committee unanimously agreed that the combination product should be approved. Only two panelists recommended that the approval not specify black patients.

The manufacturer, Massachusetts-based NitroMed Inc., will market the combination as BiDil. Each tablet contains 37.5 mg hydralazine hydrochloride and 20 mg isosorbide dinitrate, which have been approved separately for treating hypertension (hydralazine) and angina (isosorbide dinitrate) for more than 40 years.

If the approval had been for all patients, NitroMed's exclusive rights would expire in 2007. But because BiDil's approval is specifically for self-identified African Americans, the company will retain the rights until 2020 according to a published assessment (N. Engl. J. Med. 2004;351:2035-7).


JAMES REINAKER

Dr. Charles Curry lauded BiDil as an unparalleled advance for black people.

The treatment's theoretical basis is isosorbide's activity as a nitric oxide donor, and hydralazine's activity as an antioxidant that prevents nitric oxide degradation. Nitric oxide insufficiency in the black population is thought to partially explain why hypertensive black patients tend to respond better to diuretics than to ACE inhibitors or β-blockers, and why black patients with HF apparently do not respond as well to these medications either, according to the FDA briefing document.

A-HeFT compared BiDil with placebo in black men and women with moderate to severe HF who were on standard HF therapies, including ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, as well as digitalis and diuretics. Patients were titrated up to a target dose of 120 mg isosorbide and 225 mg of hydralazine, 1 tablet three times a day.

A-HeFT's primary end point, a composite score of all-cause mortality, HF hospitalization, and the change in a quality of life score at 6 months, compared with baseline, was significantly lower among those on BiDil. The relative risk of mortality was reduced by 43%, and hospitalization for HF was reduced by 39%, with an improvement in quality of life scores at 6 months.

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The study was prematurely terminated in July 2004, when the reduction in mortality was seen. At that time, 1,050 of the targeted sample size of 1,100 patients had been randomized: 40% were women, and 91% of those on BiDil and 86% on placebo completed the study.

The robust effect of the drug on mortality, on top of optimum treatment, is evidence that is "more than adequate" for recommending approval and is "a compelling argument for this population, but only for this population," said the panel chair, Steven E. Nissen, M.D., medical director of the cardiovascular coordinating center at the Cleveland Clinic at the advisory committee meeting. "We're using self-identified race as a surrogate for genomic-based medicine, and I don't think that's unreasonable." In the absence of genetic markers to "decide who's going to respond to what drug … we have to use the best evidence available to us today" from the A-HeFT trial.

But Vivian Ota Wang, Ph.D., the director of the ethical, legal, and social implications program at the National Human Genome Research Institute at the National Institutes of Health, Bethesda, Md., said that although she supported approval, she was not satisfied using self-identification as being African American as a surrogate for a biologic process, and did not support the label targeting this group because the underlying rationale of A-HeFT was a biologic reason. Skin tone is "not a great proxy" for biologic traits, she said.

The controversy over the impact of a race-based HF indication were expressed by speakers during the open public hearing. None opposed the drug's approval, but several argued against approving it specifically for black patients.

Charles Rotini, Ph.D., of the National Human Genome Center at Howard University, Washington, said that group identity is confused with ancestry, and that African Americans have a diverse ancestry. He said it would be tragic not to approve the drug, but "just as tragic" to approve it for the black population only.

Charles Curry, M.D., president of the International Society on Hypertension in Blacks and former chief of cardiology at Howard University, said he "vigorously" supported approval and called BiDil "the most important advance in the care of black people we have seen in my lifetime." But he also expressed concern about limiting a life-saving treatment to one group of patients, noting that early trials were conducted almost exclusively in white men, but have benefited all populations.

"Would anyone restrict the results of 4S [Scandinavian Simvastatin Survival Study] to Scandinavians?" asked Dr. Curry who, as an A-HeFT investigator and member of the trial's cosponsor, the Association of Black Cardiologists, received funds from NitroMed.

Those expressing unconditional support for the approval included the chair of the Congressional Black Caucus and representatives of the National Minority Health Month Foundation and the NAACP.

In A-HeFT, headache, dizziness, and hypotension were higher in the BiDil patients, and worsening of HF was more common in the placebo patients. Arthralgias were reported in 1.5% of those on BiDil, vs. 0.4% of those on placebo, about a fourfold greater rate that falls "into a category of some concern" about the potential for a drug-induced lupus-like syndrome that has been associated with hydralazine, said Jonathan Sackner-Bernstein, M.D., director of the HF program at St. Luke's-Roosevelt Hospital Center, New York, noting that such events could be monitored after approval.

Jay N. Cohn, M.D., was principal investigator of V-HeFT I, which compared the drug combination with placebo added to standard therapy in the early 1980s in male patients with mild HF, and a few years later, V-HeFT II, which compared the combination with enalapril, added to standard therapy. The results suggested benefits, but were not adequate for FDA approval.

In a retrospective analysis, Dr. Cohn found that benefit seemed more favorable in black patients, which, after discussions with the FDA, led to the A-HeFT trial. The FDA said a single positive study in an HF population could be the basis for approval as a treatment for HF in black patients, and the trial began in May 2001. Dr. Cohn, the inventor of BiDil, holds equity in and stands to receive royalties from the sale of BiDil.

The findings confirmed the hypotheses generated from V-HeFT I and II, said Clyde Yancy, M.D., medical director of the Heart Failure/Transplantation Program at the University of Texas Southwestern Medical School, Dallas, speaking for NitroMed. The black population has a high rate of HF, which appears at a younger age, often with greater left ventricular dysfunction and a less favorable prognosis, he noted.

The BiDil application may not be so precedent setting as has been portrayed, Dr. Nissen said, citing the recent approval of the fixed-dose combination of losartan and hydrochlorothiazide for reducing the stroke risk in patients with hypertension and left ventricular hypertrophy, with a label that says evidence suggests this benefit does not apply to black patients. ■