Questions

Hydralazine/ISDN
June 16, 2005

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Committee is asked to opine on whether V-HeFT I, V-HeFT II, and A-HeFT adequately support a claim that BiDil (hydralazine plus isorbide dinitrate) improves outcome in patients with heart failure. The Advisory Committee previously reviewed V-HeFT I and II as a possible basis for use of BiDil in the treatment of heart failure.

1. Claims based on A-HeFT
   - 1.1. The primary end point was a composite of all-cause mortality, hospitalizations for heart failure, and response to the Minnesota Living with Heart Failure questionnaire. By the sponsor's and the statistical reviewer's intent-to-treat analyses, BiDil was associated with an improved composite risk score (p=0.021 by the reviewer). However, the sponsor's pre-specified per-protocol analysis is not significant (p=0.46).
     - 1.1.1. Why are these results so discrepant?
     - 1.1.2. Why were 60% of subjects excluded from the pre-specified per-protocol analysis?
   - 1.2. Subjects enrolled prior to the second interim analysis, when sample size was re-estimated, comprised 30% of the total patients and 42% of the events, and they showed a nominal 7% lower risk of death on BiDil. Subjects enrolled after the second interim analysis had a nominal 62% lower risk of death on BiDil. How troubling is that difference? How comforted are you by…
     - 1.2.1. …more continuous analyses of mortality by time in study?
     - 1.2.2. …analyses of CHF hospitalization among early and late enrollees?
   - 1.3. The difference in time to first hospitalization for heart failure was large and statistically significant, while the difference in total days in hospital for heart failure or for other cardiovascular causes was small and statistically insignificant.
     - 1.3.1. For patients with heart failure, is time to (next) hospitalization a measure of overall hospitalization?
     - 1.3.2. Is postponing hospitalization a clinical benefit if one does not also shorten the total duration of hospitalization?
   - 1.4. Interpretation of the quality of life data is rendered difficult because of the early termination of the study. How persuasive is the retrospective analysis with last observation carried forward?

2. Policy issues
   - 2.1. Ordinarily, one expects to understand the role of each component in a combination product, as noted in 21 CFR 300.50.
     - 2.1.1. How important would that be…
       - 2.1.1.1. …if you believed there was an effect on mortality?

2.1.1.2. …if you believed there was only an effect on hospitalization?
2.1.1.3. …if you believed there was only an effect on symptoms?
2.1.1.4. …if there had been more than two active ingredients?
2.1.1.5. …if you suspected one component is subject to tolerance effects?
2.1.2. What is the evidence that both components of BiDil have hemodynamic effects when used together…
2.1.2.1. …short-term?
2.1.2.2. …long-term?
2.1.3. What instructions do you give for patients who do not tolerate one component of BiDil?

2.2. Ordinarily, one expects to know something about the effect of dose, and one does not in this case, for either component.
2.2.1. How does the importance of information on dose change…
2.2.1.1. …with the end point?
2.2.1.2. …with the number of active ingredients?

2.3. Subjects randomized to BiDil had lower blood pressure than those randomized to placebo.
2.3.1. Is this a plausible explanation for the differences in outcome?
2.3.2. What should labeling say about observed differences in blood pressure?

3. Population
3.1. A-HeFT enrolled only the subgroup in which BiDil appeared to work in V-HeFT I and II, namely self-identified African-Americans. How strong is the evidence that BiDil does not work in patients excluded from A-HeFT? If it were approved, what should labeling say about…
3.1.1. …excluded subgroups?
3.1.2. …the underlying genetic or cultural bases for the observed differences?
3.2. Bearing in mind experience in V-HeFT I and II, to what NYHA classes do the benefits of BiDil apply?
3.3. Are there other population-specific differences apparent?

4. Should BiDil be approved for the treatment of heart failure? If so, …
4.1. …what should labeling say about concomitant therapy to be used with BiDil?
4.2. … what advice should be given to patients who are intolerant of BiDil?