[DRAFT] Questions

Candesartan
February 24, 2005

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

The Cardio-Renal Advisory Committee is asked to opine on the candesartan development program in heart failure, a series of three studies enrolling a total of 7601 subjects.

The Division sees little controversy about use of candesartan in patients with heart failure who are not, for whatever reason, taking an ACE inhibitor. CHARM-Alternative shows it is effective in patients intolerant of ACE inhibitors and, at least, CHARM-Added is supportive of this use. The question for the Advisory Committee is whether CHARM-Added provides compelling evidence that candesartan should, under some circumstances, be recommended for use in patients on an ACE inhibitor and tolerating it.

1. The protocol for CHARM-Added required subjects to be on an ACE inhibitor and the possible choices were not limited to ones with established claims for heart failure.
   1.1. Does which ACE inhibitor matter?
   1.2. Does the dosing regimen matter?
   1.3. What is the appropriate target dose for an ACE inhibitor for which there are no empirical data?
2. The protocol required subjects to be treated aggressively with their ACE inhibitors. How was this ensured?
3. Many subjects in CHARM-Added were never on the target dose of ACE inhibitor. Does one know why?
4. The protocol appears to have permitted investigators to lower the dose of other antihypertensive drugs, including ACE inhibitor, in order to achieve the target dose of candesartan. How much of a problem was that?
5. Studies that resulted in labeling ACE inhibitors for use in heart failure used the paradigm of forcibly titrating the ACE inhibitor to the highest dose tolerated with a target of achieving the highest dose approved for blood pressure reduction. Are there data that show such aggressive dosing is unnecessary to achieve full benefit of ACE inhibitors?
6. When two drugs operate by sufficiently distinct mechanisms, one generally does not worry that the effects of the new one are demonstrated at maximum levels of the old one. Is that appropriate for ACE inhibitors and an angiotensin receptor antagonist?

7. One possible claim would be that candesartan has effects on top of maximal ACE inhibition. What evidence does CHARM-Added provide that candesartan has benefits in patients with full ACE inhibition?
   7.1. In analyses of CHARM-Added that factored in ACE inhibitor dose, does it matter that subjects were not randomized to ACE inhibitor dose?
   7.2. What loss of effect of candesartan at full ACE inhibition has been excluded by these analyses?
8. A different claim might result if one could not achieve a full effect on a system by one drug, perhaps because of system-independent tolerance problems, but could achieve a full effect with the addition of a second agent.
   8.1. What would be required to achieve such a claim?
   8.2. Does CHARM-Added have these design features?
9. If you have identified a possible pathway to approve candesartan based on questions 7 or 8, comment on the available strength of evidence.
   9.1. What are one's prior expectations based on mechanism of action?
   9.2. Is it appropriate to consider studies of other angiotensin receptor antagonists in this setting? If so, are these data supportive?
   9.3. Are there other data on the use of candesartan added to ACE inhibitors in the treatment of heart failure? If so, are these data supportive?
   9.4. Are there supportive findings in CHARM-Added? Are these findings covered by the statistical analysis plan?
10. Should candesartan be approved for use with an ACE inhibitor in the treatment of heart failure?