Questions

candesartan
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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 relative antihypertensive efficacy of a regimen containing candesartan and a regimen containing losartan. Specific guidance is sought on how to describe any relevant differences in labeling and on the adequacy of the advice that we have given sponsors to guide future development programs. There is little published experience or relevant guidance, but this issue is briefly addressed in ICH guidance E-10 (*Choice of Control Groups and Related Issues in Clinical Trials*).

In the past, the Agency has told sponsors that demonstrating superiority to another antihypertensive medication on blood pressure lowering, when both were appropriately dosed, was a relevant clinical benefit, and that such a claim required the following data:

1) Evaluation of the antihypertensive effects of the respective drugs at the highest approved doses. If the comparison was not done with the approved product, bioequivalence of the study formulation and the approved product must be demonstrated. Our recommendation has been that this evaluation should include at least two forced-titration trials to adequately assess the drug's relative antihypertensive effects. We have also said that, unless a placebo group is included in the trials, no information about absolute antihypertensive efficacy can be inferred, only comparative antihypertensive effect.

2) Data comparing the safety of the two agents, providing evidence that the 'superior' agent is not inferior with respect to safety.

The present sponsor has provided data from three randomized trials, including two forced-titration trials. These were conducted comparing candesartan force-titrated to a dose of 32 mg per day and losartan force-titrated to a dose of 100 mg per day. The Agency and the sponsor agree on the numerical results of the efficacy analyses for the three trials. At the end of 8 weeks, candesartan 32 mg reduced blood pressure by around 3/2 mmHg more at trough than did losartan 100 mg, when both were given once per day.

1. Which of the following are necessary or sufficient to establish a claim of relative superiority for an antihypertensive?
   1.1. Diastolic pressure at trough?
   1.2. Systolic pressure at trough?
   1.3. Diastolic pressure throughout the dosing interval?
   1.4. Systolic pressure throughout the dosing interval?
   1.5. 24-hour mean ABPM?
   1.6. Other measures of effectiveness?

2. The sponsor compared once-daily dosing for both products, although both products are labeled for once- or twice-daily dosing. Is a once-daily comparison a legitimate basis for a superiority claim?

3. Which of the following are necessary or sufficient to establish a claim of relative superiority for a once-daily antihypertensive?
   3.1. Beating the comparator's highest approved once-daily dose?
   3.2. Beating the comparator's most effective approved regimen?

3.3. Beating the comparator when it is dosed to its maximum effect, perhaps outside the approved dose range?

3.4. Beating the comparator when used with other approved agents (e.g., diuretics, beta blockers)?

3.5. Beating the comparator in special populations (e.g., blacks, elderly)?

4. Is it possible to claim superiority if…
   4.1. … the comparator has other outcome benefits not demonstrated by the test drug …
      4.1.1. … on clinical endpoints in hypertensive patients (*e.g.*, stroke reduction)?
      4.1.2. … in other populations (*e.g.*, heart failure, post-MI, diabetic nephropathy)?
   4.2. … the comparator has fewer potential pharmacokinetic interactions such as CYP 2D6 or CYP 3A4 inhibition?

5. In most cases, comparative data have not revealed differences between pharmacologically similar drugs. Should the Division encourage more comparative studies?

6. Overall, candesartan reduced diastolic BP by around 2 mmHg more at trough than did losartan, an effect size that would be sufficient for approval if a drug were compared with placebo.
   6.1. Is this difference clinically meaningful for a comparison between two antihypertensives?
   6.2. Are the comparative safety data submitted by the sponsor sufficient to show that the expected reduction in cardiovascular risk would not be offset by other risks of candesartan?
   6.3. Would your answer regarding the need for comparative safety data be different if the two drugs were from different drug classes (*e.g., calcium-channel blocker and diuretic)?*
   6.4. Is the comparison between candesartan and losartan *fair*, as defined by ICH E-10?

7. Do you recommend approval of candesartan for superior antihypertensive efficacy when compared with losartan? If so, how should the findings of these trials be included in the approved labeling…
   7.1. of candesartan?
   7.2. of losartan?
   7.3. of combination products containing candestartan or losartan?