Questions

Antihypertensives
June 15, 2005

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

The Advisory Committee is asked to opine on class labeling for antihypertensive drugs.

Antihypertensive drugs, with few exceptions, have no outcome claim in their labeling. This is inconsistent with their approval based on the surrogate of blood pressure and with the advice given to practitioners. This meeting is to consider how, if at all, labeling should address the relationship between blood pressure and outcome.

1. Since outcome data come from studies of drug regimens and not single agents, what can one determine about the effects of individual agents or drug classes? Is it appropriate to generalize any observed benefits to all agents or classes, or should one conclude that one does not know enough about most single agents?

2. A variety of benefits are associated with drugs that reduce blood pressure.
   - Reduction in the risk of ischemic stroke
   - Reduction in the risk of hemorrhagic stroke
   - Reduction in the risk of myocardial infarction
   - Reduction in the risk of cardiovascular mortality
   - Reduction in the risk of mortality from any cause
   - Reduction in the risk of other manifestations of coronary disease
   - Reduction in the risk of end-stage renal disease
   - Other

   2.1. Which items in the above list…
      2.1.1. …are attributable to blood pressure reduction—and would be expected of any drug that lowers blood pressure?
      2.1.2. …apply to most antihypertensive agents, with clear exceptions noted?
      2.1.3. …are benefits associated with specific classes of drugs?
   2.2. For the purposes of this discussion, are ACE inhibitors and angiotensin receptor antagonists the same class?
   2.3. Are the magnitudes of the benefits the same among members of a class?
   2.4. Are there other important distinctions among drugs in a class?
   2.5. How are the benefits affected by age, gender, diabetes, or other risk factors?

3. Most modern labels for non-antihypertensive drugs describe the supporting data under Clinical Trials and then cite the specific benefits of treatment in the Indications.
   3.1. Should labels for antihypertensive drugs follow this pattern?
   3.2. Should labeling distinguish drugs on the basis of whether the specific agent or the specific class contributed to the available outcome data?

4. Various draft statements have been included in the background package. Rather than trying to edit them, please identify which of the following should be elements of labeling?
   - 4.1. The specific benefits thought to apply
   - 4.2. The magnitude of those benefits
   - 4.3. The relationship between blood pressure and risk
   - 4.4. The interaction among cardiovascular risk factors
   - 4.5. The specific drugs with a primary role in outcome trials
   - 4.6. The drug classes with a primary role in outcome trials
   - 4.7. Whether this specific drug has outcome data
   - 4.8. Whether the specific drug's class has outcome data
   - 4.9. Factors to consider in choosing a drug class
     - 4.9.1. Other established claims in heart failure or renal disease
     - 4.9.2. Risk of hypokalemia
     - 4.9.3. Other considerations
   - 4.10. Other elements of a cardiovascular risk reduction program (control lipids, stop smoking, lose weight, get exercise, etc.)
   - 4.11. The importance of blood pressure control throughout the inter-dosing interval
   - 4.12. The importance of blood pressure control at various times of day.
   - 4.13. Other elements

5. Labeling for lipid-lowering drugs is quite explicit in recommending an approach to treatment—when to initiate treatment, what the goals are, etc. Currently, labels for antihypertensive drugs do not say whom or how to treat for hypertension. How should physicians be instructed to assess blood pressure with respect to…
   - 5.1. …what to measure (systolic, diastolic, pulse pressure)?
   - 5.2. …how many times to make the measurement during a visit?
   - 5.3. …what period of time or over how many visits?
   - 5.4. …what time of day to make measurements?
   - 5.5. …timing with respect to the last dose?
   - 5.6. …the risk of developing a cardiovascular event over the next few years?
   - 5.7. …what goals to seek? Are the goals lower in high-risk patients?
   - 5.8. …how closely to monitor during and after up-titration?
   - 5.9. …which drug classes are appropriate for initial therapy and which should be used second or later?
   - 5.10. …when to add a second drug? Note that labeling currently usually says to start a second drug only after a single drug has proven inadequate at its highest tolerated dose.

6. How, if at all, and in which labels, should one describe the results of an active-controlled study in which the various regimens were not distinguished for their primary end points?

7. If there are differences among drug classes, should the classes with fewer or less well established claims get labeled as second-line?

8. Consider the ramifications of revised labeling on…
   8.1. …pediatric studies. The Agency can require studies of antihypertensive drugs in children prior to approval for use in adults. The Agency can also promote studies in children by granting additional exclusivity for assessing the effects of antihypertensive drugs in children.
      8.1.1. Should it do either of these?
      8.1.2. Is study of effects on blood pressure adequate?
   8.2. …a drug for another indication also happens to reduce or to increase blood pressure. Should class labeling extend to it? Does it matter…
      8.2.1. …if the drug is for intermittent or short-term use?
      8.2.2. …if the effects on blood pressure are not sustained through the interdosing interval?
      8.2.3. …how large is the effect on blood pressure?