Questions

omapatrilat
19 July 2002

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

The Committee is asked to opine on the approvability of omapatrilat for hypertension. Omapatrilat is an inhibitor of angiotensin converting enzyme and neutral endopeptidase. Reviews of chemistry, pharmacology, toxicology, and biopharmaceutics present no apparent barriers to approval. Omaparilat clearly lowers blood pressure. During its initial development, an increased risk of life-threatening angioedema was noted for patients taking omapatrilat compared with other antihypertensives (including ACE inhibitors). To characterize this safety finding and to gain additional information on the relative antihypertensive efficacy of omapatrilat, the sponsor conducted the OCTAVE trial.

OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) was a randomized, double-blind study in which 25302 subjects with hypertension were randomized to once-daily enalapril or omaparilat and followed for 24 weeks. During the first 8 weeks, subjects were titrated to a maximum dose of 40 mg (enalapril) or 80 mg (omapatrilat) as needed, after which subjects who did not achieve the blood pressure goal could have additional antihypertensive agents added through week 24. At 8 weeks, 41% of subjects in the enalapril group and 33% in the omapatrilat group were on the highest recommended doses. Between weeks 8 and 24, 19 to 36% of the enalapril subjects and 13 to 26% of the omapatrilat subjects added antihypertensive therapies. At 8 and 24 weeks, omapatrilat had a significantly greater effect to lower trough blood pressure compared with enalapril, but angioedema, including serious angioedema, was significantly more common in subjects taking omapatrilat.

GRADE	ENALAPRIL N=12557	OMAPATRILAT N=12609	RATIO
Mild	65	161	2.5
Moderate	19	94	4.9
Severe	2	17	8.5
Life-threatening	0	2	?

With these results and the data from the other trials of omapatrilat, the Committee is being asked

- to characterize the risks of omapatrilat (questions 1 & 2),
- to identify and characterize the benefit to which this risk needs be compared (questions 3 to 5), and
- to discuss whether omapatrilat's benefits outweigh its risks (question 6).

1. How should one best characterize the risk of angioedema with omapatrilat?
   1.1 Are the clinical features of the angioedema associated with omapatrilat similar to those associated with approved ACE inhibitors?
   1.2 In the original development program, about twice as many subjects were exposed to omapatrilat 20 mg than to 10 mg, as an initial dose, and the rate of any angioedema was about 3-fold higher in subjects initially receiving 20 mg. OCTAVE's primary safety hypothesis was that starting omapatrilat at a low dose and titrating up would reduce the risk of angioedema of any severity to no more than twice that of enalapril. Was this hypothesis supported by the study?

1.3 In OCTAVE, there were 2 cases of life-threatening angioedema among 12000 subjects treated for about 6 months. In the original development program, there were 4 such cases in a population about 1/3 as large. Estimate the risk of life-threatening angioedema to expect post-marketing, and estimate the upper confidence limit for that risk.

1.4 The sponsor has proposed a risk management plan focusing on patient education by pharmacists. To what extent can a risk management program based on patient education be expected to reduce the risk of death from angioedema?

2. The sponsor has shown the results of OVERTURE, a comparison of omapatrilat and enalapril in the treatment of chronic heart failure. If the results of this study are as presented, …
   2.1 … how relevant are these data to the approval of omapatrilat for hypertension?
   2.2 … how reassuring are these data with respect to the use of omapatrilat in a hypertensive population?

3. Consider the antihypertensive effects of omapatrilat relative to other drugs.
   3.1 Is omapatrilat superior to enalapril? What results support this?
   3.2 Is omapatrilat superior to lisinopril? What results support this?
   3.3 Is omapatrilat superior to amlodipine? What results support this?
   3.4 Is omapatrilat superior to losartan? What results support this?

4. With what potential benefit should the risk of angioedema be balanced? OCTAVE allowed the addition of no new antihypertensive drugs during the first 8 weeks, at which time the blood pressure was about 3/2 mmHg lower on omapatrilat. During the following 16 weeks, other drugs were to be added to meet blood pressure goals, but at the end of 24 weeks, the blood pressure difference was still 3/2 mmHg. What explains the persistence of the differential effect at 24 weeks?
   4.1 Is a regimen including omapatrilat able to lower blood pressure to an extent that combinations of enalapril and other drugs cannot? If so, is the risk-benefit comparison between the risk of angioedema and the expected reduction in cardiovascular events attributable to this blood pressure difference?
   4.2 Is the persistence of a blood pressure difference at 24 weeks a consequence of trial design, e.g., the goal blood pressure, or to the inadequate use of additional drugs? If so, is the risk-benefit comparison between the risk of angioedema and the avoidance of adverse events associated with additional antihypertensive drugs?

5. Depending on the Committee's answer in question 4, identify a target population and estimate the magnitude of the expected benefit.

6. Should omapatrilat be approved for the treatment of hypertension? If so…
   6.1 … in what population should it be indicated?
   6.2 … in what population should it be contraindicated?
   6.3 … what is the starting dose?