Questions

HOPE

1 May 2000

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

Ramapril's current Indications read as follows:

> "**Hypertension**
>
> "ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics....
>
> "In considering use of ALTACE, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (See WARNINGS, Angioedema.)
>
> "**Heart Failure post myocardial infarction**
>
> "Ramapril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risk of failure-related hospitalization and progression to severe/resistant heart failure. (see CLINICAL PHARMACOLOGY, Heart Failure post-myocardial infarction for details and limitations of the survival trial.)."

The labeling request is to add the following to the indications:

> **"Prevention of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes.** In patients 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), ALTACE is indicated as an adjunctive therapy to significantly reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. In addition, ALTACE is indicated to significantly reduce the incidence of these pre-selected clinically relevant secondary end-points: coronary revascularization procedures, complications related to diabetes, and heart failure."

1. Does the HOPE study adequately establish a beneficial effect of ramipril, compared to placebo, on the combined end-point of myocardial infarction, stroke, and death from cardiovascular causes? If so, ...

1.1 ... does the proposed labeling adequately describe the cardiovascular risk factors of the HOPE study population?

1.2 ... does the proposed labeling adequately describe the characteristics of the population that should be treated?

1.3 ... should "all-cause mortality" be included in the Indications portion of labeling?

2. Were there differences in the primary end point with respect to ...
2.1 ... gender? If so, how, if at all, should the label reflect the differences?
2.2 ... age? If so, how, if at all, should the label reflect the differences?
2.3 ... race? If so, how, if at all, should the label reflect the differences?
2.4 ... geographic region? If so, how, if at all, should the label reflect the differences?

3. Were the effects of ramipril on the primary end point in the diabetic sub-population ...
3.1 ... a new finding, warranting explicit mention in the Indications section?
3.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
3.3 ... a source of comfort, but not warranting explicit description in the label?

4. Were the effects of ramipril on the incidence of new diabetes ...
4.1 ... a new finding, warranting explicit mention in the Indications section?
4.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
4.3 ... a source of comfort, but not warranting explicit description in the label?

5. Were the effects of ramipril on glycemic control ...
5.1 ... a new finding, warranting explicit mention in the Indications section?
5.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
5.3 ... a source of comfort, but not warranting explicit description in the label?

6. Were the effects of ramipril on diabetic nephropathy ...
6.1 ... a new finding, warranting explicit mention in the Indications section?
6.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
6.3 ... a source of comfort, but not warranting explicit description in the label?

7. Were the effects of ramipril on microvascular complications of diabetes (retinopathy, microalbuminuria, etc.) ...
7.1 ... a new finding, warranting explicit mention in the Indications section?
7.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
7.3 ... a source of comfort, but not warranting explicit description in the label?

8. Were the effects of ramipril on the need for coronary revascularization ...
8.1 ... a new finding, warranting explicit mention in the Indications section?
8.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
8.3 ... a source of comfort, but not warranting explicit description in the label?

9. Were there effects of ramipril on congestive heart failure? If so, ...
9.1 ... upon what data is the conclusion reached?
9.2 ... were these effects ...
9.2.1 ... a new finding, warranting explicit mention in the Indications section?
9.2.2 ... a new finding, warranting explicit mention in the Clinical Trials section?
9.2.3 ... a source of comfort, but not warranting explicit description in the label?