Questions

Pravastatin/Aspirin

18 January 2002

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 benefits and risks of a fixed-dose combination product consisting of pravastatin and aspirin for use in patients who are prescribed these two products as individual entities. It is common knowledge that FDA will accept applications for fixed-dose combination products when 2 (or more) approved drugs are commonly prescribed together, for convenience (and perhaps for better compliance).

In discussions of such products, we have said that availability of such convenience formulations should not alter health care provider's prescribing practices (*e.g.* by not providing a full range of useful doses). Generally that means that a full range of dosing strengths of each individual entity should be available for the combination product, thereby providing convenience but not influencing selection of doses or dosing regimens of individual entities.

Further, the Division has asserted that it should be well established that both entities should be taken concomitantly, since the existence of a fixed-dose combination product implies that they **should** be taken together not just that they **can** be taken together. Generally speaking, the Division has required for fixed dose combination antihypertensive products that the effects of the combination (A + B) be greater than the effects of either one alone (A or B). Moreover, the effects of several doses of A in combination with several doses B be evaluated (often in a factorial trial) so that some description of the use of A+B can be compared with either A or B alone.

The sponsor has chosen a single dose of pravastatin (40 mg) and two doses of buffered aspirin (81 and 325 mg) to combine. Thus there will be two formulations of the fixed-dose combination marketed, 40 mg pravastatin/81 mg buffered aspirin and 40 mg pravastatin/325 mg buffered aspirin. Although initial marketing will be accomplished by co-packaging, formulations of fixed-dose combinations have been prepared and are awaiting completion of stability studies. The fixed-dose combinations will be marketed as soon as data are available. Although the application is for a co-packaged product, the Advisory Committee is asked to consider the issue the same as that of marketing of a fixed-dose combination product.

Pravastatin is approved for use in a) Primary Prevention in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors, b) Secondary Prevention of cardiovascular events, total mortality and stroke, and c) for the treatment of Hyperlipidemia.

Aspirin is for use in the following patient populations: a) Secondary Prevention of death and stroke in patients who have had Transient Ischemic Attacks, or stroke (all CNS indications related to thrombotic events), b) Secondary Prevention in patients who have survived a myocardial infarction, and c) patients who are suspected of having an acute myocardial infarction, patients with unstable angina, and patients who are having revascularization procedures (coronary or carotid) who have underlying occlusive vascular disease. Aspirin is given for life, according to the dosing and administration section for patients who have had unstable angina or PTCA.

1.0 Can you define a patient population for whom pravastatin plus buffered aspirin would be indicated?

1.1 If yes, please define the population; this would be the population named in the indications section for the combination product.

1.2 Are there patient populations where there might be net harm from giving both pravastatin and buffered aspirin together?

1.2.1 If so, please define some of these populations.

2.0 There are no data from any trial prospectively-designed to test the hypothesis that pravastatin (at any dose) **plus** buffered aspirin (at any dose) produced a better clinical outcome (measured by any clinical end-point) than either pravastatin or buffered aspirin **alone**.

2.1 Is that sufficient reason to **cease** consideration of approval of the fixed dose combination product? In other words, is it necessary to have the results of specifically designed controlled clinical trials to consider approval of this fixed dose combination product?

2.2 If not, what might be sufficient?

3.0 One could argue that, for the patient population you have defined, since the purported mechanisms of action for the demonstrated clinical benefit of each agent are very different (something to do with lipids for pravastatin and something to do with platelets for aspirin), showing that there were no important pharmacokinetic or pharmacodynamic interactions (using surrogates) would be an adequate basis for approval of the fixed dose combination product.

3.1 Do you agree with this? If so,

3.1.1 Are there sufficient data present to support the presence of or lack of significant pharmacokinetic interaction?

3.1.2 Are there sufficient data present to support the presence of or lack of significant pharmacodynamic drug interaction?

4.0 The sponsor has provided 3 different meta-analyses (data from 5 placebo-controlled trials, the total number of randomized patients being 14,617) that address whether or not administration of pravastatin **plus** buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone. Some of the selected trials required that patients have greater than normal levels of serum cholesterol; others did not.

4.1 Do these 14,617 randomized patients represent a reasonable approximation of the patients for whom this combination product would be indicated?

4.2 From the results of the meta-analyses, do you conclude that the data show that pravastatin **plus** buffered aspirin has a greater effect than either buffered aspirin or pravastatin alone;

4.2.1 Using as a standard of 2 trials at a $p < 0.05$, is the strength of evidence from the meta-analyis as strong as this standard?

4.2.2 Using as a standard of one trial at a $p < 0.05$, is the strength of evidence from the meta-analysis as strong as this standard?

4.3 Which of the models offered by the sponsor (Cox Proportional Hazard, Bayesian hierarchical Cox proportional hazards, or Model 3) is most supportive, are they all equally supportive, or are they equally non-supportive?

5.0 Upon what basis was the dose of buffered aspirin chosen, for use in the fixed-dose combination product?
    5.1 Do you consider this reasonable?
    5.2 What alternative doses can you recommend?
    5.3 Should one wait, prior to approval, on settling the question of buffered aspirin dose?

6.0 Upon what basis was the dose of pravastatin chosen, for use in the fixed-dose combination product?
    6.1 Do you consider this reasonable?
    6.2 What alternatives can you recommend?
    6.3 Should one wait, prior to approval, on settling the question of pravastatin dose?

7.0 Assuming that you have concluded something about the strength of evidence that pravastatin and buffered aspirin should be taken together and that the doses to be available in the fixed- dose combination product are appropriate, what is the strength of evidence that a fixed-dose combination product (taking a single pill), has increased clinical benefit with respect to taking two pills (not necessarily together)?
    7.1 Should we require better demonstration of additional benefit provided by “convenience”?
    7.2 What kind of demonstration would be better?

8.0 How likely is it that the availability of the fixed dose combination product would encourage:
    8.1 Inappropriate use of buffered aspirin for primary prevention?
    8.2 Inappropriate use of a dose of 40 mg pravastatin?
    8.3 Inappropriate use of a dose of 325 mg buffered aspirin?
    8.4 Inappropriate use of a dose of 81 mg buffered aspirin?

9.0 Do you recommend approval of the fixed-dose combination of product of pravastatin plus buffered aspirin?