Questions for Consideration of the Joint Meeting
Nonprescription Drugs Advisory Committee &
Endocrinologic and Metabolic Advisory Committee

July 14, 2000

Food and Drug Administration: Center for Drug Evaluation and Research
Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda MD

Pravachol® NDA 21-198, Bristol Myers Squibb

Efficacy and Safety in the Proposed ~~Indication~~Target Population

1. The sponsor proposes an indication, based upon an expectation of cardiovascular benefit, for the use of pravastatin~~/prava~~ 10 mg in individuals with TC 200-240 mg/dL and LDL-C > 130 mg/dL, regardless of HDL-C level, and without CHD or diabetes. Current ~~NCEP~~ guidelines for the treatment of hypercholesterolemia do not target such individuals for drug treatment. Based on the data submitted in the NDA, has the sponsor adequately demonstrated a clinical benefit of pravastatin~~/prava at this dose~~ 10 mg in the target population?
   a. If yes~~so~~, what is the nature and magnitude of the benefit?
   b. If no, what additional data are needed to demonstrate a clinical benefit in the target population?

2. Statins have been associated with myopathy, including rare cases of rhabdomyolysis, as well as with elevations in hepatic transaminases (although the association between use of these drugs and serious hepatic disease is less clear). Intercurrent illness, undefined individual susceptibility factors, and interactions with other drugs and/or foods may increase the risk for rhabdomyolysis with statins. Taking into account these and other safety issues, has the sponsor presented adequate data to support the safety of pravastatin ~~/prava~~ 10 mg in the target population?
   a. If no, what additional data are needed to demonstrate safety?

3. Taking into consideration the balance of risk and benefit, has the sponsor presented data that are adequate to support the use of pravastatin~~a/prava~~ 10 mg in the low-risk ~~primary prevention~~ population with TC 200-240 mg/dL, LDL-C > 130 mg/dL, regardless of HDL-C level, without CH~~A~~D or diabetes?
   a. If no, what additional data are needed to support such an indication?

OTC Considerations

4. Assuming an indication for the use of pravastatin 10 mg ~~/prava~~ in the proposed target population can be justified based upon an expectation of clinical benefit, has the sponsor adequately demonstrated that consumers can achieve such a clinical benefit in an OTC setting? In responding to this question, please consider the following:
   a. The ability of consumers to appropriately self-select (and de-select) based upon cholesterol levels ~~(including total-C, LDL-C, and HDL-C)~~ and other risk factors.
   b. The ability of consumers to evaluate response to treatment ~~understand treatment goals~~ and to monitor cholesterol levels~~,~~ (including understanding of how to undertake a fast~~, duration of a fast~~ and the frequency of re-testing)~~ls~~.
   c. The ability of consumers to adhere to chronic therapy with prava~~/prava~~statin 10 mg.
   d. The need for the physician or other healthcare professional in the effective treatment and follow up of dyslipidemia.
   e. The capacity of the proposed label to direct consumers in the effective use of prava~~/prava~~statin 10 mg OTC.

5. Assuming that ~~the drug~~pravastatin 10 mg is deemed ~~-~~adequately safe when used for the proposed indication in the target population, has the sponsor presented adequate evidence that consumers will be able to use pravastatin~~/prava~~ 10 mg safely in an OTC setting? In responding to this question, please consider the following:
   a. The ability of the consumer to identify adverse reactions to pravastatin and to act appropriately.
   b. The ability of the consumer to monitor hepatic safety including the need for monitoring of hepatic transaminases and the ability of the consumer to perform such monitoring if needed.
   c. The need for and ability of the consumer to identify and avoid interacting drugs and other substances.
   d. The likelihood of use of pravastatin~~/prava~~ 10 mg at higher than recommended doses (1 tablet per day) ~~(i.e., understanding of how to titrate doses)~~.
   e. The ability of women who are pregnant or likely to become so to appropriately avoid use of pravastatin~~/prava~~ 10 mg.
   f. The need for the physician or other healthcare professional in the safe treatment and follow up of dyslipidemia.
   g. The capacity of the proposed label to direct consumers in the safe use of prava~~/prava~~statin 10 mg OTC.

~~What information would need to be conveyed on the label to adequately inform consumers of the benefits and the risks of treatment with (product name)?~~

~~Does the label adequately inform consumers about treatment success and failures? If not, what additional information should be incorporated into labeling (carton and package insert)?~~

Approvability

6. Assuming that the answer to Question 3 is yes (i.e., the sponsor has provided sufficient information to support the safety and effectiveness of prava~~/prava~~statin 10 mg for the proposed indication in the target population), has the sponsor provided

sufficient evidence that pravastatin/~~prava~~ 10 mg can be used safely and effectively in an OTC setting?

a. If yes, are any additional studies needed post-approval? What are the key messages that need to be conveyed to the consumer in the product label (carton and package insert) to provide for the safe and effective use of pravastatin 10 mg OTC? ~~Are there any recommendations with regard to labeling that you would make?~~
b. If no, what additional studies are necessary to support approval for OTC marketing?