MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 9, 2000

FROM: OTC Pravastatin Sodium (Pravachol) Review Team

THROUGH: Directors, Office of Drug Evaluation II and V

SUBJECT: July 14, 2000 Advisory Committee Meeting to discuss proposed Rx to OTC switch for Pravastatin Sodium (Pravachol)

The purpose of this memorandum is to provide pertinent background summary information and to raise points to consider as you prepare for the upcoming meeting on July 14, 2000. The package that you have been provided contains the draft agenda and reviews that will be addressed at this meeting. Additional reviews (that will not be presented) have also been provided for your information in your package and will be identified as such.

Background

Pravastatin sodium (Pravachol) has been marketed in the United States since 1991 as a prescription drug, at doses of 10 mg a day to 40 mg a day. It is indicated for use as an adjunct to diet for the reduction of elevated total and LDL cholesterol in patients with primary hypercholesterolemia (Types IIa and IIb), when the response to diet restricted in saturated fats and cholesterol and to other nonpharmacological measures alone has been inadequate. It is also indicated in the primary and secondary prevention of coronary and cardiovascular events.

The association between elevated serum cholesterol levels and risk of atherosclerotic cardiovascular disease has been established by data from animal models, epidemiological and observational cohort studies, interventional trials, and diseases of abnormal lipid metabolism. Recently

the results of AFCAPS/TexCAPS (see References at the end of the packet) have suggested the potential for cardiovascular benefit in middle-aged and elderly men and women (males > 40 years old and post-menopausal women) without CHD or diabetes with total cholesterol in the range of 200-240 mg/dl and LDL-C > 130 mg/dl, and below-average HDL-C levels.

In NDA 21-198, Bristol-Myers Squibb (BMS) has presented the rationale for over-the-counter access to pravastatin at 10 mg a day. The population being targeted consists of individuals who have been told by their physicians to lower their cholesterol but have not been placed on prescription therapy. Thus, men and women in good health without diabetes or coronary heart disease (CHD), having a total cholesterol levels between 200 and 240 mg/dl and LDL-C levels greater than 130 mg/dl, are considered to be the OTC population who might benefit from OTC therapy (there is no inclusion criterion specifying low HDL-C). Despite the evidence that treatment of hypercholesterolemia with lipid-altering drugs results in clinical benefit, BMS contends that the U.S. population remains inadequately treated. Further, BMS contends that based on the efficacy and safety data supporting the prescription approval, the motivated OTC population will benefit from its availability. Of note, current NCEP guidelines do not recommend drug therapy as initial therapy for individuals having cholesterol levels within this range.

In support of the OTC program, the sponsor has submitted 3 studies. These studies were as follows:

- PREDICT: randomized, open-label actual use study of behavior, compliance, efficacy, and safety; included simulated prescription (Rx) versus simulated OTC environments in which patients expressing an interest were randomized and then superficially screened before initiating therapy
- OPTIONS: 3 month uncontrolled, actual use, self-purchase, behavior, compliance, and safety study in patients enrolled in an HMO setting and to see if consumers would follow-up appropriately with a health care provider
- Label comprehension trial

Because the NDA raises some precedent-setting issues, the Agency has established dialogue with both scientific and consumer representatives on the merits and disadvantages of OTC availability of cholesterol lowering drugs. The issue of OTCness of cholesterol-lowering drugs has been addressed previously at two joint advisory committee meetings (Nonprescription Drug Advisory Committee (NDAC) and Endocrine and Metabolic (E & M) Advisory Committees) on September 27, 1995 and on June 30, 1997, in which an application for the switch of Questran was discussed. Following that meeting the Agency published a guidance

indicating that hypercholesterolemia was not an OTC indication.

As noted in the sponsor's package and in the FDA reviews contained within this package, there are several issues that have been targeted for discussion.

Specific Issues

1. Results of Clinical Trials/Actual Use Trials

The data presented in the actual use trials demonstrated lowering of LDL-C in compliant individuals from the target population, but no CHD outcome data were generated. Only a minority (approximately 15%) of those interested and actually purchasing the drug would fit into the target population as specified in the entry criteria. The majority of participants had a cholesterol value out of range or had already reached the desired cholesterol goal. Adherence to drug was <50% at endpoint (12 and 24 weeks). Adherence was better in the Rx group in the PREDICT study. Compliance, however, with recommended physician follow-up was low. In the OPTIONS study only 44% saw a physician within 2 months, as required by the labeling. The adherence decreased further for trials of longer duration.

2. Safety

The data collected in these trials to assess the safety of 10 mg of pravastatin in the OTC population did not include clinical laboratory determinations. The reported adverse events from the clinical trials were, in general, non-serious in nature and were mainly gastrointestional (nausea, bloating, flatulence, diarrhea). It should be noted, however, that cases of myalgias were reported, although the incidence was lower (0.6%) than seen in the 3 placebo controlled clinical trials (2.3%) involving doses of 10 mg presented in the original NDA for Rx use. In addition, the rate of discontinuation was higher in the simulated OTC groups of both clinical trials (58.3% for PREDICT and 51.4% of OPTIONS) than the Rx group. No information was collected to address the safety of consumer use of higher doses that would fall within the prescription dose range. No cases of rhabdomyolysis or serious hepatic disease were reported, although the extent and duration of exposure were limited in these trials.

3. Label Comprehension

The label comprehension studies did not test whether persons with particular medical conditions could choose appropriately whether or not to use the product. Although hypothetical questions were asked about use by persons with medical conditions mentioned on the label, there were no questions specifically asking the consumer if they were eligible to use the product. Further, the study did not ask questions that would require participants to

understand that users must meet several criteria simultaneously before using the product, relating to levels of total cholesterol and LDL-C, age, and menopausal status, for females. No information was provided to address the extent to which consumers would be able to apply the label information, to combine all of these elements to achieve the appropriate use of the product.

The studies tested were done at fairly low levels of understanding. Scenario-type questions were not employed. Primarily due to the questionnaire design, the study provides inadequate information about whether consumers can understand the label well enough to self-select and use the product appropriately.

As a result of the low levels of comprehension documented for some information in this trial, most notably being consumers' failure to understand some information about who should not use the product, the label was modified significantly following this study. However, the currently proposed label and insert have not been studied for consumer comprehension.

4. Miscellaneous Information

New analyses of pre-existing data have been submitted, with a proposed modification to the current pregnancy labeling (currently, this product is classified as pregnancy category X).

Points to Consider

Whether the overall benefit of having pravastatin available as an OTC product outweighs the potential risk will be the subject for discussion at this advisory committee. There is substantial marketing experience with pravastatin (which has been available as a prescription product since 1991). Issues pertaining to the proposed OTC availability of this product revolve around its safety and effectiveness in OTC use, and the more general issue of the appropriateness of treatment of hypercholesterolemia in the OTC consumer population. Questions include whether consumers will accurately self-select for (or against) embarking on this treatment; their ability to understand the proposed regimen and adequately monitor the treatment; and their ability to comply with the program for an extended period of time, in order to reap any potential cardiovascular benefit. Further, there are questions as to whether the population-averaged efficacy in the proposed OTC population can be relied on as reasonably estimating the potential for cardiovascular benefit. Additional safety concerns and cautions with pravastatin use, as described in the current prescription label, such as liver

function monitoring for potential enzyme elevations, muscle adverse events, drug interactions, and potential risks of use in pregnancy, also require additional examination in considering the proposed OTC availability of this product.

During the advisory committee discussion, these issues, as well as the fundamental question of whether this treatment is appropriate for OTC availability, will be the focus of the discussion.