

**MEMORANDUM
SERVICES**

DEPARTMENT OF HEALTH AND HUMAN

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

RESEARCH

DATE: June 9, 2000

FROM: OTC Lovastatin (Mevacor) Review Team

THROUGH: Directors, Office of Drug Evaluation II and V

SUBJECT: July 13, 2000 Advisory Committee Meeting to discuss proposed Rx to OTC switch for Lovastatin (Mevacor)

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 13, 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

Lovastatin (Mevacor) has been marketed in the United States since 1987 as a prescription drug, at doses of 20 mg a day to 80 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 to slow the progression of coronary atherosclerosis in patients with coronary heart disease, as part of a treatment strategy to lower total and LDL cholesterol to target levels.

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 21-213, Merck has presented the rationale for over-the-counter access to lovastatin at 10 mg a day. The population being targeted consists of individuals (men over the age of 40 and postmenopausal women) without coronary heart disease (CHD) who have total cholesterol levels between 200 and 240 mg/dl and LDL-C levels greater than 130 mg/dl (there is no inclusion criterion specifying low HDL-C). The sponsor estimates (based on calculations published from AFCAPS/TexCAPS and NHANES III) that approximately 15.5 million men and women in the U.S. would be eligible for treatment if the above criteria are used. Thus, the sponsor contends that given the individual and population risks for developing CHD in the target population, consumers will benefit from unrestricted access to lovastatin 10 mg. 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 10 studies. These studies were designed to evaluate the following:

- 1 efficacy study in the target population – designed as a placebo-controlled, randomized, double-blind, diet run-in study, to assess lipid altering effect of lovastatin as primary end-point (Protocol 075)
- 3 uncontrolled, efficacy and tolerability actual use studies involving either self- or study staff pre-screening followed by use of the dispensed (non-purchased) drug (Protocols 076, 077 and 079). [Protocol 077 was terminated early by the sponsor.]
- 1 uncontrolled, tolerability/compliance actual use study, involving label comprehension and self-pre-screen, and requiring purchase for drug (Protocol 081)
- 3 label comprehension trials – 2 (Reference study 199 and 200) were designed as companion trials to the actual use trials. 1 was designed to address the deficiencies found in the previous 2 trials. (Reference studies 199, 200, and 201)
- 1 study to assess the pharmacokinetics of multiple daily dose lovastatin 10 to 40 mg
- 1 study to assess the interaction of lovastatin 40 mg with CYP3A4 inhibitors and substrates

Because the NDA raises 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

The data presented in the efficacy and actual use trials (075, 076 and 079) demonstrated the expected degree of LDL-C lowering in individual compliant subjects representative of the target population. No CHD outcome data were generated. Approximately 1 in 10 of those recruited were actually eligible for the studies, with the most common exclusion being "cholesterol out of range." Self-selection errors were frequent, even though coaching by the investigators and telephone contacts occurred (more guidance than would be expected if the consumers were to pick up the product off of the shelf). Approximately 72% (at 6 months) and 63% (at 2 months) of people, who are enrolled in trials 076 and 079, respectively, completed the trials. "Compliance" and "persistence" measures were used to characterize the extent to which consumers actually used the medication. The percentages obtained, however, may not be very precise in describing how consumers would use the tablets or the quantity of pills that might be taken, considering the definitions used (refer to Medical Officers reviews). Extensions of these trials have been performed; however, complete data have not yet been submitted to the Agency for review.

2. Safety

The data collected in these trials to assess the safety of 10 mg of lovastatin in the OTC population did not include clinical laboratory determinations, and no specific assessments of clinical tolerability were reported. The reported adverse events from the clinical trials were, in general, non-serious in nature and were mainly gastrointestinal (bloating, flatulence, diarrhea), but cases of myalgias were also reported. 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 diseases were reported, although the extent and duration of exposure were limited in these trials.

3. Actual Use

The reported "persistence" and "compliance" rates for the periods of study were <50% for each of the 3 actual use trials analyzed. (One actual use trial was terminated early because of poor recruitment.) Self-selection errors were frequent, as many consumers did not have accurate knowledge of their cholesterol values or concomitant medical conditions. Consumers were found to be non-compliant in that they did not take the product regularly or they took it concomitantly with an excluded medical condition or medication. The trials were not of long enough duration to identify any clinical benefit in this population at low risk for CHD.

4. 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 consumers if they were eligible to use the product. In addition, there was no actual checking of the consumer responses against their listed medical conditions. 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. For example, for the label tested for lovastatin, users must have a certain total cholesterol, a certain LDL-C, men must be >40 years old, and women must be 1 year post-menopausal. 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 aimed for fairly low levels of understanding. Scenario-type questions were not employed. Primarily due to the questionnaire design, the studies provided 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 in the last trial, most notably being consumers' failure to understand who should not use the

product, the label was modified slightly following the final study.

5. Miscellaneous Information

Pharmacokinetic information has been presented in this application to address the issues of drug interaction, since lovastatin is metabolized by the cytochrome P450 isoform 3A4. In addition, information has also been provided to address the proposed change in the pregnancy category (currently category X).

Points to Consider

Whether the overall benefit of having lovastatin 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 lovastatin (which has been available as a prescription product since 1987), and much is known about the safety and effectiveness of this product for its indicated prescription uses. 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 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 lovastatin use, as described in the 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.