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Non-Prescription Drugs Advisory Committee
Endocrinologic And Metabolic Drugs Advisory Committee
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attention: Cathy A. Groupe

Statements Filed For Consideration By The Non-Prescription Drugs Advisory Committee And The Endocrinologic And Metabolic Drugs Advisory Committee With Regard To The Safety And Efficacy Of Over-the-Counter Use Of Mevacor

These comments are respectfully submitted by Teva Pharmaceuticals USA Inc. for consideration by the Non-Prescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee on January 13-14, 2005, in connection with Merck & Co.'s supplemental new drug application ("sNDA") 21-213, for an Rx→OTC switch of Mevacor® (lovastatin) 20 milligram tablets. As discussed herein, the proposed OTC switch of Mevacor is medically unwise, legally unfounded, would create serious safety risks for patients, and may result in higher costs to consumers. Accordingly, we urge the NDAC and EMDAC to recommend that FDA deny the proposed OTC switch of Mevacor.

I. BACKGROUND -- Rx AND OTC DRUGS

A. Prescription Drug Criteria

Prior to 1951, drug manufacturers were generally free to determine the category under which their drug would be marketed, as the Federal Food, Drug, and Cosmetic Act ("FDCA") did not specify grounds, or a mechanism, for determining prescription or OTC status. However, Congress came to recognize that for some drugs, it was impossible to provide a lay person with adequate directions for safe use, and that in order to protect the public health and safety, a drug must not be available over-the-counter if the drug is too difficult or dangerous for consumers to use or administer without medical guidance and supervision. Thus Congress passed the Durham-Humphrey Amendments of 1951, which amended the FDCA by establishing two classes of drugs: prescription and Over-the-Counter ("OTC"). *See* 21 U.S.C. § 353. Specifically, section 353(b)(1) provides that,

However, prescription drugs are exempt from the adequate directions for use requirement because the required intervention of a physician (who has read and understood the approved complete prescribing information required by 21 C.F.R. §§ 201.50-201.57) is presumed to provide the patient with the necessary information to use the drug appropriately. *See* 21 U.S.C. § 353(b)(2).

Thus, there exist clear legal and medical distinctions between prescription and OTC drugs. These distinctions are based upon, and apply to, the ability of patients to use the drug without little or no initial or ongoing physician involvement, from diagnosis, informed risk assessment, the need for expert medical intervention during use, and ability to know when treatment may be stopped. As discussed below, the proposed Rx→OTC switch for Mevacor 20 mg would obfuscate these distinctions and create a drug product and labeling that would not provide for the necessary physician supervision to: (i) diagnose the existence and cause of a patient's hypercholesterolemia; (ii) determine if the patient's disease is appropriate for OTC treatment with Mevacor; (iii) monitor the ongoing safety and effectiveness of the drug; and (iv) recognize or attend to the safety risks associated with the administration of the drug. Because professional involvement is necessary for these purposes, any OTC Mevacor product would necessarily fail to provide adequate directions for safe and effective OTC use.

II. A PRESCRIPTION TO OTC SWITCH FOR MEVACOR WOULD FAIL TO MEET THE STATUTORY DISTINCTIONS CREATED BY THE FDCA

As noted above, a prescription drug such as Mevacor may not be approved for OTC use if "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug." 21 U.S.C. § 353(b)(1). FDA regulations implement the procedures for approving an Rx→OTC switch as follows:

> Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.

21 C.F.R. § 310.200(b) (emphasis added).

Even under the reported proposed OTC labeling, Mevacor 20 mg cannot meet these legal requirements. Moreover, the proposed OTC conditions of use would effectively create a third, hybrid type of drug -- neither completely OTC nor completely prescription -- and such a category of drug is not authorized under the FDCA.

A. Mevacor Has Serious Risks That Preclude Safe OTC Use Under Any Conditions

Mevacor has been marketed in the United States since 1987 as a prescription drug, at doses of 20 mg to 80 mg a day. It is indicated for primary prevention of coronary heart disease, to slow atherosclerosis on patients with coronary heart disease, and (relevant to the proposed OTC switch) to

- Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) returns to normal.

- In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously

- All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected.

Thus, the prescription use of Mevacor, even at a 20 mg dose, requires a primary assessment by a physician as to the potential benefits versus possible risks for the individual patient. This primary assessment necessarily requires a risk-benefit analysis based on an expert medical understanding of the patient's physical condition and susceptibility to risks related to liver, kidney, and muscle functions. The use of Mevacor also requires ongoing physician monitoring of the patient's cholesterol and liver functions by the prescribing physician. However, Merck's proposed labeling for OTC 20 mg Mevacor fails to adequately address and assure that patients will receive the necessary medical attention when using the product.

B. Patients Cannot Adequately Self-Diagnose The Need For OTC Mevacor

Treatment of high cholesterol is an indisputably important public and individual health goal, but it is one that fundamentally must involve professional medical care and advice, especially given the risks of statins such as Mevacor. As a primary matter, simply discovering through an OTC cholesterol test that a patient has elevated total cholesterol, even within a specified range as might be proposed in OTC labeling, is not enough to conclude that self-treatment with Mevacor is appropriate. As FDA has concluded, as reflected in the approved prescription Mevacor labeling, there are multiple potential causes for high cholesterol, and some of those causes can be both life threatening and preclude the use of Mevacor. Any proposed OTC Mevacor 20 mg labeling cannot adequately address the current prescription labeling requirement that prior to initiating therapy with Mevacor, secondary causes for hypercholesterolemia (*e.g.*, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total cholesterol ("total-C"), HDL cholesterol ("HDL-C"), and plasma triglyceride ("TG"). Only a physician can diagnose diabetes, hypothyroidism, nephrotic syndrome, etc., yet any OTC Mevacor labeling would essentially dispense with this important diagnostic step altogether.

Moreover, the proposed OTC labeling suggests that patients test their LDL cholesterol levels after six weeks of an OTC Mevacor regimen and to discontinue the medication and see a physician if their LDL cholesterol exceeds 129 mg/dL. However, such testing and assessment of LDL cholesterol must necessarily be performed in a licensed medical diagnostic facility or under the supervision of a licensed physician, because there are no approved or cleared OTC tests for LDL cholesterol.

it is unlikely that an individual patient would have the ability to make a rational assessment of liver function prior to embarking on, or during, an OTC Mevacor regimen, even if a patient could perform such testing (which they cannot).

D. Approval of OTC Mevacor Would Create An Unauthorized Third Class of Drugs

Any potential approval of OTC Mevacor would necessarily involve one of two things. First, the FDA-approved OTC labeling would disregard the important safety role pre- and intra-treatment LFTs and differential lipid profile analysis play for patients taking Mevacor. There simply is not substantial clinical evidence to support approval of an OTC drug under such circumstances, and we trust that the Committee will not recommend such an approach.

Alternatively, to the extent Mevacor is made available OTC, but has labeling requiring specific and ongoing physician intervention of the sort described above, the product would not in fact qualify as an OTC drug under the FDCA, because the labeling would provide some, but not all, of the required "adequate directions for use," while leaving other collateral measures necessary for the safe use of the drug (i.e., initial and ongoing diagnoses, liver function tests, and lipid profile analysis) to the chance that the patient would consult appropriately with a physician. Although there are some approved OTC switch drugs that require an initial physician's diagnosis prior to initiation of therapy (e.g., bronchodilators for treating asthma after a doctor's diagnosis), and others that recommend seeing a doctor if symptoms do not improve within a specified time (e.g., OTC NSAIDs, such as ibuprofen, for pain), the collateral conditions necessary for the safe use of Mevacor OTC go far beyond the limited physician intervention recommended in the labeling of OTC bronchodilators and NSAIDs. Thus, FDA approval of OTC Mevacor under such circumstances would be contrary to the mandate of section 503(b)(1) and would by fiat create a third, unauthorized, category of human drug product. Although it may be argued that such a third category of drug would be good public policy, it is not within FDA's authority to unilaterally create such a category in the face of statutory provisions that clearly preclude such a result.

III. APPROVAL OF OTC MEVACOR COULD BE COSTLY TO CONSUMERS

FDA should carefully consider the potential effects an OTC Mevacor product could have on the ever-growing consumer healthcare cost burden. First, prescription lovastatin is currently available from numerous generic drug companies, and the price is both very affordable, and is covered by most if not all health insurance plans. Approval of an OTC Mevacor would, as a practical matter, destroy the generic lovastatin market because (1) Merck would claim, and likely receive, a three-year exclusivity for switching the product to OTC, thus precluding any competition for OTC Mevacor for three years, and (2) most generic companies are not in the business of selling OTC drugs, and thus, other than a handful of companies that specialize in selling drugs to "store brand" OTC distributors, most suppliers of generic lovastatin will discontinue their product, reducing competition. Second, most insurance plans do not cover the cost of OTC drug products. Thus, patients who have been

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levels often rise immediately, but alkaline phosphatase and gamma-glutamyltransferase levels do not become elevated for several days. *See*, David E. Johnston, Special Considerations in Interpreting Liver Function Tests, 59 Am. Fam. Physician 2223 (1999).