CVS/pharmacy®

January 4, 2005

Cathy A. Groupe
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Re: Written Comments for Submission to the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee January 13 and 14, 2005

Dear Ms. Groupe,

On behalf of the CVS Pharmacy organization, I wish to submit the following written comments to be reviewed at the upcoming joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee on January 13 and 14, 2005.

As it pertains to the committee's discussion regarding NDA 21-213, which proposes the over-the-counter use of Mevacor (lovastatin) 20 mg, we are respectfully submitting the enclosed White Paper entitled: *Non-prescription designation of HMG-CoA Reductase Inhibitors: Patient Care Concerns*. This document has been prepared by CVS Pharmacy to articulate our concerns regarding the potential approval of Mevacor (lovastatin) 20 mg as a non-prescription drug product.

Thank you for your review and consideration of the enclosed information. If I may be of assistance in providing additional information, please feel free to contact me directly at 401-770-3131.

Sincerely,

Thomas G. Davis, R,Ph.
Director, Brand Category Management & Patient Care Programs

TGD/dmf

Enclosures

cc: Hilda F. Scharen, Center for Drug Evaluation and Research – FDA
Chris W. Bodine, Executive Vice President Merchandising and Marketing
Matthew J. Leonard, R.Ph., Vice President Pharmacy Merchandising

Non-prescription Designation of HMG-CoA Reductase Inhibitors: Patient Care Concerns

White Paper Submission to the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee – January 13 to 14, 2005
by CVS Pharmacy, Inc.

SUMMARY:

Regarding the application before the FDA for approval of Mevacor 20mg as a non-prescription product:

(1) CVS recommends the FDA not approve an over-the-counter (OTC) classification of Mevacor 20mg due to the risks to patient safety and potential for reduced patient access to affordable therapy that would result.

(2) If the FDA decides the benefits outweigh these risks, CVS recommends several actions the FDA should take to bolster consumer safety, while still achieving the broader access desired in an OTC product.

PRIMARY RECOMMENDATION: Approval of Mevacor 20mg for OTC indication is unwarranted given the health and access issues of a switch.

A switch to OTC would present health risks and additional cost to consumers. Removing the physician as gatekeeper to statin therapy will create a tremendous void – with respect to the appropriate use and clinical monitoring of this class of drug – resulting in excessive risk to the consumer.

- **Inappropriate use by consumers:** Elevated cholesterol levels can only be diagnosed by a blood test. In an OTC environment, no assurance exists that patients will obtain the necessary blood test to establish the need for therapy. Additionally, non-prescription status lacks the involvement of a medical professional to evaluate the consumer for contraindications prior to initiation of therapy. This needlessly exposes some consumers to potential serious adverse reactions and drug interactions.
- **Lack of clinical monitoring, such as liver function tests:** This lack of monitoring will increase the risk of potentially life threatening adverse events. Liver function abnormalities, degenerative muscle conditions, and a host of drug-drug (e.g., warfarin, gemfibrozil, and others)/drug-food (e.g., grapefruit juice) interactions inherent to the statin category are possible. OTC availability increases the risk that pregnant women may use the product inadvertently – Rx labeling limits use in women of childbearing age to those instances where such patients are highly unlikely to conceive.
- **Poor patient compliance:** Misunderstanding/ignoring labeled product instructions will increase patient risk. Recent studies show that only about one quarter of consumers read OTC labeling for either indications or interactions[1]. Despite best efforts to craft an easy to understand label, consumers will likely deviate from the printed instructions. Patients have a tendency to increase the dose of their OTC medications beyond the labeled instructions. Adverse reactions in this class of drug, such as those noted above, are dose-related and will increase as the dose is elevated. Therefore, a patient who unilaterally doubles or triples their 20mg OTC dose defeats the applicant's proposed "low dose statin" safety concept.
- **OTC availability will not lead to increased patient access to therapy:** The likely retail price of $20-30 for OTC Mevacor is significantly higher than the $2-10 generic co-pays charged to most people for the currently available generic versions of Mevacor. Additionally, as it pertains to those patients who are currently without prescription coverage, their out of pocket cost for a one month supply of generic Rx Mevacor dispensed under the care of their Pharmacist does not differ significantly from the anticipated cost of OTC Mevacor.

[1] visiongain 2002, "Rx-to-OTC Switching"

- **Generic prescriptions provide greater access to affordable therapy and pharmacist expertise:** A generic version of Mevacor – lovastatin – is currently available and already provides a lower cost option than branded Mevacor, with a cash price to uninsured consumers in retail pharmacies similar to the likely retail price of the proposed OTC product. Over the next few years other statins will likely have generic equivalents available (e.g., Pravachol and Zocor) which will provide patients with additional lower cost options for statin therapy. Encouraging generics more broadly is a key element of FDA policy to help contain the cost of prescription drugs in the U.S. To that end, generic Mevacor already provides the affordable access to low-dose statins that the FDA seeks for uninsured people, while maintaining the appropriate clinical monitoring performed by the physician and pharmacist found in the prescription environment.
- **Past Managed Care Organization (MCO) practices have limited access to therapy following OTC switch:** Historically, MCOs have changed their Rx plan coverage designs following an OTC switch. These plan changes often create barriers to both proper therapy (e.g., institution of step-based therapies) and access to therapy (e.g. discontinuing coverage, shifting co-pays to the highest tiers.) *See appendix for description of the recent introduction of Prilosec OTC to the marketplace.* The historical precedents set by the managed care community to limit patient access to appropriate therapy following an OTC introduction must be taken into consideration as future OTC switches are contemplated.

See the appendix for detailed notes discussing safety issues and Prilosec case study

SECONDARY RECOMMENDATION: If OTC Mevacor is approved, implement safeguards to ensure consumer safety and access.

If the Advisory Committee reaches the conclusion that Mevacor 20mg can be distributed safely as an OTC product, CVS proposes several steps the FDA should take to ensure that consumers receive the safest, most affordable treatment:

- **Work with MCOs to discourage actions that will limit patient access:** MCOs must not reduce or discontinue coverage for the higher strength statins required by people with serious cholesterol issues, especially in light of recent studies demonstrating the additional benefit of higher strength drugs.
- **Limit future OTC approvals to lower dose statins:** The FDA should acknowledge that the safety profile of the higher dose products demands professional and clinical monitoring for safety and efficacy.
- **Require pharmacist involvement in OTC sale:** Given the substantial role the FDA expects pharmacies to play in assisting patient drug selection and therapy for this type of drug, it should require OTC statins to be sold only where physical access to a pharmacist is possible (e.g., placing behind the pharmacy counter or limiting product placement to within a specified distance to a pharmacy counter currently staffed with a pharmacist.)
- **Facilitate development of reimbursement model for pharmacist time:** Unlike the prescription drug model, there is currently no reimbursement model that compensates pharmacies for the broader actions and professional services the FDA may request to support the OTC availability of statins. Therefore, if the FDA expects greater pharmacist participation, then the manufacturers need to offer an economically viable reimbursement model. To ensure patient access to OTC statins with active pharmacist participation, the FDA could make its approval contingent on the development and adoption of such an economic model.

Appendix of Patient Safety Concerns & Prilosec OTC Case Study

Statins OTC: Patient Safety Concerns

Elevated blood cholesterol levels are completely asymptomatic. Having "high cholesterol" is a risk factor for the development of coronary artery disease, which can ultimately manifest itself through time in the form of unstable angina or myocardial infarction (i.e. a heart attack), a leading cause of death in the United States.

If one was to consider the highly remote possibility that Mevacor could be safely employed in an OTC setting, then theoretically three key elements would need to be satisfied: The first is the patient's ability to correctly determine that initiation of treatment is warranted and appropriate. The second is the determination that no pre-existing medical conditions, drug interactions, or other contraindications exist prior to starting therapy. The third is the patient's ability to comply with the written label instruction versus the clinical consequence of non-compliance.

It is unrealistic to assume that the average customer would either be able to (or willing to) fulfill all of the steps safely to navigate himself or herself through self-medication with Mevacor OTC.

1. Appropriate Treatment:

Due to the asymptomatic nature of the condition, the only way to determine elevated cholesterol levels is through a blood test. The appropriate use of Mevacor OTC is predicated upon the patient first determining that he or she has an elevated cholesterol reading. To make this determination, they must either see a healthcare professional or rely upon an "at home" cholesterol screening test. In either case, the patient is going to incur some level of personal financial expense. It is reasonable to assume that some percentage of patients would forego the cost of cholesterol testing and simply initiate therapy with Mevacor OTC. In an OTC environment there is no gatekeeper to medication access to prevent this from occurring. Additionally, it is important to note that the currently available "at home" cholesterol screening tests offer only a total cholesterol measurement. Lipid panel analysis (HDL, LDL, VLDL, and total cholesterol) are only available through physician ordered clinical laboratory testing.

Correct diagnosis of the condition prior to treatment is essential to avoid unnecessary treatment. In an OTC environment, it is impossible to ensure that patients will seek appropriate testing and self-select themselves for treatment. By removing the physician as a gatekeeper to treatment, the associated risks of Mevacor OTC (contraindications, adverse reactions and drug to drug interactions) are greatly magnified as a larger population of patients (those not requiring treatment) is needlessly subjected to the medication.

2. Pre-existing medical conditions, drug interactions, or other contraindications:

Upon reading and understanding the package labeling, a patient, prior to initiation of therapy, would have to be able to determine that he or she does not have any pre-existing medical conditions, drug interactions, or other contraindications that would prohibit therapy.

Based upon current Mevacor (RX) product labeling and established standards of care, liver function testing must be performed prior to the initiation of therapy, and then again at 6 and 12 weeks post therapy induction, and yearly thereafter. Liver function testing must be ordered and interpreted by a physician. This test is performed for two key reasons: the first is to rule out any pre-existing liver disease, as this would be a contraindication to therapy. The second is to monitor the liver's reaction to treatment with Mevacor. Liver enzymes can be dangerously elevated in some patients as a result of therapy with

Mevacor requiring the need for dosage adjustment, treatment discontinuance, migration to a different statin, or a change to a lipid lowering agent in a different therapeutic class (such as bile acid sequestrants).

It is impractical to assume that patients are going to be appropriately monitored for liver function testing in a Mevacor OTC environment. The current OTC distribution model does not contain any mechanisms to ensure that this type of clinical monitoring occurs.

Additionally, Mevacor interacts with a number of other types of medications. Certain of these interactions can cause an increase in the incidence rate of rhabdomyolysis - the degenerative muscular condition that prompted the removal of Baycol from the US market in 2001. It is seemingly unrealistic to assume that patients will be able to accurately screen at therapy inception, and during therapy, for any drug interactions that may occur.

3. Compliance to written label instructions:

Mevacor is in the class of drugs known as HMG-CoA reductase inhibitors. This is a complicated class of drugs insofar as adverse reactions, contraindications, warnings, drug/food interactions, and safe use are considered. The likelihood of the average patient reading, let alone understanding, all of the information that would need to be contained on the label is extremely remote.

The propensity for significant adverse reactions (liver function abnormalities, muscle disorders) to occur is high relative to the intentional or unintentional misuse of the product as a result of non-compliance to the package labeling. As an example, consider the tendency for patients to increase the dose of medication beyond that of the labeled instructions. The general mindset of the public at large is that over-the-counter medications are very safe, and generally speaking, less potent than prescription medications. This mindset has been fostered through time by the traditional approval of OTC medications at half-strength to their prescription counterparts (H2 blockers such as Zantac, and Tagamet / NSAIDS such as Motrin, Naprosyn, et. al.). It is safe to assume that some percentage of the general population routinely increases their dose of OTC medications (beyond that of the labeled instruction) based upon this pre-existing bias. This is of major concern in the case of Mevacor as all adverse reactions associated with this medication are dose related and increase as the dosage increases. This could pose significant risk to those patients who unilaterally double or triple their dose of Mevacor OTC.

Based upon the foregoing, Mevacor, in the OTC arena, would clearly present greater risk than benefit to the population at large. This is primarily due to the complexity of the therapy, the asymptomatic nature of the condition, and the propensity for patient misuse - thus resulting in adverse reactions or other patient mis-adventures.

Case Study: Prilosec Rx-to-OTC switch

Following the September 2003 introduction of Prilosec OTC, MCOs took a variety of actions to limit patient access to appropriate therapy. Many MCOs immediately ceased coverage of prescription Prilosec including the generic Rx versions (which, from a consumer copay perspective, are significantly less expensive than Prilosec OTC.) Some MCOs reacted to Prilosec OTC by shifting all prescription drugs in this therapeutic class to the highest copay tiers, thereby creating an economic barrier to therapy access. Other organizations have instituted a step-based therapy approach that requires patients to have a documented failure on Prilosec OTC therapy prior to granting a prior authorization for a prescription product in the class. Most concerning is the fact that all of these actions were taken by MCOs despite the fact that Prilosec OTC is not equivalent to prescription Prilosec (product formulation, dosage form, approved indications, approved use/duration of therapy, and product labeling are significantly different between the OTC and Rx versions).