The Serious Public Health Dangers of Prescription-to-OTC Switch of Lovastatin

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In testimony before the FDA in June, 2000 concerning general switching principles for any drug, I discussed several prerequisites for the safe and effective switching of drugs from prescription to OTC status. They included:

> **1. Ease/possibility of accurate self-diagnosis--**presence or absence of symptoms which can accurately make the diagnosis (eg. pain, itching, cold, allergy symptoms) for which the drug is effective.
> **2. Benefit/risk ratio and its continued evaluation**--The continued evaluation of benefit and risk by the patient--arguably without any input from the physician--can significantly alter the ratio and hamper the need to keep it favorable for the patient. An elaboration of this is: **The number of adverse drug reactions or interactions and the ease of detecting them--** If there are numerous adverse reactions or interactions which may not be fully known to the patient (or physician who is not aware the patient is also using an OTC drug), there is even more cause for concern than the already-troublesome situation involving only prescription drugs. If the detection of the adverse reaction is hampered by the absence of signs which the patient can detect--such as abnormal laboratory tests which are an early signal of liver toxicity--the frequent absence of the physician's involvement because the drug is available OTC may be dangerous.

If any one of these criteria is not met, the decision to switch a drug to OTC is wrong from an overall public health perspective. If none of the conditions are met, the switch is likely to be an even greater public health disaster, having an overall negative effect on health. For the switch of any statin, in this case lovastatin, none of the conditions are met and it is virtually certain that more harm than benefit would accrue to such an ill-advised regulatory decision. Despite Merck and its highly-paid academic partners' efforts to paint this switch as something positive, the analysis by FDA, with which I concur, seriously undermines any such conclusion.

1. **Ease/possibility of accurate self-diagnosis.** Since the proposed use is primary prevention in people without symptoms, the correct assessment relies entirely on lab tests and the assessment of other risk factors. The data from Merck's studies of label comprehension and, separately, the actual use of lovastatin---despite the misleadingly positive spin by Merck---yield unacceptable results as far as the ability of very many patients to accurately assess all of the factors necessary to qualify as a candidate for OTC use of lovastatin.

a/ Label comprehension: "One percent of the respondents who stated they could use Mevacor OTC "right away" actually self-selected correctly according to the label. Ninety-nine percent of all the respondents who reported that they could start Mevacor OTC right away, self-selected incorrectly because they had at least one contraindication or did not meet eligibility criteria for use." (Page 2, FDA executive summary of Label Comprehension Study)

b/ Actual use study: "The current paradigm for the treatment of hypercholesterolemia is individualized, based on serum cholesterol levels and the presence of certain number of risk factors for CHD. The results of the Actual Use study show that the majority of consumers cannot correctly self-select to use lovastatin without an input of a health care provider." (page 65 of FDA Review of Consumer Behavior and Safety Data for the Non-Prescription Mevacor® 20 mg). On page 46 of this FDA document, the reviewer stated that "The most disturbing results are in self-selection. Over 80%v of subjects in the study did not self-select appropriately...Only 484 users initially self-selected correctly...and of those only 68 were able to do this without a physician's input. Nearly 1/3 of all users had a 10-year risk for CHD [coronary heart disease] of less than 5% [a level that clearly does not call for statin therapy."

2. **Benefit/risk ratio, its continued evaluation and adverse drug reactions or interactions and the ease of detecting them.** The continued evaluation of benefit and risk depends in part on the follow-up cholesterol levels to see if the drug is working and many patients did not have follow-up cholesterol levels. Among the adverse drug reactions that may be difficult to detect, in the absence of physician involvement in a prescription for this drug, and thereby intervene are asymptomatic elevations in liver enzymes after taking lovastatin and asymptomatic liver disease before using the drug. The onset of myositis (muscle inflammation), a possible predecessor to life-threatening rhabdomyolyis, may not alert the patient who is not necessarily under the supervision of a physician that reduction of dose or cessation of therapy may be necessary. A recent large case-control study from Italy has found a significant excess of peripheral nerve damage in patients using statins which the authors cautiously describe as hypothesis-generating that will have to be followed up with further investigation. The possible connection between this kind of problem and statin use may not be perceived by patients.[1]

Summary: Since, as is the case for a substantial percentage of those choosing to use the OTC version of this drug, their risk for CHD is so low that there is no evidence they will benefit from the drug, they are being subjected to the various risks of adverse reactions without any possibility of benefit. Thus the risks clearly outweigh

[1] Lipid lowering drug prescription and the risk of peripheral neuropathy: an exploratory case-control study using automated data bases. J Epidemiol Community Health 2004;58:1047-1051

the benefits for this group. These appalling results showing massive, incorrect self-selection for using this drug alone should prevent approval. In addition, it is clear that the availability of easy-to-get OTC statins will deter many from safer, less expensive preventive measures. Prevention of cardiovascular disease must be a multi-pronged strategy to reduce risk. The use of heavily advertised statins, out of the context of medical consultation, may impair the development of an integrated long-term strategy for preventing strokes or heart attacks. Diet and exercise, critically important components, may be thought to be less important if the primary strategy seems to be a statin drug.

The safety problems, although somewhat rare for statins other than Crestor, are especially hard to detect and monitor without physician involvement and, as mentioned above, must be viewed as unacceptable for the large proportion of people who can not possibly benefit from the drugs. Even for those who might theoretically benefit, the small fraction who self-selected properly, there is a serious question as to whether the 20 milligram dose confers any clinical benefit. In the FDA statistician's summary, there is a quote from Merck stating that because ½ the patients were titrated to the

40 mg dose [twice the OTC dose of 20 mg].... In fact the applicant [Merck] stated that because of the titration, "direct estimation of the

benefit of 20 mg ... is not possible" (page D-61 of the NDA). As was the case in 2000, your advisory committees and the FDA should promptly reject this application.