FDA Panels Vote Against Lovastatin's OTC Switch

Several panel members said a 'behind-the-counter' option would be optimal for the low-dose statin.

BY ELIZABETH MECHCATIE
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BETHESDA, MD. — Concerns about the ability of consumers to correctly select themselves for treatment without the advice of a health care professional, less-than optimal therapy in people who need higher doses, and unintended pregnancy exposures were among those cited by Food and Drug Administration advisory panel members who voted against making low-dose lovastatin available over the counter.

At a joint meeting of the FDA's Nonprescription Drugs and Endocrinologic and Metabolic Drugs advisory committees last month, the panel voted 20-3 against recommending approval of the 20-mg dose of lovastatin (Mevacor) for OTC use. Merck proposed that the daily 20-mg dose—at a price of about $1 per pill—be approved for OTC marketing for men aged 45 and older and women 55 and older who have a moderate risk for coronary heart disease (CHD), an LDL-cholesterol level of 130-170 mg/dL, and two risk factors.

Merck developed an OTC label to guide consumers in determining whether they are candidates for treatment, and conducted a large, actual use study and a label comprehension study. This is the second time the company has requested an OTC switch for lovastatin: in 2000, the 10-mg dose was reviewed and rejected by the advisory panels and FDA for OTC use because of safety and efficacy concerns.

Panel members unanimously agreed that the target population proposed by Merck for the 20-mg dose merited cholesterol-lowering treatment with a statin, and that 20 mg/day was an effective dosage that would help a proportion of the population reach an LDL-cholesterol level below 130 mg/dL.

They also agreed that the 20-mg lovastatin dose was safe to use in the nonprescription setting without monitoring liver function, and, except for one member, agreed that the risk of muscle toxicity associated with the 20-mg lovastatin dose was "acceptable for an OTC drug."

Several panel members who voted no said that they would have supported making the drug available OTC if there had been the option of "behind-the-counter" dispensing, which would give the pharmacists a role in counseling patients. This option is available in the United Kingdom, where the 20-mg dose of another Merck statin, atorvastatin (Zocor), was approved for OTC use last July. U.K. pharmacists are required to go over a questionnaire with prospective users and help them determine whether they are candidates for the lipid-lowering drug.

Michael McClung, M.D., director of the Oregon Osteoporosis Center, Portland, said he voted against approval not because he was concerned about effectiveness, but because of "my uncertainty about prospective patients to adequately assess their needs for choosing to take the therapy … and about whether this strategy is actually better than a physician-based approach."

Neal Benowitz, M.D., chief of the division of clinical pharmacology, University of California, San Francisco, said he was in favor of nonprescription lovastatin, "but not for the system as proposed." He said there needs to be a more adequate discussion of its benefits, better protection in terms of pregnancy risk, better care at the pharmacy level, and intervention on the part of the FDA to ensure that it would be marketed in a balanced way, if approved.

The three voting in favor of the approval included the panel chair, Alastair Wood, M.D., who said he believed that the 20-mg dose of lovastatin was safe and effective without the intervention of a physician.

"The vast majority of these [at risk] patients are receiving no therapy right now and should be," agreed Dr. Wood, professor of medicine and pharmacology, Vanderbilt University, Nashville.

One panelist noted that with mass marketing, women younger than the target range would ultimately buy this medicine, and put themselves at risk.

The actual use study presented to the panel was an uncontrolled, multicenter study of 3,316 people in 14 shopping malls across the country, aimed primarily at observing the initial decisions consumers made in deciding whether to purchase lovastatin, and to continue using it.

JAMES REINAKER

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Presenting the FDA analysis of the study, Daiva Shetty, M.D., of the division of OTC drug products, said that no new serious safety signals emerged, but the results indicated that OTC lovastatin would likely be used by women of childbearing age, consumers with contraindicated conditions, consumers with no or low CHD risk, and consumers at high risk for CHD.

Nearly 70% of users needed more information to decide whether to buy or use the product, nearly 48% were able to identify their LDL-cholesterol level, and 33% of users did not know their LDL-cholesterol levels at the initial visit. In addition, nearly 43% of users had fewer than two CHD risk factors, and 55% of users had one or more relative contraindications that were listed on the label. Of the users, 63% had a follow-up cholesterol test, as advised on the label, and 36% of those had achieved the LDL goal on the follow-up test.

Considering the actual use study, most of the panel said that while they agreed that the 20-mg dose was safe and effective, the results did not support the conclusion that the dose could safely and effectively be used in an OTC setting because of self-selection issues and the behavior of users after starting treatment. A large proportion of people in that study relied on a physician's advice for correctly self-selecting or self-diagnosing their need for a 20-mg dose, and most of the panel said that once OTC lovastatin was available, they would not expect consumers would have this much interaction with health care professionals about using it.

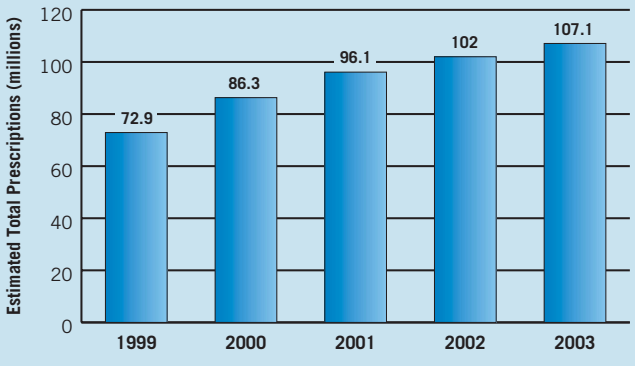
Furthermore, panelists generally agreed that the warning on the proposed label stating that the drug should not be used if pregnant or breast-feeding was inadequate. In the actual use study, nearly 41% of the users were women, but nearly 38% of these women were under age 55 and 22% were between the ages of 40 and 50 years, which includes women of childbearing potential, the FDA reviewer pointed out.

Like all statins, lovastatin is labeled pregnancy category X because there are no well-controlled studies in pregnant women, and there have been some postmarketing reports of fetal adverse effects on live births in pregnancies with first trimester exposure, as well as fetal and neonatal effects in animal studies, including skeletal anomalies at maternally toxic oral doses. This evidence would usually not result in a pregnancy contraindication for a drug, but because there is no benefit to temporarily treating hyperlipidemia during pregnancy, it is rated X.

Although lovastatin is available in generic form, if approved for OTC use, Merck would have exclusive rights to market it for 3 years. In December, Bristol-Myers Squibb announced plans to pursue approval of the 20-mg pravastatin (Pravachol) dose as an OTC treatment. ■

DATA WATCH

Statin Prescribing by All Physicians



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Statins Don't Raise Risk of Cancer

The longest follow-up of patients randomly assigned to receive either statin therapy or placebo has shown that the drugs do not raise cancer incidence or cancer mortality, though they do continue to exert beneficial cardiovascular effects, said Timo E. Strandberg, M.D., of Kuopio (Finland) University, and associates.

"Most statin trials, which generally last 5-6 years, have not shown any rise in cancer incidence in statin-treated participants, but in two studies some excess of cancer was reported," Dr. Strandberg and associates said. They examined cancer risk by extending the follow-up in their trial of more than 4,000 subjects in five Nordic countries (Lancet 2004;364:771-7).

During 10 years of follow-up, 100 subjects who had received placebo and 85 who had received simvastatin died from cancer, reflecting a slight but statistically insignificant reduction in cancer mortality with statin use. Similarly, the risk of developing cancer was 12% lower in the statin group than in the placebo group, a nonsignificant difference, the investigators said.

—Mary Ann Moon