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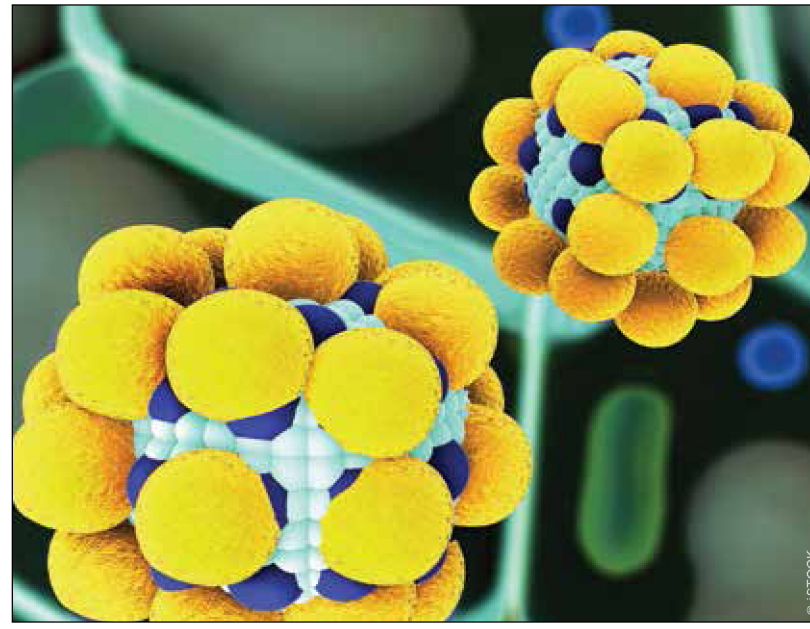
New Statin Risks and the Battle for OTC Status

The prescription-to-nonprescription switch process is a dynamic movement that has radically expanded the number of medical conditions for which consumers can self-medicate. Recent Rx-to-OTC switches include products for gastroesophageal reflux, overactive bladder in women, weight loss, and allergic conjunctivitis. However, the goal of moving cholesterol-lowering medications to nonprescription status has been elusive, despite vigorous efforts initiated by the manufacturers of these products.



Statins lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver.

The Push Begins

In 1997, the FDA revealed that "several sponsors" had approached the agency about the possibility of marketing nonprescription medications for hypercholesterolemia.[1] In response, the FDA stated that its Center for Drug Evaluation and Research (CDER) had determined that nonprescription status would not be appropriate. The FDA also announced the availability of a newly created guidance document that reflected its thinking on the issue. This document stated that hypercholesterolemia is a "chronic, asymptomatic condition" that requires an "accurate diagnosis, risk assessment, and potentially clinical testing to prevent atherosclerotic cardiovascular disease, and that the medical management should be directed by a healthcare professional."[2]

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The 2000 FDA Meeting

On June 1, 2000, the FDA announced that it had scheduled a joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee.[3] The meeting would consider two New Drug Applications (NDAs) submitted in 1999.[2] Merck proposed to switch Mevacor (lovastatin 10 mg) to OTC status, and Bristol-Myers Squibb wished to switch Pravachol (pravastatin 10 mg). In both cases, the patents were nearing their expiration date, and moving the products to nonprescription status could have extended the patent life for a few additional years.[4] Both manufacturers sought approval for treating patients with total cholesterol levels of 200 to 240 mg/dL and low-density lipoprotein (LDL) levels >130 mg/dL. Mevacor would have been labeled for men aged >40 years and postmenopausal women who did not have established cardiovascular disease or diabetes. Pravachol would have been labeled for individuals who did not have established cardiovascular disease or diabetes.

The FDA presented a set of slides for each NDA concluding that nonprescription status would not be appropriate, for a variety of reasons.[5,6] Among the deficiencies and remaining questions in one or both studies were: 1) concerns that a 10-mg dose of lovastatin might not be effective in altering lipids in the target population; 2) the study population was not representative of the overall U.S. population; 3) there was low consumer understanding of

specific serum cholesterol values; 4) patients in the study made a substantial number of self-selection errors; 5) there was poor adherence to therapy; and 6) significant numbers of patients may not understand who should not use the products.[2] Ultimately, committee members concluded that consumers would not be able to safely and appropriately self-manage hypercholesterolemia.

Guidance Document Withdrawn

Even though the outcome of the 2000 meeting was negative, the FDA recognized that "the public interest in the availability of safe and effective therapies to treat hypercholesterolemia warranted communication between FDA and industry to evaluate the feasibility of such therapies OTC."[2] Therefore, the FDA withdrew the guidance document, allowing the issue to be explored further. The FDA also sent a detailed letter to Merck describing the many deficiencies in its NDA for the lovastatin switch.[2]

The 2004 Lovastatin Resubmission

Apparently, Merck did not view the matter as closed. The manufacturer resubmitted its NDA in 2004, addressing the deficiencies listed by the FDA.[2] The proposed dosage was raised to 20 mg of lovastatin. Merck also published the results of the Consumer Use Study of OTC Mevacor (CUSTOM).[7] This actual use study found that a multifaceted cholesterol self-management program was effective in allowing patients to self-identify and safely use nonprescription lovastatin 20 mg. In response, the FDA announced another joint meeting of the same two committees to consider the switch of Mevacor for January 2005.[8]

Pharmacy Support Builds

Built into the 2004 resubmission was a proposal from Merck that lovastatin be dispensed only by pharmacists.[9] This required Merck to solicit the support of pharmacists for the switch. Major support arose in the American Pharmacists Association (APhA). The APhA began to speak of a "Pharmacy Care OTC" class of medications. The APhA created a task force to address the issue and presented its findings to the 2005 FDA meeting.[10,11] The remarks to the FDA meeting specifically spoke to lovastatin. While the stated mission of the task force was not limited to lovastatin, it is critical to note that the APhA apparently ceased its efforts to support the Pharmacy Care OTC category (at least under that name) after an FDA denial for the lovastatin switch appeared to be inevitable.

The 2005 FDA Meeting

At the 2005 meeting, committee members expressed concern that there were insufficient data regarding efficacy of a 20-mg dose of lovastatin when compared to usual care.[2] Furthermore, the results of the CUSTOM study were judged inadequate to support nonprescription sales of lovastatin. The FDA sent a letter to Merck detailing many deficiencies in its resubmission and denied the application. One member of the committee was quoted as stating that the CUSTOM study was a "failed study," adding that it was unconvincing.[12]

The 2007 Lovastatin Resubmission

Merck still saw a chance for OTC lovastatin. The manufacturer conducted two label comprehension studies; designed and carried out a self-selection study (known as the SELECT study); and amassed additional safety data, including an examination of safety in patients with underlying hepatic disease.[2] Merck also included a preliminary copy of a nonprescription package, complete with consumer labeling for the product, to be known as Mevacor OTC.[2]

The 2007 FDA Meeting

On October 23, 2007, the FDA announced that it would once again convene the two committees to consider the Merck submission at a meeting to be held on December 13, 2007.[13] News sources reported that the outcome was negative.[14] Apparently, in a study examining consumer behavior, 25% of people who wished to purchase Mevacor OTC had cholesterol levels so low that they were not at risk for heart disease. Even more compelling, 30% of people who were high-risk (having heart disease, diabetes, or stroke) wished to purchase Mevacor OTC, even though they should have chosen to seek the care of a physician. Additionally, 30% of patients already taking a stronger version of a prescription statin said they would stop taking that prescription statin and begin self-treatment with low-dose Mevacor OTC. The committee was concerned that this last group of patients would sacrifice proven protection and be at higher risk for heart attack.

Recent FDA Consumer Warnings

It is entirely possible that statin manufacturers still entertain hopes of gaining nonprescription status (see **SIDEBAR**), even though the matter appears to have been dormant since 2007. For this

Is There a Future for OTC Lipitor?

Lipitor (atorvastatin) was once the top-selling medication in the U.S., but sales nosedived when the generic version became available several years ago. The drug's manufacturer, Pfizer, is actively exploring an OTC switch for Lipitor in an effort to regain lost sales. The company enrolled 1,200 patients in a study to determine their ability to self-manage LDL-cholesterol with OTC Lipitor 10 mg.[18] Patients would be responsible for obtaining blood tests and making therapeutic decisions based on their results. If study outcomes proved to be positive, Pfizer would proceed with its FDA submission. The FDA website does not show such a submission at this time, so the matter may still be under consideration.

reason, it is instructive to examine recent FDA publications regarding statins. In early 2014, the FDA addressed several statin risks in a paper directed to consumers and professionals.[15] The agency stressed that package inserts would be revised to reflect any changes. For example, liver injury was characterized as a possible but rare risk of statin use. The FDA once required labeling recommending that statin users have regular liver enzyme tests. That warning was revised to recommend testing before beginning statin use and then as needed if there are symptoms of hepatic damage (e.g., unusual fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice of the skin or eyes).

The FDA also warned consumers that statins can cause memory loss, and that patients should speak to their physician if they experience symptoms of cognitive impairment, such as forgetfulness, memory loss, confusion, and unfocused thinking. The FDA also warned that statins raise blood glucose and may lead to type 2 diabetes, so that physicians should assess blood glucose levels during statin therapy. Finally, the FDA pointed out that it was revising the label for lovastatin to stress that there is an increased risk of myopathy when it is taken with certain medications.[15]

The 2014 NIH Cataract Warning

In December of 2014, the National Institutes of Health (NIH) issued a cataract warning about statins.[16] It summarized the results of a study that appeared in the *Canadian Journal of Cardiology*.[17] Researchers examined databases of statin users that spanned 8 years (British Columbia) and 11 years (U.S.); a total of 207,000 patient records were included. Among those who had taken statins for ≥1 year, the increased risk of developing cataracts that required surgery was 27% for Canadians and 7% for U.S. patients.

The NIH was careful to make several important points for readers: 1) statins protect many patients from heart attack and stroke; 2) the study under discussion was observational, so there is no positive proof that the statins were the direct cause of the cataracts; 3) the lifetime risk of developing cataracts is 100%, and statins may simply keep patients alive long enough for cataracts to develop; 4) cataracts are easily treatable with surgery that is quick and painless, and has a success rate of 99.9%; and 5) since patients are bound to develop cataracts, it is in their best interest to take statins, considering the far greater risk to their health of ceasing to take them.[16]

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PATIENT INFORMATION

How to Fight High Cholesterol

It is now common knowledge that there is a firm link between high cholesterol and heart disease. It is hard to know if you have high cholesterol, since it seldom causes any symptoms.

If you are worried about your risk for heart disease and wish to explore the possibility of high cholesterol, there are some actions you can take.

Ask Your Physician for a Blood Test

The first step is to ask your physician for a blood test to determine your blood cholesterol. The exam is known as a *lipoprotein profile*, and its purpose is to measure four markers: 1) total cholesterol, which should be below 200 mg/dl; 2) LDL or "bad" cholesterol, which should be less than 100 mg/dL; 3) HDL or "good" cholesterol), which should be 40 mg/dL or above; and 4) triglycerides, which should be less than 150 mg/dL. If your values are out of the normal range, your physician can create a treatment plan for you.

Begin a Healthy Diet

One of the primary risk factors for high cholesterol is a poor diet that results in obesity. Eating heathier foods has been proven to lower cholesterol. It is critical to avoid saturated fats, trans fats, and dietary cholesterol. Saturated fats are found in the following foods (which should be minimized as much as possible or avoided completely): high-fat cheese, high-fat meat cuts, whole milk, cream, butter, ice cream, palm oil, and coconut oil. To minimize trans fats, avoid fatty meat and dairy products (as above), and also hydrogenated oils. Dietary cholesterol is found in meat, poultry, egg yolks, and whole milk. The best advice for all of these issues is to switch to a low-fat diet and ingest only fat-free dairy products. Eating foods high in fiber can lower cholesterol as well.

Healthy Lifestyle Tips

There are several other lifestyle tips to keep cholesterol down and increase your chances of living a long, healthy life. Avoiding alcohol is important, as this can also keep triglycerides down. If you smoke, it is critical that you quit immediately. Smoking is damaging to your blood vessels, speeding the process of hardening of the arteries. If you stop smoking, you lower your risk of heart disease and stroke. A sedentary lifestyle is a major risk factor for high cholesterol. To combat this problem, begin an exercise program. Start slowly, with advice from your physician. In addition, if you also have diabetes or high blood pressure, follow your physician's advice to control these conditions.

PHARMACY STAMP

Common Cholesterol-Lowering Medications

You cannot self-treat high cholesterol by taking nonprescription products, no matter what the advertisements promise. In fact, no herbal supplement or vitamin is safe or effective for this use. However, there are several medications that your physician can prescribe. The most common is the group known as the *statins*. They include atorvastatin (Lipitor), lovastatin (Mevacor), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). Statins block one of the chemicals your body needs to make cholesterol. These drugs are generally safe, and your pharmacist or physician can explain the risks of their use.

Remember, if you have questions, Consult Your Pharmacist.