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Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville MD, 20857

Petition To Require A Box Warning on All HMG-CoA Reductase Inhibitors ("Statins")

Dear Dr. Woodcock:

We have analyzed 385 recent reports (from October 1997 through December 2000) of rhabdomyolysis (toxic destruction of muscle) in persons using the widely-prescribed class of cholesterol lowering 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor drugs known as (and hereafter referred to as) "statins" not including those in people using the recently withdrawn Baycol (cerivastatin). On the basis of these data, Public Citizen, representing 135,000 consumers nationwide, hereby petitions the FDA pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and C.F.R. 10.30, to add a black box warning and additional consistent bolded warnings about this serious problem to the label of all statins marketed in the United States. These include: atorvastatin (Lipitor, Pfizer), fluvastatin (Lescol, Novartis), lovastatin (Mevacor, Merck), pravastatin (Pravachol, Bristol-Myers Squibb), and simvastatin (Zocor, Merck). In addition, consumers must be warned through FDA-approved Medication Guides how to recognize early symptoms and take measures to prevent the evolution of this potentially life-threatening adverse effect of statins.

The importance of the relationship between statins and rhabdomyolysis has been heightened by the recent withdrawal of cerivastatin (Baycol, Bayer Corporation), due to reports of this adverse effect.[1] While cerivastatin accounted for slightly more than half of the 772 reported cases of rhabdomyolysis between October 1997 and December 2000, 385 cases of rhabdomyolysis and 52 rhabdomyolysis deaths were reported in association with the other statins. Most patients with rhabdomyolysis required hospitalization. An additional 29 deaths from rhabdomyolysis in people using statins other than cerivastatin were reported to the FDA prior to October, 1997 for a total of 81 deaths from rhabdomyolysis caused by statins other than cerivastatin. Despite the emphasis on the increased risk of rhabdomyolysis in people using both a statin and fibrates (other cholesterol drugs such as gemfibrozil), most of the cases of rhabdomyolysis in people using other statins--88%--occurred in those not using a fibrate.

Current labeling of those statins still on the market is extremely inconsistent and inadequate. While all labels discuss the risk of myopathy and rhabdomyolysis, none of them

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Seventy-two deaths were reported as a result of all of these cases (9.3% of the cases) including 52 deaths from statins other than cerivastatin, and over 85% of the cases required hospitalization. Deaths were reported with each of the six statins as seen in Table 2. Further analysis of FDA Adverse Event reports from 1966 through October 1997 (although Baycol was not marketed until early 1998, the first statin, lovastatin, was marketed in 1987) found an additional 29 deaths (22 with lovastatin, 6 with simvastatin, 1 with pravastatin) where the statin was listed as the "Suspect" and "myopathy " was listed as the adverse event (in the earlier data, rhabdomyolysis was not a search term). Thus, the 81 total number (52+29) of rhabdomyolysis deaths with the currently remaining statins include atorvastatin (Lipitor) 13 deaths; fluvastatin (Lescol) 1 death; lovastatin (Mevacor) 27 deaths; pravastatin (Pravacol) 10 deaths; and simvastatin (Zocor) 30 deaths.

Although much has been said of the increased risk of rhabdomyolysis in people using a statin and a fibrate, more than two-thirds (67.9%) of the reported cases of statin-associated rhabdomyolysis cases occurred when statins were not used concurrently with fibric acid derivatives. Three-quarters (75.0%) of the reported deaths occurred in the absence of concurrent therapy with fibrates. When cerivastatin is excluded from the analysis, 86.5% of reported deaths (88% of all cases) occurred in the absence of concurrent fibrate therapy.

Any analysis of the actual frequency of adverse events is complicated by the problem of under-reporting inherent in a voluntary reporting system such as the FDA AERS. Under-estimation of the frequency of actual events causes an under-estimation of the risks associated with a given drug based on spontaneous reporting alone. Estimates of the extent of under-reporting vary, usually ranging from 1% to 10%, and the reporting itself may be subject to biases relating to reporting environment, length of time on the market, and quality of data. In light of these limitations, it should be understood that the reports discussed in this petition represent an extremely conservative estimate of the true magnitude of the risks discussed. In addition, the data which the FDA has made available to the public only goes through the end of 2000 and thus our data does not include additional cases of rhabdomyolysis including deaths which were reported since then.

The October 1997 through December 2000 FDA database contains 399,142 manufacturer-reported adverse reaction reports. 1,804 reported cases of rhabdomyolysis are reported in the database. Cases of rhabdomyolysis associated with the use of statins account for 42.7% of these 1,804 cases. In contrast, of the 399,142 adverse reaction reports in the FDA database, 24,747, or 6.2% were for the six statins listed above. This 6.9-fold over-representation of statin use among cases of rhabdomyolysis strongly supports the causal role of these drugs.

Actions Requested

Black Box Label for HMG-CoA reductase inhibitors (statins)

The following black box warning should be required in the doctor and pharmacist labeling for all statins sold in the United States:

Rhabdomyolysis has been reported as a serious adverse effect of the use of all HMG-CoA reductase inhibitors. This is an infrequent but potentially life-threatening class effect of these drugs.

The risk of rhabdomyolysis has been reported to be increased with the concurrent use of certain in drugs, especially fibric acid derivatives such as gemfibrozil (see DRUG INTERACTIONS). However, most cases of rhabdomyolysis have occurred in people treated with HMG-CoA reductase inhibitors without concurrent fibrate therapy.

Onset of rhabdomyolysis is often preceded by muscle pain, muscle tenderness muscle weakness, tiredness and/or increases in serum creatine phosphokinase (CK) levels. Dark urine and fever may also be present in later stages of the disease. All patients using statins should be provided with this information.

The onset of muscle pain, muscle tenderness, muscle weakness or tiredness calls for immediate withdrawal of HMG-CoA reductase inhibitors and further evaluation by a physician including CK tests.

Strengthened Warning Labeling for all Statins.

Rhabdomyolysis has been reported with all statins currently marketed in the United States (see Table 1). Currently, only lovastatin and simvastatin contain any discussion of ways to reduce the risk of myopathy and rhabdomyolysis. This warning, in addition to the box warning, should be included on all statin labels.

WARNING – SKELETAL MUSCLE

Reducing the risk of myopathy.

1. **General measures. Patients starting therapy with statins should be advised of the risk of myopathy, and told to promptly report unexplained muscle pain, tenderness or weakness.** Elevated serum creatine phosphokinase (CK) levels are also indicative of myopathy. **Statin therapy should be immediately discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolve.
2. **Measures to reduce the risk of myopathy caused by drug interactions. Physicians contemplating combined therapy with statins and any of the interacting drugs (see DRUG INTERACTIONS) should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, weakness or tiredness.** Periodic CK determinations may be considered but there is no assurance that such monitoring will prevent myopathy.

Medication Guide–Informing the Public

It is mandatory that the public have information about this adverse reaction. The public must know when and how to react to protect themselves at the first sign of an adverse drug reaction. Serious muscle and kidney damage, and potentially death, may be averted only if the patients taking statins stop the drugs at the first sign of muscle pain or weakness.

In its announcement proposing Medication Guides (patient package inserts) to provide prescription drug customers with comprehensive and reliable drug information, the FDA stated "FDA believes that improved dissemination of information about prescription drug products is necessary to fulfill patients' need and right to be informed." Medication Guides are intended to be used in products "that pose a serious and significant public health concern" requiring immediate distribution of drug information to the public."[3]

The accumulating evidence presented in this petition clearly identifies the statins as drugs that pose a significant public health concern.

The following language is suggested for inclusion in all patient Medication Guides for all statin drugs:

> **The drugs known as statins include: atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), and simvastatin (Zocor). These drugs have been reported to cause rhabdomyolysis, a serious reaction characterized by the destruction of muscle tissue which can lead to kidney damage and death.**
>
> **This is an infrequent but potentially life-threatening adverse effect of all of the statin drugs.**
>
> **At the first sign of muscle pain, muscle tenderness, muscle weakness, tiredness or darkened urine, stop taking any statin drugs to reduce the likelihood that further muscle damage might occur and contact your doctor immediately to get a blood test for creatine phosphokinase (CK) and to discuss the use of alternative treatment plans. You should refrain from excessive exercise until the diagnosis of serious muscle damage can be excluded.**

Dear Doctor Letter

> Immediately require companies to inform all U.S. physicians about the risk of rhabdomyolysis with statin therapy through a "Dear Doctor" letter by registered mail.

Conclusion

Rhabdomyolysis is a serious adverse event associated with therapy with statins. If recognized early and treated properly, the progression from muscle pain and muscle weakness to myopathy and rhabdomyolysis can usually be arrested without any deleterious effects to the patient. In order to ensure that patients are aware of this potentially life-threatening adverse

reaction, regulated patient Medication Guides must be distributed with all prescriptions. In order to ensure that physicians and patients are properly informed of this adverse reaction and properly evaluate the risks and benefits of statin therapy, black box and bolded warnings must appear on all statin labels. A "Dear Doctor" letter is necessary to properly inform all physicians of these and any other changes to the labels of these drugs.

The withdrawal of cerivastatin due to cases of fatal rhabdomyolysis, along with the absence of any clear data indicating why any of the other statin drugs should be considered unique with regards to their association with drug-induced rhabdomyolysis illustrates the need to properly inform patients and physicians of the risks of this serious and preventable adverse event.

Environmental Impact

Nothing requested in this petition will have an impact on the environment.

Certification

We certify that, to our best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Chris Fischer, Staff Researcher

Sidney M. Wolfe, MD, Director

Larry Sasich, Pharm. D., MPH,
Staff Researcher

Peter Lurie, MD, MPH
Deputy Director

Table 1. Cases of Statin-Associated Rhabdomyolysis by Drug (October 1997 through December 2000

Drug	Number of Cases	Percent of Total Cases	Cases without Fibrates	Percent of cases without Fibrates
Atorvastatin	86	11.1%	73	84.9%
Cerivastatin	387	50.1%	187	48.3%
Fluvastatin	10	1.3%	8	80.0%
Lovastatin	32	4.1%	30	93.8%
Pravastatin	70	9.1%	62	88.6%
Simvastatin	187	24.2%	164	87.7%
TOTAL	772		524	67.9%

Table 2. Deaths reported in Statin-Associated Rhabdomyolysis (October 1997 through December 2000)

Outcome	Number of Cases	Percent of Total Deaths	Cases without Fibrates	Percent of cases of each drug without Fibrates
Deaths				
Atorvastatin	13	18.1%	11	84.6%
Cerivastatin	20	27.8%	10	50.0%
Fluvastatin	1	1.4%	1	100%
Lovastatin	5	6.9%	5	100%
Pravastatin	9	12.5%	8	88.9%
Simvastatin	24	33.3%	19	79.2%
TOTAL	72*		54**	75.0%

*- 2 deaths were reported where there was use of 2 statins concurrently (1 with cerivastatin and simvastatin, 1 with pravastatin and simvastatin)

** - 1 death with use of 2 statins (pravastatin and simvastatin)

[1] MacCarthy EP. Dear Healthcare Professional letter. Re: Market Withdrawal of Baycol (cerivastatin). August 8, 2001. http://www.fda.gov/medwatch/safety/2001/Baycol2.htm. Accessed August 10, 2001.

[2] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Journal of the American Medical Association. 2001;285:2486-2497.

[3] Food and Drug Administration. Prescription drug product labeling; medication guide requirements. *Federal Register* Vol. 60, No. 164. August 24, 1995.