

CITIZEN PETITION TO CHANGE THE LABELING FOR
ALL STATIN DRUGS (MEVACOR, LESCOL, PRAVACHOL, ZOCOR,
LIPITOR, AND ADVICOR) RECOMMENDING USE OF
100-200mg PER DAY OF SUPPLEMENTAL CO-ENZYME Q10
TO REDUCE THE RISK OF STATIN-INDUCED MYOPATHIES
(INCLUDING CARDIOMYOPATHY AND CONGESTIVE
HEART FAILURE).

May 24, 2002

Petitioner:

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Before the
Department of Health and Human Services
Food and Drug Administration
Washington, D.C.

In Re: Petition to)
Change the Labeling)
for all Statin Drugs (Mevacor,) Docket No. _____
Lescol, Pravachol, Zocor, Lipitor,)
and Advicor) to Recommend Use)
of 100 to 200mg Per Day of)
Supplemental Co-enzyme Q10 to)
Reduce the Risk of Statin-induced)
Myopathies (including Cardiomyopathy)
and Congestive Heart Failure))

CITIZEN PETITION

Julian M. Whitaker, M.D., by counsel, hereby submits this petition under Chapter 21,
Section 201.57 (e) and (f), of the Code of Federal Regulations.

I. ACTION REQUESTED

The undersigned requests that the Commissioner of Food and Drugs act immediately to
require that the labeling for all HMG Co-A reductase inhibitors (statins)' include the following
warning statement:

Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of **an** essential co-factor,
coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ is associated
with impairment of myocardial function, with liver dysfunction and with myopathies
(including cardiomyopathy and congestive heart failure). All patients taking HMG CoA
reductase inhibitors should therefore be advised to take 100 to 200 mg per day of
supplemental coenzyme Q₁₀.

¹ The statin drugs are Mevacor (lovastatin), Lescol (fluvastatin), Pravachol (pravastatin), Zocor
(simvastatin), Lipitor (atorvastatin), and Advicor (lovastatin).

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11. STATEMENT OF GROUNDS

A. Interest of the Parties

Dr. Julian M. Whitaker is a physician licensed to practice medicine in California and Washington state. He is the Clinical Director of the Whitaker Wellness Institute in Newport Beach, California. He is the editor of *Health & Healing*, the nation's largest single editor health newsletter with approximately 500,000 subscribers. Dr. Whitaker is the author of numerous books concerning aging and heart-related diseases, including *Reversing Heart Disease* (1985), *What Your Doctor Won't Tell You About Bypass* (1995), and *Is Heart Surgery Necessary: What Your Doctor Won't Tell You* (1997). Dr. Whitaker recommends the use of CoQ10 as a dietary supplement and also licenses the use of his name and likeness in connection with the manufacturing and sale of high quality dietary supplements, including CoQ10.

Dr. Whitaker prescribes statin drugs and is informed that long-term statin use may induce in some patients liver dysfunction and myopathies, including cardiomyopathy and congestive heart failure (CHF), due to the fact that statins block the endogenous biosynthesis of an essential co-factor required for energy production, coenzyme Q10. He therefore requests that the Commissioner of Food and Drugs act without delay to compel inclusion in all labeling for statin drugs, the above-referenced warning statement. The failure to do so promptly unnecessarily leaves long-term statin drug users (an estimated 125,000 to 575,000 patients) at risk of statin-induced liver dysfunction and myopathies, including cardiomyopathy and congestive heart-failure.

B. Nature of the Problem

1. Current Safety Concerns with Statin Drugs

HMG-CoA reductase inhibitors (also known as statins) are widely recognized as an effective method for lowering LDL cholesterol. While effective, there have been several adverse events associated with statins in humans. Reported adverse events include liver dysfunction, general muscle myopathy, skeletal muscle myopathy (rhabdomyolysis), and persistent elevations in serum transaminases. See, Physician's Desk Reference (PDR), pp. 809, 1695, 1778, 1863, and 2187 (52nd ed. 1998). The incidence of those adverse events increases with increases in the dose amounts administered. For those consuming 10mg to 20mg doses, the incidence is estimated at 0.2%. PDR at 2187. For those consuming 40mg doses, the incidence is estimated at 0.6%. Id. For those consuming 80mg doses, the incidence is estimated at 2.3%. Id.

Additionally, the PDR states that rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with Zocor (simvastatin) therapy. PDR at 1778. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the normal limit occurred in 0.5% of patients in the Mevacor clinical trials and in 0.1% of patients in the Pravachol clinical trials. PDR at 1696 and 809.

While current prescribing information for the various statin drugs contains some general information regarding the above-mentioned risks, there are no specific warnings available for physicians and patients in the prescribing information.

2. Statin Drugs and CoQ10

Statins have been shown in well-designed clinical trials to deplete an essential co-factor required for energy production, coenzyme q10 (“CoQ10”). As discussed in detail in the attached scientific report, CoQ10 is a substance found within the mitochondrial enzymes, which aids in the function of (by supplying energy to) cells with particularly high metabolic demands, such as those within the heart muscle. CoQ10 also has antioxidant functions and is the only known naturally occurring lipid soluble antioxidant for which the body has enzyme systems capable of regenerating the active reduced ubiquinol form. CoQ10 is thus a necessary and essential element in cellular energy production and in the functioning of the heart muscle due to the heart’s extraordinary energy requirements.

Statin drugs work by blocking the cellular production of cholesterol. That interaction occurs in the mevalonate pathway, where cholesterol is biosynthesized. The mevalonate pathway is also responsible, however, for the biosynthesis of CoQ10. Thus, the method by which statin drugs work to block cholesterol also causes them to block the production of CoQ10.

3. Dangers of CoQ10 Depletion

As the scientific report of Dr. Langsjoen’s explains (attached as Exhibit A), throughout various statin clinical trials there has been a frequent and significant depletion in CoQ10 levels, particularly when higher doses have been administered (and most notably in the elderly). With that depletion, studies have shown detrimental cardiac effects in humans (with pre-existing cardiac dysfunction) and in animals. CoQ10 is also known to be deficient in humans suffering from congestive heart failure. In patients with pre-existing congestive heart failure, the addition of statin therapy causes a decrease in blood CoQ10 levels and a decline in myocardial function. That decline can lead to the onset of cardiomyopathy, a disease that weakens the heart muscle

and may result in death. Because statin drugs have become some of the most widely prescribed drugs in America with many millions of patients taking them on a regular basis (and since the National Cholesterol Education Program guidelines call for millions more with low-normal LDL levels to be treated with statins), it is imperative that physicians be forewarned about the very real risks associated with CoQ 10 depletion and of the need for prophylactic supplementation with CoQ10 to reduce those risks.

In apparent recognition of the dangers associated with statin-induced CoQ 10 depletion, Merck has obtained patents to combine CoQ10 with its statin drugs. See Exhibit B (the Merck patents). Merck describes the risks of CoQ10 depletion as follows: “The most serious reported adverse effects of lovastatin, a commercially available HMG-CoA reductase inhibitor, are myopathy and asymptomatic but marked and persistent increases in liver transaminases. . . . [CoQ10] is . . . an essential co-factor in the generation of metabolic energy and may be important in liver function.” Exhibit B, Patent No. 4,929,437, at 2. A second Merck patent states: “[CoQ 10 supplementation] would be of considerable benefit to counteract the myopathy observed in a small percent of patients. Since CoQ10 is of benefit in congestive heart failure patients, the combination with [statins] should be of value in such patients who also have the added risk of high cholesterol levels.” Exhibit B, Patent No. 4,933,165, at 2. Merck’s patents would preclude other companies from combining CoQ 10 with statins in a single-dose form. That fact underscores the critical need for FDA to add the requested Warning statement to alert physicians of the need for CoQ 10 supplementation to offset statin-induced CoQ10 depletion arising from use of those statins that are not combined with CoQ 10 in a single-dose form.

According to the PDR, an estimated 0.5% to 2.3% of patients who use statins experience adverse events (including myopathies). Physicians’ Desk Reference, pp. 1696 and 2187 (52nd

ed. 1998). Applying that percentage to the universe of patients now treated with statins (approximately 25,000,000 people worldwide*) yields an estimated 125,000 to 575,000 patients who can be expected to experience adverse events, including myopathies.

4. Benefits of CoQ10 Supplementation

Fortunately, the decrease of CoQ10 levels associated with statin drug medication is not irreversible. Replenishing the diminished levels of CoQ10 can be achieved through oral supplementation. Oral supplementation is necessary, as CoQ10 is not obtainable from daily dietary sources in the amounts (i.e., 100-200 mgs) needed to bolster statin-induced reductions in CoQ10 deficiency levels.

In the attached report, Dr. Langsjoen concludes that the ingestion of supplemental CoQ10 can prevent statin-induced CoQ10 deficiencies without affecting the cholesterol-lowering efficacy of statins. He also states that supplementation can reverse any CoQ10 depletion that may have occurred as a result of the statins.

CoQ10 supplementation is an easy, economically-feasible remedy to prevent and/or reverse the dangerous CoQ10 depletion effects of statins. The FDA should therefore act immediately to protect public health against foreseeable patient risks, including heart damage and death, by requiring use in all statin labeling of the Warning recommended here.

5. CoQ10 Safety

According to Dr. Langsjoen's attached report, Coenzyme Q₁₀ is sold in the United States and abroad as an over-the-counter dietary supplement and is widely recognized as completely safe with no reported toxicity in over a thousand published human and animal trials. As he discusses, the most recent animal safety study was published in 1999 by Williams et al. Potential CoQ₁₀ toxicity was assessed in rats administered CoQ₁₀ by oral gavage for 1 year at 100,300,

² Q & A: Heart Drugs Study, BBC News, November 13, 2001.

600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology results were observed.

III. Environmental Impact

The requested action will not result in the introduction of any substance into the environment and is thus categorically excluded under the provisions of 21 C.F.R. 525.30.

IV. Conclusion

In addition to potential risks of liver dysfunction and rhabdomyolysis, all prescribing physicians and pharmacists need to be informed that statin drugs produce a depletion in CoQ10, which increases the risk of myopathies and which in settings of pre-existing CoQ10 deficiency, such as congestive heart failure and aging, may worsen markedly myocardial function.

Accordingly, to reduce that risk, the Commissioner of Food and Drugs should act immediately to require the following warning in the labeling for all statin drugs:

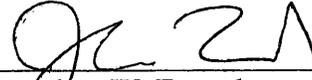
Warning:

HMG CoA reductase inhibitors block the endogenous biosynthesis of an essential co-factor, coenzyme Q₁₀, required for energy production. A deficiency of coenzyme Q₁₀ is associated with impairment of myocardial function, with liver dysfunction, and with myopathies (including cardiomyopathy and congestive heart failure). All patients taking HMG CoA reductase inhibitors should therefore be advised to take 100 to 200 mg per day of supplemental coenzyme Q₁₀.

V. Certification

The undersigned certifies, that, to his 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 petitioner, none of which is unfavorable to the petition.

Respectfully submitted,
DR. JULIAN M. WHITAKER



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