

CITIZEN PETITION FOR AN ORDER REQUIRING ISSUANCE  
AND DISTRIBUTION OF A MEDICATION GUIDE 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:

Dr. Julian M. Whitaker, M.D.

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

In Re: Petition for an Order Requiring )  
Issuance and Distribution of a )  
Medication Guide for )  
all Statin Drugs (Mevacor, ) Docket No. \_\_\_\_\_  
Lescol, Pravachol, Zocor, Lipitor, )  
and Advicor) Recommending )  
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), and Section 208 of the Code of Federal Regulations, requesting that  
the Commissioner of Food and Drugs declare statin-induced deficiency of coenzyme Q10  
(CoQ10) a “serious and significant concern” and thus order distribution of a Medication Guide  
defining the adverse health effects possible with all statin drugs.’

**I. ACTION REQUESTED**

FDA requires the distribution of patient labeling, called Medication Guides, for certain  
products that pose a serious and significant public health concern. Under 21 C.F.R. 218.1, ,  
patient labeling is required if FDA determines that any of the following circumstances exists:

- 1) the drug product is one for which patient labeling could help prevent serious adverse effects;
- 2) the drug product is one that has serious risk(s) (relative to benefits) of which patients should  
be made aware because information concerning the risk(s) could affect patients’ decision to use,

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

or continue to use, the product; or 3) the drug product is important to health, and patient adherence to directions for use is crucial to the drug's effectiveness.

Because the various adverse events associated with statin drugs, including liver dysfunction, myopathies (including cardiomyopathy and congestive heart failure), and statin-induced coenzyme Q10 depletion (described *infra*), pose a threat to patient health, the undersigned requests that the Commissioner of Food and Drugs declare such adverse events a "serious and significant concern" and that he order the issuance and distribution of a Medication Guide defining the adverse health effects possible.

## **II. STATEMENT OF GROUNDS**

### **A. Interest of the Parties**

Dr. Julian 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 health 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. He 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 Drug act without delay to order the issuance and distribution of a Medication Guide defining the adverse health effects possible from the use of statins. 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 (52<sup>nd</sup> 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 or medication guides 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**

The scientific report of Dr. Langsjoen (attached as Exhibit A) explains that statins induce frequent and significant depletions 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 CoQ10 depletion and of the need for prophylactic supplementation with CoQ10 to reduce those risks.

In apparent recognition of the dangers associated with statin-induced CoQ10 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: “[CoQ10 supplementation] would be of considerable benefit to counteract the myopathy observed in a small amount 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 CoQ10 with statins in a single-dose form. That fact underscores the critical need for FDA to issue the requested Medication Guide to alert physicians

and patients of the need for CoQ 10 supplementation to offset statin-induced CoQ 10 depletion arising from use of those statins that are not combined with CoQ10 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 (52<sup>nd</sup> ed. 1998). Applying that percentage to the universe of patients now treated with statins (approximately 25,000,000 people worldwide<sup>2</sup>) 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 CoQ 10 is not obtainable from daily dietary sources in the amounts (i.e., 100-200 mgs) needed to counteract statin-induced reductions in CoQ 10 levels.

In the attached report, Dr. Langsjoen concludes that the ingestion of supplemental CoQ10 can prevent statin-induced CoQ 10 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.

CoQ 10 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 liver dysfunction, rhabdomyolysis, heart damage and death, by requiring distribution of the Medical Guide recommended here.

## **5. CoQ10 Safety**

According to Dr. Langsjoen's attached report, Coenzyme Q<sub>10</sub> 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 CoQ<sub>10</sub> toxicity was assessed in rats administered CoQ<sub>10</sub> by oral gavage for 1 year at 100, 300, 600, and 1200 mg per kg body weight per day. No adverse changes in mortality, clinical signs, body weight, food consumption, or clinical pathology 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. §25.30.

### **IV. Conclusion**

In addition to potential risks of liver dysfunction and rhabdomyolysis, all patients need to be informed that statin drugs produce a depletion in CoQ<sub>10</sub>, which increases the risk of myopathies and which in settings of pre-existing CoQ<sub>10</sub> deficiency, such as congestive heart failure and aging, has the ability to worsen myocardial function. Accordingly, to reduce that risk, the Commissioner of Food and Drug should act immediately to require that a Medication Guide warning of the dangers and explaining the need for CoQ<sub>10</sub> supplementation be included with statin drug prescriptions.

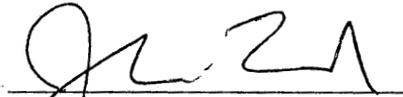
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<sup>2</sup> Q & A: Heart Drugs Study, BBC News, November 13, 2001.

**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

A handwritten signature in black ink, appearing to read 'J. W. Emord', written over a horizontal line.

Jonathan W. Emord  
Jonathan I Goodman  
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