



08-12-04P03:38 RCVD

August 10, 2004

**BY FEDERAL EXPRESS**

Lester Crawford, DVM, Acting Commissioner  
Food and Drug Administration (HF-1)  
5600 Fishers Lane  
Rockville, MD 20857

RE: Adverse Event Reporting for CRESTOR® (rosuvastatin calcium)

Dear Dr. Crawford:

AstraZeneca Pharmaceuticals submits this letter in response to the letter submitted on August 3, 2004 by Sidney M. Wolfe, M. D., Director of the Public Citizen's Health Research Group ("HRG"), unjustly accusing AstraZeneca of delaying the submission of adverse event reports associated with CRESTOR. HRG's accusations are without basis in either fact or law and its request for a "criminal investigation" must be rejected.

HRG's position is that AstraZeneca must report all cases of rhabdomyolysis or kidney failure associated with CRESTOR within 15 days under FDA regulations. It claims that under those regulations, rhabdomyolysis and kidney failure constitute an "unexpected" adverse event subject to the 15-day reporting requirement. HRG argues that rhabdomyolysis is "unexpected" because the label for CRESTOR refers to rhabdomyolysis only at 80mg dosages. This, however, is simply not true. As HRG knows and as is shown below, the labeling for CRESTOR specifically and prominently identifies rhabdomyolysis as a possible adverse event without limiting the event to a particular dosage. In addition, the label separately identifies "rhabdomyolysis" and "kidney failure" in the adverse reactions section. Because these events are identified in the labeling, they are "expected" and not subject to the 15-day reporting requirement.

I. Background

HRG's letter is the latest chapter in an ongoing crusade to damage the reputation of AstraZeneca and CRESTOR. On July 9, 2003, HRG was afforded the opportunity to present its views about CRESTOR's approval at an FDA Advisory Committee meeting. HRG's presentation focused on claims of rhabdomyolysis and kidney toxicity, primarily at the 80 mg dose for which AstraZeneca did not seek marketing approval. Despite HRG's arguments, the Advisory Committee unanimously recommended that CRESTOR be approved and, on August 12, 2003, FDA agreed.

In March of 2004, HRG again attacked CRESTOR by submitting a Citizen's Petition demanding that FDA withdraw approval of CRESTOR. See FDA Docket No. 2004P-0113. The petition recycled essentially the same arguments that were presented to the Advisory Committee in 2003. In July 2004, AstraZeneca submitted a well-documented response to

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2004-4456

HRG's petition demonstrating that HRG's accusations were based on faulty science and failed to recognize CRESTOR's substantial benefits.

Shortly after AstraZeneca responded to HRG's petition to withdraw CRESTOR, HRG renewed its attack on CRESTOR. In its August 3, 2004 letter, HRG contends that AstraZeneca has received reports of adverse events involving rhabdomyolysis or primary kidney failure, but has failed to report many of them as 15-day alerts. HRG's contention, however, rests on the inaccurate premise that AstraZeneca was required to report all rhabdomyolysis or kidney failure events as 15-day alerts. As is shown below, AstraZeneca was not required to report the events at issue as 15-day alerts and in fact reported each and every one of them in a timely and responsible manner. Thus, AstraZeneca has fully complied with FDA's reporting requirements.

## II. AstraZeneca Fully Complied With FDA's Reporting Requirements

Section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act requires manufacturers of drugs approved under an NDA to "establish and maintain such records, and make such reports to the Secretary of data relating to clinical experience." 21 U.S.C. § 355 (k)(1). FDA's implementing regulations require a manufacturer to "report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant." 21 C.F.R. § 314.80(c)(1)(i). An "unexpected adverse drug experience" is defined as "any adverse drug experience that is not listed in the current labeling for the drug product. . . . Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling). . . ." 21 C.F.R. § 314.80(a).

Contrary to HRG's claim that the label for CRESTOR only references rhabdomyolysis with respect to the 80 mg dosage of CRESTOR, the package insert (enclosed as Exhibit A) clearly includes this potential adverse event in several sections, without reference to a particular dose. In particular, the label describes *in bold print* under the Warnings section that

**Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.**

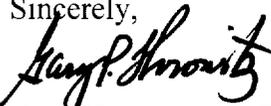
This warning contains no reference to any particular dose of CRESTOR. Furthermore, the label separately identifies "rhabdomyolysis" and "kidney failure" in the adverse reactions section. Again, these potential adverse events are not linked to any particular dose of CRESTOR.

Because these events were identified in the labeling for CRESTOR, they are not "unexpected adverse drug experiences" requiring a 15-day alert. An adverse event that is not unexpected must be reported to FDA in a "periodic" report, which for the first three years following

approval must be submitted on quarterly basis. 21 C.F.R. § 314.80(c)(2). HRG's letter acknowledges that AstraZeneca reported all of these events in its periodic reports.

HRG also points out that AstraZeneca has reported several events to FDA involving rhabdomyolysis as 15-day alerts. In some instances, however, other serious adverse events were also reported that were not included in the labeling, thus prompting the 15-day reporting. In addition, on a few occasions, AstraZeneca submitted a 15-day alert, in accordance with 21 C.F.R. § 314.80(a), if the event was considered of greater severity or specificity than might otherwise be expected. The fact that AstraZeneca submitted these reports, therefore, should not be taken to mean that every event involving rhabdomyolysis or kidney failure is reportable as a serious and unexpected adverse event.

AstraZeneca's highest priority is patient safety. The Company is committed to the active review and monitoring of all safety information regarding all its products, including CRESTOR. HRG's letter threatens to cause undue concern for the millions of patients that rely on CRESTOR to help manage their cholesterol levels. AstraZeneca appreciates your consideration of these issues and would be willing to provide additional information or arrange a meeting in order to facilitate a prompt resolution.

Sincerely,  
  
Gary Horowitz, Ph.D  
Executive Director, Regulatory Affairs

Enclosure

cc: Glenn Engelmann, Esq.  
Vice President, General Counsel & Compliance Officer  
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