



November 3, 2004

Lester Crawford, DVM, Acting Commissioner
Department of Health and Human Services
Food and Drug Administration
HF-1, Room 1471
5600 Fishers Lane
Rockville, MD 20857

Re: CRESTOR[®] (rosuvastatin calcium) Tablets
Response to the recent Public Citizen's Health Research Group Letter

Dear Dr. Crawford:

Enclosed please find the response of AstraZeneca Pharmaceuticals LP (AstraZeneca) to the Public Citizen Health Research Group's letter of October 29, 2004 to you regarding CRESTOR[®] (rosuvastatin calcium) Tablets.

We are simultaneously forwarding the required copies of this response to the Dockets Management Branch of the Food and Drug Administration for filing to the open citizen petition docket (FDA Docket #2004-0113) regarding CRESTOR[®] (rosuvastatin calcium) Tablets.

Most sincerely,

A handwritten signature in black ink that reads "Anthony F. Rogers" with a stylized flourish at the end.

Anthony F. Rogers
Vice President, Regulatory Affairs
Telephone: (302) 886-2127
Fax: (302) 885-5334

AFR/giw
Enclosures

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Dr. Steven K. Galson, Center Director
Department of Health and Human Services
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-001, Room 7100
5515 Security Lane
Rockville, MD 20852

Dr. John Jenkins, New Drugs Director
Department of Health and Human Services
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-020, Room 7220
5515 Security Lane
Rockville, MD 20852

Dr. Robert Temple, Associate Director for Medical Policy
Department of Health and Human Services
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-40, Room 7201
5515 Security Lane
Rockville, MD 20852

Dr. Robert Meyer, Office of New Drug Evaluation Director
Department of Health and Human Services
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-102, Room 13B28
5600 Fishers Lane
Rockville, MD 20857

Dr. David G. Orloff, Review Division Director
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-510, Room 14B-45
5600 Fishers Lane
Rockville, MD 20857

Division of Dockets Management
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20857

November 3, 2004

Lester Crawford, DVM, Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20854

Dear Dr. Crawford,

We have received the October 29, 2004 “supplement” to the Public Citizen Health Research Group (HRG) petition concerning CRESTOR[®] (rosuvastatin calcium). Once again, we find ourselves compelled to respond to the inaccurate and misleading claims made by that organization to ensure that you and the millions of CRESTOR patients around the world have the most complete, up-to-date, and accurate information on CRESTOR. Left unchecked, HRG’s inaccurate and misleading claims could unnecessarily alarm physicians, other healthcare providers, and their patients. Importantly, these claims may lead to reduced use of statins in patients who need these medications.

At the outset, it should be clear that AstraZeneca’s highest priority is patient safety. AstraZeneca operates diligently in accordance with FDA reporting procedures and the ongoing pharmacovigilance program for CRESTOR. CRESTOR has been on the market for more than 18 months and has been prescribed more than 11.5 million times. All of the data continue to confirm a proven safety profile that is in line with that of other marketed statins. Moreover, to ensure that up-to-date scientific information about CRESTOR is fully accessible to prescribing physicians and their patients, we recently launched our scientific web site www.rosuvastatininformation.com, where information on clinical studies and post-marketing data for CRESTOR are fully accessible. AstraZeneca has shared these data with the FDA.

In response to specific allegations made in HRG’s letter, please consider the following:

Comprehensive and thorough analysis of the safety data for CRESTOR continues to demonstrate a positive benefit-risk profile.

- According to the FDA Freedom of Information database, there are reports of renal failure, renal impairment and renal disorders in patients taking each of the currently marketed statins. Such reports are very rare (<0.01%) and those for CRESTOR are no exception.
- HRG has based its claims on 29 US spontaneous reports of renal failure from the FDA Adverse Event Reporting System (AERS) database. AstraZeneca reviews all safety reports for CRESTOR on an ongoing basis. To date, a medical review of all reports of acute renal failure or renal insufficiency, including those in the FDA AERS database, as mentioned by HRG, have either limited information for evaluation or have confounding factors suggestive of an alternative cause other than CRESTOR for the renal events. The clinical evidence does not suggest a causal relationship between CRESTOR and these renal events.
- HRG again reports that preapproval, cases of rhabdomyolysis were seen with CRESTOR in clinical trials. This statement is misleading. In fact, there were no cases of rhabdomyolysis reported for CRESTOR before approval in the marketed dose range of 5–40mg. Since approval, in clinical trials worldwide, with over 45,000 patients having received CRESTOR, only 2 cases of rhabdomyolysis have been reported (<0.01%). This rate is very much in line with the reported rate for rhabdomyolysis seen in large-scale trials with statins.¹
- HRG cites that the post-marketing rate of reported rhabdomyolysis for CRESTOR is similar to that reported for cerivastatin in the first year following approval. This comparison is inaccurate and misleading. Importantly, at the time of withdrawal in August 2001, cerivastatin had been prescribed about 9.8 million times and there had been reports of 31 fatal cases of rhabdomyolysis,

as reviewed by the FDA.² In contrast, with over 11.5 million CRESTOR prescriptions worldwide to date, there have been no fatal cases of rhabdomyolysis meeting the FDA criteria, as reported by Staffa et al.²

AstraZeneca uses the most appropriate, accurate and complete resources and data to analyze the wealth of renal information pertaining to comparator statins and CRESTOR specifically.

- The most accurate way to measure a drug's effects on renal function is through well-controlled clinical studies, which have greater scientific rigor than unsubstantiated spontaneous adverse event reporting.
- In data from clinical trials with over 10,000 patients receiving CRESTOR at its recommended dose range for up to 3.8 years, renal function, as assessed by glomerular filtration rate, was stable or slightly improved during CRESTOR therapy, even in patients with pre-existing renal disease or other risk factors for same.³
- In clinical trials, dipstick-positive proteinuria was seen in a small number of patients receiving CRESTOR, comparator statins, or placebo.³ This finding, when seen with CRESTOR, was generally transient and was not associated with worsening renal function.^{3,4}

The frequency of reported cases of renal failure for CRESTOR remains very rare and consistent with the data from preapproval clinical trials.

- Data from large epidemiologic evaluations show the incidence of acute renal failure in the community to be estimated at approximately 200 cases per million, distributed over the entire population independent of age or renal disease risk factors.⁵⁻⁷
- The reported rate of renal failure in patients receiving CRESTOR is less than the background incidence rate observed in the community.

We appreciate your consideration of these facts and look forward to working closely with you and healthcare providers to ensure that patients have access to all the facts about CRESTOR. AstraZeneca is fully confident in the safety and efficacy of CRESTOR and will continue to support its appropriate use for the millions of patients around the world who struggle to successfully manage their elevated cholesterol levels. We, once again, reiterate our request that HRG's petition concerning CRESTOR be denied.

Thank you for your consideration.

AstraZeneca Pharmaceuticals LP
Wilmington, Delaware
www.astrazeneca-us.com

References

1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Saf* 2000;23:197-213.
2. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. Correspondence. *N Engl J Med* 2002;346:539-540.
3. Vidt DG, Cressman MD, Harris S, Pears JS, Hutchinson HG. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology* 2004;102:52-60.
4. CRESTOR (rosuvastatin calcium) US prescribing information.
5. Liano F, Pascual J. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. *J Kidney Int* 1996;50:811-818.
6. Metcalfe W, Simpson M, Khan IH, Prescott GJ, Simpson K, Smith WC, MacLeod AM; Scottish Renal Registry. Acute renal failure requiring renal replacement therapy: incidence and outcome. *QJM* 2002;95:579-583.
7. Robertson S, Newbigging K, Isles CG, Brammah A, Allan A, Norrie J. High incidence of renal failure requiring short-term dialysis: a prospective observational study. *QJM* 2002;95:585-590.