



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 11 2005

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Sidney M. Wolfe, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, N.W.
Washington, DC 20009-1001

Re: Docket No. 2004P-0113/CP1

Dear Dr. Wolfe:

This responds to your citizen petition submitted March 4, 2004 (Petition), requesting that the Food and Drug Administration (FDA) immediately remove from the market Crestor (rosuvastatin), manufactured by AstraZeneca Pharmaceuticals LP (AstraZeneca), before additional cases of rhabdomyolysis and kidney failure or kidney damage occur.

We have carefully reviewed your petition and the supplements you submitted on May 18 and October 29, 2004, and March 10, 2005. We also reviewed comments on the petition submitted by AstraZeneca on July 20, August 16, and November 5, 2004, as well as comments submitted by John Blenkinsopp, M.D., on August 11, 2004. For the reasons stated below, your request that we immediately remove Crestor from the market is denied. To address certain concerns related to the use of Crestor, AstraZeneca has agreed to revise Crestor's labeling and to issue a Dear Healthcare Professional letter describing these changes. We will continue to closely monitor ongoing clinical trials and adverse event reports involving Crestor, and we will take further action if needed to protect patients.

I. BACKGROUND

A. Rosuvastatin

Rosuvastatin is a lipid-altering drug in the class of drugs known as *statins*. As a class, statins have been shown to lower cholesterol, which can further reduce the risk of cardiovascular mortality and morbidity. The new drug application (NDA) for Crestor was the seventh NDA for a statin that we approved. Rosuvastatin exhibits the following characteristics:

- Rosuvastatin is 2 to 4 times as potent per mg for lowering low-density lipoprotein (LDL) as atorvastatin, a frequently prescribed, potent statin and the last statin that we approved before Crestor.
- Rosuvastatin is not metabolized by CYP 3A4, an enzyme involved in the metabolism of numerous drugs. This is an important safety distinction

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between rosuvastatin and simvastatin, lovastatin, and atorvastatin, which are metabolized by CYP 3A4. Concomitant use of drugs that inhibit CYP 3A4 (e.g., cyclosporine, ketoconazole, erythromycin) with simvastatin, lovastatin, and atorvastatin has been a common factor in numerous instances of myopathy and rhabdomyolysis. Rhabdomyolysis is the most severe manifestation of muscle toxicity and an extremely rare event among users of marketed statins (estimated at 1 in 10,000 patients).

Crestor was the first statin NDA considered for approval after the August 2001 withdrawal of the statin Baycol (cerivastatin) from worldwide markets. We estimate that Crestor has one-twentieth to one-tenth the potency per mg of Baycol for lowering LDL.

B. Baycol Withdrawal

Baycol was withdrawn because the risk of muscle toxicity with Baycol far exceeded that of other statins. Comparisons of the myotoxic potential of Baycol and other statins demonstrated that no constant relationship between cholesterol-lowering effect and myotoxicity exists across the class, which was contrary to widespread assumptions before the withdrawal of Baycol. Specifically, Baycol was markedly myotoxic at doses that were relatively ineffective in lowering cholesterol. Although the myotoxicity of Baycol only became clear following the approval (in a supplement to the NDA) of the 0.8-milligram (mg) dose, based on the relatively poor efficacy of even this highest dose of cerivastatin, we concluded that the risk-benefit balance for cerivastatin was far inferior to that of other statins.

C. FDA Review and Approval of Crestor

AstraZeneca submitted the NDA for Crestor in June 2001, requesting approval of 10-mg, 20-mg, 40-mg, and 80-mg doses of rosuvastatin. During the first review cycle, two safety issues arose. First, there were six cases of rhabdomyolysis among 1,365 patients exposed to the 80-mg dose dose (0.4 percent incidence).

In addition, urine abnormalities, specifically proteinuria (an excess of serum proteins in the urine) and hematuria (blood in the urine), not previously noted in the review of other statin drug applications and not known to occur with this class, were observed sporadically in a small percentage of rosuvastatin-treated patients, with the highest incidence occurring at the 80-mg dose.¹ The incidences of proteinuria and hematuria in these Crestor patients were detected through dipstick assays on spot urine specimens. The absence of adequate controls (e.g., patients receiving a placebo) and of formal, timed urine collections did not permit a full assessment of the nature and magnitude of this presumed drug effect on the kidney.

¹ Although proteinuria and hematuria might be signals of renal injury, they are also a part of normal physiological processes. For example, humans secrete/excrete a small amount of protein in urine, and exercise may produce microscopic hematuria.

Two cases of renal failure and one case of renal insufficiency occurred in patients treated with rosuvastatin 80 mg. The patient who developed renal insufficiency had a positive dechallenge (the adverse event resolved after administration of the drug ceased) and a positive rechallenge (resuming administration of the drug led to return of the adverse event) with both rosuvastatin and atorvastatin, suggesting an idiosyncratic sensitivity to statins. The two cases of renal failure were significantly confounded by diagnoses predisposing patients to renal disease as well as by potential clinical contributors to the development and/or progression of renal disease, making attribution of the adverse event to rosuvastatin far from definitive.

These findings necessitated a thorough evaluation to ensure that rosuvastatin had a favorable risk-benefit profile. Consequently, we required AstraZeneca to provide additional data to demonstrate that the myotoxic potential across the proposed doses of rosuvastatin was not markedly different from that of other statins relative to LDL-lowering efficacy. We also required additional investigations of the renal effects of rosuvastatin to determine whether these urinary findings represented a true "toxic" effect and thus a risk for serious kidney injury.

Because the 80-mg dose of rosuvastatin had been associated with multiple cases of rhabdomyolysis and was only marginally more effective than the 40-mg dose, we concluded that the 80-mg dose was not acceptable for marketing. We made this decision despite the fact that the proposed 80-mg dose would have been labeled for use only in patients with severe hypercholesterolemia and marked coronary heart disease (CHD) risk (e.g., heterozygous familial hypercholesterolemia).

The question remained whether the cases of rhabdomyolysis observed at 80 mg were simply indicative of having "pushed" the dose of rosuvastatin too far, engendering rhabdomyolysis, which is a known, accepted, and not always avoidable adverse effect of sufficiently high doses of all statins. Alternatively, these events might have marked a drug with greater intrinsic myotoxicity than the marketed statins. We needed to resolve this question before we could approve any doses of rosuvastatin. Relatively few patients had been treated with the 20-mg and 40-mg doses of rosuvastatin in the original submission. As a result, the database was inadequate to exclude the possibility that rosuvastatin was, like Baycol, unacceptably myotoxic when compared to other statins at doses with comparable or greater LDL-lowering effects.

Therefore, on May 31, 2002, we sent AstraZeneca an approvable letter for Crestor requiring more extensive clinical exposure and safety data at the 20-mg and 40-mg doses to address concerns of muscle and renal toxicity. We also asked AstraZeneca to submit manufacturing and clinical data for approval of a 5-mg dose of rosuvastatin to provide a safe and effective dose for special populations of patients who might be at greater risk for muscle toxicity.

AstraZeneca submitted a response to the approvable letter in February 2003 (Crestor resubmission). The clinical safety and efficacy data on Crestor were reviewed and presented before the Endocrine and Metabolic Drugs Advisory Committee (Advisory Committee) on July 9, 2003. A nephrologist from the Cardio-Renal Advisory Committee participated in the meeting because renal safety issues were to be discussed. The Advisory Committee unanimously (9 to 0) recommended approval of Crestor with recommendations that labeling include discussion of the renal findings in the clinical trials. The committee members also unanimously agreed that AstraZeneca had provided sufficient evidence that the myotoxic potential per LDL-lowering efficacy of rosuvastatin was similar to that of currently marketed statins. We approved Crestor on August 12, 2003.

II. DISCUSSION

You base your request that Crestor be withdrawn from marketing on adverse event reports concerning rhabdomyolysis and renal failure or renal insufficiency in patients treated with Crestor. As set forth below, we examined three sources of data on the safety of rosuvastatin:

- (1) the clinical studies supporting approval of Crestor,
- (2) the Phase 4 (postapproval) clinical studies on Crestor, and
- (3) the reports on Crestor in FDA's Adverse Event Reporting System (AERS) database.

On the basis of these data, we conclude that the available evidence concerning Crestor's safety does not warrant the withdrawal of Crestor from the market.

Following is a discussion of the data you cite concerning adverse event reports on Crestor and our analysis of the totality of safety data on Crestor, regarding (1) myopathy and rhabdomyolysis and (2) renal failure and renal insufficiency, respectively.

A. Crestor and Rhabdomyolysis

You state that you have obtained information from FDA and health agencies in Canada and the United Kingdom concerning seven postmarketing adverse event reports as of March 2, 2004,² involving rhabdomyolysis in patients mostly using lower doses of rosuvastatin. You state that rosuvastatin is the only statin for which there were any cases of rhabdomyolysis prior to approval (you state that there were seven cases of rhabdomyolysis in patients receiving Crestor before its approval) (Petition at 1).

In your May 2004 supplement, you refer to 11 additional cases of rhabdomyolysis in patients using Crestor (including at least 10 in the United States). Of these 10 newer

² You state that the information on these reports was obtained from the following: (1) reports involving Crestor in AERS as of March 2, 2004; (2) data from the Canadian Adverse Drug Reaction Monitoring Program through October 2003; and (3) data from the U.K. Medicines and Healthcare Products Regulatory Agency as of December 2, 2003 (Petition at 1, Footnote 1).

cases, you state that 7 of them involved the 10-mg dose of Crestor and three were at the 20-mg dose (May 2004 Supplement at 1).

In your October 2004 supplement, you state that as of August 24, 2004, there were 65 U.S. reports of rhabdomyolysis among patients taking Crestor. You state that there had been 4.5 million prescriptions for Crestor, which meant there were 14.4 rhabdomyolysis reports per million Crestor prescriptions. You compare this reporting rate to Baycol with 42 reports out of 2.8 million prescriptions for a rate of 15 reports per million. You therefore claim that the rhabdomyolysis reporting rate for Crestor is in the range much closer to the rate of rhabdomyolysis reports for Baycol than that of any other statin (October 2004 Supplement at 2).

In your March 2005 supplement, you state that the rhabdomyolysis reporting rate for Crestor, based on your analysis of reports from October 1, 2003, through September 30, 2004, is 13.1 per million prescriptions. You state that this rate is 6.2 times higher than the rate for all other statins combined (2.1 reports per million prescriptions) (March 2005 Supplement at 1).

As explained below, we believe that the available evidence, including but not limited to adverse event reports, indicates that Crestor does not pose a greater risk of myopathy or rhabdomyolysis than the other approved statins.

1. *Myopathy and Rhabdomyolysis in Crestor Clinical Trial Database*

The safety of rosuvastatin was evaluated in an extensive premarketing clinical trial program with total exposures that far exceeded those of any other statin development program to date. Over 12,000 patients received rosuvastatin 5 mg to 80 mg in clinical trials conducted prior to the approval of Crestor.³ Over 4,000 patients were exposed to the highest marketed dose of rosuvastatin (40 mg) prior to its approval. Nearly 5,000 patients received either 40 mg or 80 mg of rosuvastatin for 6 weeks or longer. Over 1,100 patients received 40 mg or 80 mg for 48 weeks or more. From this extensive database, AstraZeneca addressed the safety concerns raised in the review of the initial submission and cited in the approvable letter.

Muscle toxicity associated with statins has a spectrum of clinical presentations. The least severe, and most common, manifestation is marked by mild, often intermittent muscle aches and pains. Minor muscle weakness may be an accompaniment, and the entire symptom complex is readily reversible with discontinuation of the drug or a reduction in dose. In assessments of muscle effects of statins, the term *myopathy* has been used to designate the condition involving muscle aches and pains accompanied by blood levels of the muscle protein, creatine kinase (CK), that are elevated above 10 times the upper limit of normal (ULN). This definition has been used in multiple NDAs for statins. The most severe presentation of statin-associated muscle toxicity is rhabdomyolysis. No single set

³ See Appendix, Table A1, for a summary of the patient exposure database in the February 2003 resubmission for Crestor.

of diagnostic criteria for rhabdomyolysis has been applied across all analyses of statin muscle effects, whether by FDA or others. According to standard textbooks, *rhabdomyolysis* is defined as a clinical syndrome of multiple causes characterized by severe muscle injury with massive cell destruction, release of myoglobin into the blood, and consequent myoglobin-induced renal failure. Even full-blown rhabdomyolysis is often reversible, although clearly it can be catastrophic, sometimes resulting in death, and this has occurred with statins. It is important to note that safety assessments of statins often pool reports of myopathy and rhabdomyolysis because they are both manifestations of statin muscle toxicity and presumably share a common mechanistic etiology.

FDA review of the Crestor resubmission of February 2003 compared the incidence of myopathy, defined as CK serum concentration > 10 times ULN with muscle pain, across all doses studied. The observed percentages of patients who met this definition (patients affected per total patients) of myopathy for the currently marketed doses (5 mg to 40 mg) were from 0.1 to 0.4 percent.⁴ The rate at the 80-mg dose, which is not marketed, was 0.9 percent.

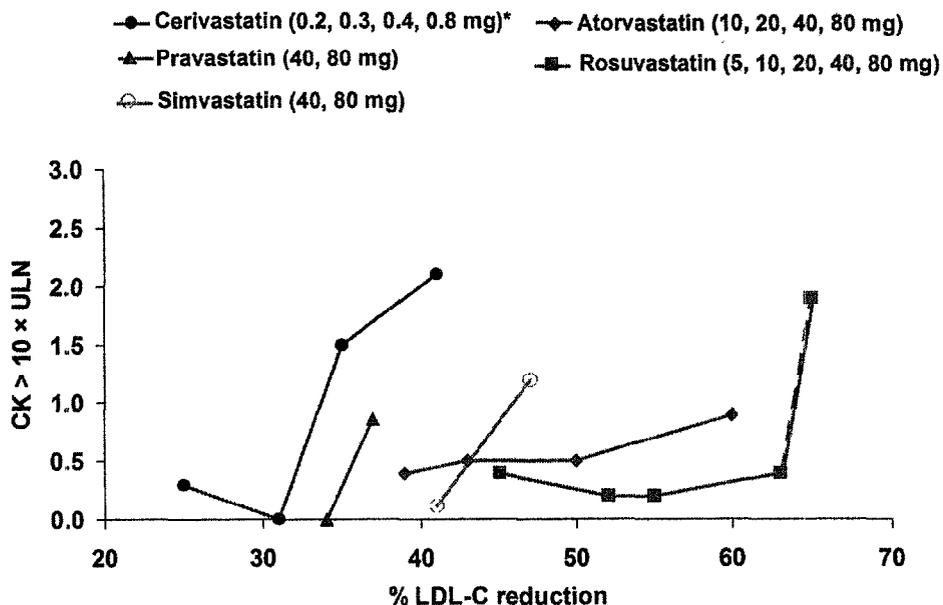
In the Crestor resubmission, AstraZeneca presented data on the percentage of patients developing marked CK elevations as a function of LDL-lowering efficacy with each dose studied in the rosuvastatin clinical program and in the preapproval clinical programs of several other marketed statins. This analysis was designed to examine whether the risks of muscle injury with Crestor were similar to or distinct from those of other marketed statins. In particular, we wanted to know whether the risk of muscle injury relative to LDL-lowering effect with Crestor was more like Baycol's (e.g., excessive risk per benefit) or more like that of other marketed statins.⁵ Figure 1 below plots the frequency

⁴ See Appendix, Table A2.

⁵ You refer (Petition at 3) to an editorial on Crestor by Dr. Richard Horton in the October 25, 2003, issue of *The Lancet*. The editorial states that AstraZeneca withdrew its request for approval of an 80 mg dose of rosuvastatin and that "[s]ome critics are even anxious about the 40 mg dose." The editorial further states: "Since there are no reliable data about efficacy (that is, actually decreasing heart attacks and strokes, not merely lowering cholesterol levels) and safety—and AstraZeneca is facing unusually acute commercial pressure to force rosuvastatin into the market—doctors should pause before prescribing this drug." This characterization of the efficacy and safety of rosuvastatin is misleading. While to date there are no clinical trial data demonstrating that Crestor-mediated reductions in LDL-cholesterol translate into reductions in cardiovascular risks, there is no reason to question whether this would be the case. For certain other statins, in studies conducted after approval, final proof of concept of the benefits of statin-associated lipid changes on cardiovascular risk has been achieved. Those studies, with durations of up to 5 years or longer and with patients (across multiple different trials and statins) numbering in the many tens of thousands, also provide additional safety information about individual statins and about the class (e.g., incidence of rhabdomyolysis) beyond what is currently known about Crestor. We based our assessment of the risks and benefits of Crestor at the time of approval on the results of trials of more than 12,000 patients, a number 3 to 4 times that studied for any other statin at the time of approval. As discussed in section II of this response, the experience with Crestor since its approval provides additional evidence of the overall safety of the drug and of a favorable risk-benefit profile in reducing heart disease risk by lowering LDL-cholesterol.

of CK elevations > 10 times ULN of several marketed statins against the average percent reduction in LDL-cholesterol associated with the dose of the statin.

Figure 1. Frequency of CK >10xULN Elevations of Different Statins (Across Dose Range) Normalized for LDL-Lowering (Presented by AstraZeneca at 7-9-03 AC Meeting)



*Individual doses of each drug are shown in increasing strengths (left to right) along each of the curves.

As is evident from the figure, treatment with cerivastatin (Baycol) 0.4 mg or 0.8 mg was associated with frequencies of development of marked CK elevations/myopathy that exceeded those with all other statins studied at doses that lowered LDL to comparable degrees as those doses of cerivastatin. Indeed, at those two doses of cerivastatin, the observed rates of myopathy exceeded those with **all** marketed doses of **all** marketed statins. (Moreover, the labeled LDL-lowering effects of cerivastatin 0.4 mg and 0.8 mg are inferior to those of all marketed doses of rosuvastatin.) By contrast, the observed absolute rates of marked CK elevations/myopathy in the extensive rosuvastatin trials program (for marketed doses) were not different from those observed with any other statin. The data in Figure 1 supported a conclusion that for any degree of LDL lowering, rosuvastatin is as safe, and may well be safer than, any other marketed statin with regard to muscle toxicity, particularly if rosuvastatin's nonsusceptibility to CYP 3A4-based drug interactions is considered. Furthermore, based on these data, rosuvastatin is distinctly different from cerivastatin, as are the other currently marketed statins.

The observed absolute rates of marked CK elevations/myopathy in patients treated with rosuvastatin 80 mg rendered that dose unacceptable for marketing in the United States. However, the fact that these cases were observed at 80 mg did not and should not lead to the conclusion that the risk of myopathy per LDL-lowering effect for Crestor's entire proposed dosage range was unacceptable (e.g., similar to Baycol's risk). Instead, the evidence of low myotoxicity at doses of rosuvastatin half as high and lower supports a conclusion that the proposed 80-mg dose simply pushed the upper dose limit too far.

These findings on rosuvastatin and myopathy were supported by a review of rosuvastatin clinical trial databases with a data cut-off date of December 2003 (including an additional 6 months of clinical trial data, for a cumulative total of more than 13,000 patients). The overall rate of myopathy for all doses of rosuvastatin was 0.2 percent.⁶ This is similar to rates cited in published literature for other currently marketed statins.⁷ In a recent review published in the *Journal of the American Medical Association*, the rates of statin-associated myopathy observed in five large-scale, controlled clinical trials of statins ranged from 0.1 percent to 0.6 percent.⁸ In this same article, the rates of rhabdomyolysis observed in controlled clinical trials of statins were 0.03 percent to 0.05 percent. Across all approved doses of rosuvastatin, the rate of rhabdomyolysis in the over 13,000 patients treated in controlled trials through December 2003 is 0.01 percent, based on a single case in a patient receiving the 20-mg dose.

All pharmaceutical clinical development programs are limited in their capacity to detect very rare drug-related adverse events. A typical clinical development program for a chronic use drug that might expose 3,000 patients to the drug for sufficient duration has a very good chance (95 percent) of containing a single case of a drug-induced adverse event known to occur at a rate of 1 per 1,000 patients treated. In a clinical development program, such as rosuvastatin's, that exposes four times this number of patients, there is a very good chance (95 percent) of observing a drug-induced adverse event known to occur in 1 in 4,000 patients treated for sufficient duration. Among the 11,000 patients treated with doses of 10-mg to 40-mg rosuvastatin daily, only a single case of rhabdomyolysis occurred in a patient treated with the 20-mg dose. To put this in further perspective, in the Heart Protection Study, which randomized 10,000 patients each to simvastatin 40 mg or placebo for an average of approximately 4 years, five cases of rhabdomyolysis were observed in patients taking simvastatin (1 per 2,000). In short, the size of the sample alone (in conjunction with the prevalence of factors that either increase or decrease the risk of adverse effects) bears critically on the chance of observing a particular drug-induced adverse effect. Because of the size of the rosuvastatin clinical experience, not only do we understand the myopathic risk associated with the 80-mg dose, but we have

⁶ See Appendix, Table A3.

⁷ See Omar, M. et al., Rhabdomyolysis and HMG-CoA reductase inhibitors, *Ann Pharmacother* 2001;35:1096-1107; Evans M. and Rees A., Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Safety* 2002; 25 (9):659-663.

⁸ Thompson, P.D. et al., Statin-associated myopathy, *JAMA* 2003; 289(13):1681-1690.

greater assurance as to the muscle safety of the marketed doses (5 mg to 40 mg), both in absolute terms and relative to other marketed statins.⁹

In conclusion, the safety findings with rosuvastatin 5 mg to 40 mg daily from the clinical trial database provide no evidence that the risk of myopathy or rhabdomyolysis with rosuvastatin is greater than with currently marketed statins, particularly relative to LDL-lowering efficacy.

2. *Myopathy and Rhabdomyolysis in Crestor Phase 4 Studies Database*

As part of the approval of Crestor, AstraZeneca agreed to conduct a postmarketing (Phase 4) study to evaluate the pharmacokinetic differences of rosuvastatin in Asian Americans compared to Caucasians. In addition, a large Phase 4 clinical development program is ongoing to evaluate the effects of rosuvastatin on the atherosclerotic process as determined by arterial imaging and ascertainment of clinical outcomes. Many of the lipid-altering efficacy trials initiated premarketing continue in open-label extension studies with collection of additional long-term safety data. These studies include baseline and on-treatment monitoring of urine and serum chemistries. To date, approximately 17,800 patients have been enrolled in the rosuvastatin arms of these clinical trials.

Adverse events in these Phase 4 studies are reported to the investigational new drug application (IND) for the study and are reviewed by an FDA medical officer. As of June 11, 2004, the rate of rhabdomyolysis in the clinical development program for rosuvastatin 5 mg to 40 mg is 2/17,800 (0.01 percent), unchanged from December 2003, and within the range observed for other statins. The Phase 4 studies on rosuvastatin have not provided any evidence that the risk of myopathy with rosuvastatin differs from that of other approved statins.

3. *Adverse Event Reports on Crestor Concerning Myopathy and Rhabdomyolysis*

a. Background on nature and significance of adverse event reports

In considering the significance of the adverse event reporting rates (reports received per 100,000 prescriptions) for rhabdomyolysis and renal insufficiency/failure associated with

⁹ You state that although the seven patients who developed rhabdomyolysis during the clinical trials for Crestor had all received the 80-mg dose, a small patient receiving the 40-mg dose might be receiving the same amount of drug per pound of body weight (Petition at 1-2). We disagree. Based on population pharmacokinetic studies, there is no evidence that rosuvastatin drug levels are affected by body weight. Especially given that physicians are advised in the labeling to prescribe the lowest effective statin dose that will achieve the desired cholesterol goal, the clinical trial safety data appear to support a conclusion that in both absolute terms and relative to LDL-lowering efficacy, the myotoxic potential of rosuvastatin may be lower than that of other marketed statins, and is distinctly lower than that of Baycol.

rosuvastatin use, and in particular the comparison to rates associated with the use of other statins, several points are relevant. First, it is well known that reporting rates for any particular drug might not reflect actual adverse event incidence. The proportion of total incident cases that are reported is variable and can only be estimated. Furthermore, the true number of people exposed to a drug cannot be calculated precisely, because prescription data do not reflect either total patients treated or duration of therapy.

Second, the quantity and quality of information in postmarketing adverse event reports is highly variable. This further limits our ability to accurately determine whether the drug played a causal role in any particular case.

Third, there are multiple factors that influence the rate of reporting of adverse events. These factors may well vary in their influence from one time period to another over the history of marketing of a particular drug. Such influences might tend to induce reporting in some instances and inhibit it in others. For example, in some cases, public perception (based, for example, on statements in drug labeling) of the risks associated with use of a particular drug might stimulate the reporting of labeled adverse events, both those caused by the drug and those occurring purely coincidentally with drug use.¹⁰ As discussed in section I of this response, rosuvastatin was the first statin considered for approval after the withdrawal of cerivastatin. Concern about statin-associated myopathy is clearly heightened in this “post-Baycol” era. The Advisory Committee meeting on rosuvastatin brought safety concerns about this drug to the public’s attention. This awareness may well stimulate reporting of rhabdomyolysis in association with statin use generally and with rosuvastatin in particular, even in the absence of a true increased frequency of the event overall or of an increased risk with rosuvastatin relative to other statins.

In addition, in considering postmarketing reporting rates, it is important to note that there is no control group with similar underlying risks (medical conditions, treatment with other drugs) for adverse outcomes of interest. This means that, using standard statistical approaches, it is not possible to reach a definitive conclusion about a potential causal role of the drug in these adverse events.

Notwithstanding the quantitative limitations of the data and of the mathematical approaches to analysis of adverse event reports, these reports do contribute to the overall evaluation of drug safety because they emerge from “real-life use” of a drug. Furthermore, after a drug is approved, total patient exposure, while never exactly known, will eventually (often very rapidly) exceed that in premarketing clinical trials. This provides a much broader experience with the drug and an increased opportunity for occurrence and ascertainment of rare adverse events. However, conclusions about the safety of a drug should not be based entirely on postmarketing adverse event reports and reporting rates. Rather, we must consider the totality of evidence derived from premarketing studies, ongoing controlled clinical trials, and postmarketing safety data.

¹⁰ Scott, H.D. et al., Physician reporting of adverse drug reactions: results of the Rhode Island Adverse Drug Reaction Reporting Project, *JAMA* 1990; 263(13):1785-1788.

b. FDA review of myopathy/rhabdomyolysis adverse event reports

In your citizen petition and May 2004 supplement, you identified a total of 18 adverse event reports of rhabdomyolysis from the AERS database associated with the use of rosuvastatin. At our request, you submitted the identifiers for these listings. There were 17 unduplicated cases of rhabdomyolysis.

Rhabdomyolysis is a known adverse effect of all statins and has been reported for all approved statins except for fluvastatin, which is not used much because of poor LDL-lowering efficacy. The descriptions of the adverse event reports involving rhabdomyolysis add little to our understanding of the safety profile of rosuvastatin, although they do suggest that certain aspects of Crestor labeling should be strengthened. (As discussed in section III of this response, AstraZeneca has agreed to revise several aspects of Crestor labeling.)

We compared the reporting rates of rhabdomyolysis reported in association with rosuvastatin use during three different time periods with the reporting rates associated with six other statins (lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin). These time periods were: (1) from August 2003 through February 2004 (reflecting the first 6 months of Crestor's marketing, which is the period you examined in your petition); (2) from August 2003 through May 2004 (in response to your May 2004 supplement); and (3) from August 2004 through October 2004 (in response to your October 2004 supplement). Each successive reporting time period includes cumulative data from the preceding time period.

We searched our AERS database for reports containing the following terms: myopathies, aldolase increased, blood CK increased, blood CK-MB fraction increased, myoglobin blood increased, myoglobin urine present, myoglobinuria, and skeletal muscle enzymes increased. These are broad search terms intended to capture a large number of reports that we then reviewed individually. The reports were further classified according to the following case definitions:

- (1) A clinical diagnosis of rhabdomyolysis or muscle signs and symptoms, and CK levels > 10,000 ULN
- (2) A clinical diagnosis of rhabdomyolysis and CK < 10,000 ULN
- (3) A clinical diagnosis of rhabdomyolysis but no CK value provided
- (4) A clinical diagnosis of myopathy or elevated CK values in asymptomatic patients

The application of a prospectively defined case definition in the selection of reports for analysis is intended to lend precision to the process and to address potential bias in the selection or rejection of cases. This is a commonly applied methodology in epidemiological investigation and is the accepted approach to conducting this type of analysis.

We used Case Definition #1 when we evaluated the postmarketing reports of muscle injury in association with cerivastatin use in 2001. To maintain consistency in evaluating the risk of muscle toxicity of statins, we used this definition to select cases in the analyses of adverse event reports on muscle injury with rosuvastatin use.

As you did in your petition and supplements, we reviewed adverse event reports in our AERS database.¹¹ These reports are submitted to FDA through the MedWatch program and are then available to the public under the Freedom of Information Act. However, despite using the same database, the number of cases of rhabdomyolysis that you identified differs somewhat from the number that we identified. This might be due to the definition of rhabdomyolysis that you used to identify reports for analysis. It is not clear what definition you used to identify cases of rhabdomyolysis or to what extent you corrected for duplicative reporting.

- ***Reporting Time Period From August 2003 Through February 2004 for Rosuvastatin Compared to First 6 Months of Marketing for Comparator Statins***

Table 1 below shows the number of adverse event reports for myopathy/rhabdomyolysis for rosuvastatin and for different doses of six other statins during the first 6 months that the drug or a particular dosage of the drug was available:

¹¹ You state in your petition that you obtained information from FDA and health agencies in Canada and the United Kingdom concerning adverse event reports concerning Crestor, without specifying how many of those reports were domestic; however, your October 2004 supplement, in which you state that there were 14.4 rhabdomyolysis reports per million Crestor prescriptions, refers only to U.S. reports. In examining the adverse event reporting rates for Crestor and other statins, we considered only domestic reports because we only have access to U.S. prescription data. However, we did include 8 foreign cases along with 30 domestic cases as part of our clinical review of adverse event reports concerning renal insufficiency or failure (see section II.B.3 of this response).

Table 1. U.S. Reporting Rates of Myopathy/Rhabdomyolysis During 6-Month Interval Postapproval

| Statin | No. of Cases | No. of Prescriptions* | Cases/100,000 Rx |
|-----------------------------|--------------|-----------------------|------------------|
| Lovastatin (all doses) | 0 | 928 | 0 |
| Pravastatin (up to 40 mg) | 0 | 329 | 0 |
| Simvastatin (up to 40 mg) | 0 | 86 | 0 |
| Fluvastatin (all doses) | 0 | 392 | 0 |
| Atorvastatin (all doses) | 1 | 1,626 | 0.06/100,000 |
| Cerivastatin (up to 0.3 mg) | 0 | 59 | 0 |
| Rosuvastatin (all doses) | 2 | 763 | 0.3/100,000 |
| Simvastatin 80 mg | 0 | 35 | 0 |
| Pravastatin 80 mg | 0 | 59 | 0 |
| Cerivastatin 0.4 mg | 5 | 250 | 2/100,000 |
| Cerivastatin 0.8 mg | 25 | 165 | 15.2/100,000 |

*In thousands; IMS Health, National Prescription Audit Plus

Using Case Definition #1, there were only three statins with domestic reports of myopathy/rhabdomyolysis during the first 6 months of marketing. These three included rosuvastatin, atorvastatin, and cerivastatin (at doses of 0.4 mg and 0.8 mg; there are separate data for these doses of cerivastatin because they were approved several years after the original NDA application). There were two cases of rhabdomyolysis with rosuvastatin out of 763,000 prescriptions, for a reporting rate of 0.3/100,000. In contrast, the reporting rates for the two dosages of cerivastatin, which were subsequently withdrawn from the market, were 2/100,000 for the 0.4-mg dose (5 cases out of 250,000 prescriptions) and 15.2/100,000 for the 0.8-mg dose (25 cases out of 165,000 prescriptions). The latter rate is 50 times higher than the rate for rosuvastatin.

The data show that the reporting rate for rosuvastatin of 0.3/100,000 was 5-fold higher than that for atorvastatin (1 case in 1,626,000 prescriptions, for a rate of 0.06/100,000). However, one cannot conclude on the basis of these data that there is a greater risk of muscle toxicity for rosuvastatin given the very small number of cases contributing to these reporting rates. Specifically, one case with atorvastatin and two cases with

rosuvastatin constitute inadequate data on which to make any conclusions about comparative risk, particularly given the above-noted limitations associated with assessing adverse event reports.

- ***Reporting Time Period From August 2003 Through May 2004***

For the period from August 2003 through May 2004, we identified in adverse event reports eight domestic cases of myopathy/rhabdomyolysis in patients taking Crestor meeting Case Definition #1. The estimated number of prescriptions was 2,557,000, resulting in a reporting rate of 0.3 per 100,000, the same as in the earlier period.

Several aspects of these cases are worth noting. Three cases of rhabdomyolysis were reported in patients who were started on therapy at the 40-mg dose. The labeling for Crestor recommends the 10-mg dose as the usual start dose with the 5-mg dose recommended for those requiring less aggressive cholesterol lowering.¹² In addition, one patient was switched from another statin directly to rosuvastatin 40 mg. These patients may well have eventually developed myopathy or rhabdomyolysis if they had in time been dose escalated (in order to meet LDL goals) to 40 mg. However, it is conceivable that they might have developed mild muscle symptoms at lower doses, directing clinical intervention and obviating rhabdomyolysis (e.g., by limiting dose, trial of another statin, or careful review of potentially reversible contributing factors). This is the rationale behind the approach to dosing described in current labeling for rosuvastatin and the rationale for limiting the starting doses of other statins (e.g., atorvastatin, simvastatin, pravastatin) to submaximal doses.

Along with conducting an updated assessment of the myopathy/rhabdomyolysis reporting rate for Crestor, we examined reporting rates for other marketed statins for the period from initial approval of each statin to July 2001 (the last month that cerivastatin was marketed in the United States). These data on other statins were obtained from a comparison of marketed statins to cerivastatin that was published last year.¹³ The reporting rates for rhabdomyolysis for other approved statins, excluding cerivastatin, ranged from 0 to 0.18 per 100,000 prescriptions. The reporting rate of 0.18 was for lovastatin, which we approved in 1987. While there is a slightly higher rate for rosuvastatin relative to lovastatin (0.3 compared to 0.18), this does not provide a

¹² You state that although the majority of cases of rhabdomyolysis were in people using the 10-mg dose, AstraZeneca warned physicians that patients should start at that dose, "blaming the four cases of rhabdomyolysis they report on higher doses but failing to mention the seven patients who suffered from rhabdomyolysis at the 10 milligram dose" (May 2004 Supplement at 1-2). Given that myopathy and rhabdomyolysis are known adverse effects of statins, and the majority of use of rosuvastatin is at the 10-mg dose, it is not surprising that the majority of cases of rhabdomyolysis were at the 10-mg dose. It is also not surprising that the reporting *rate* for rhabdomyolysis with rosuvastatin is higher at 40 mg than at 10 mg, because higher doses are expected to have a greater risk of toxicity.

¹³ Chang et al., Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy, *Pharmacoepidemiology Drug Saf.* 2004; July 13(7):417-426.

sufficient basis for concluding that rosuvastatin poses a greater risk of muscle toxicity than does lovastatin. The reporting time period for lovastatin was 13 years (1988 until July 2001), which is markedly longer than the 10 months for rosuvastatin. During those 13 years, 150 cases of myopathy/rhabdomyolysis were reported for lovastatin out of approximately 99.5 million prescriptions. The longer period of marketing for lovastatin might contribute to a decreasing tendency over time to report incident adverse events as prescribers become aware of this labeled event and therefore do not submit MedWatch reports to FDA. Moreover, the reporting period for lovastatin in this analysis preceded the withdrawal of cerivastatin and the attendant heightened sensitivity regarding rhabdomyolysis and statins, which might further contribute to the difference in reporting between lovastatin and rosuvastatin.

- ***Reporting Time Period From August 2003 Through October 2004***

We conducted a third review of the myopathy/rhabdomyolysis adverse event reports that covered the first 14 months of marketing for rosuvastatin. For the time period of August 2003 through October 2004, we identified 26 domestic cases of myopathy/rhabdomyolysis meeting Case Definition #1, while the total prescriptions had reached an estimated 6,071,000. This yielded a reporting rate of 0.43 per 100,000 prescriptions for rosuvastatin. Thus, as shown in Table 2 below, the reporting rate for the first 14 months of marketing of rosuvastatin has not changed appreciably.

Table 2. Summary of Reporting Rates of Myopathy/Rhabdomyolysis for Rosuvastatin During 3 Different Reporting Time Periods

| Time Period | No. of Cases | Estimate No. of Rx* | Reporting Rate/100,000 Rx |
|---------------------------|---------------------|----------------------------|----------------------------------|
| August 2003-February 2004 | 2 | 763,000 | 0.3 |
| August 2003-May 2004 | 8 | 2,557,000 | 0.3 |
| August 2003-October 2004 | 26 | 6,071,000 | 0.43 |

*IMS Health National Prescription Audit Plus Database

Table 2 shows that even as the number of Crestor prescriptions (and thus the number of patients exposed) has increased massively, no postmarketing signal for excessive myotoxicity similar to the problems with cerivastatin has emerged. This is consistent with the extensive clinical trial experience with rosuvastatin discussed in section II.A.1 of this response.

In your March 2005 supplement, you state that the rhabdomyolysis reporting rate for Crestor is 6.2 times higher than the rate for all other statins combined. You considered AERS reports for the period from October 1, 2003, through September 30, 2004. As stated above, in our most recent analysis of the adverse event reports concerning rhabdomyolysis, we examined a longer period, from August 2003 through October 2004. As with your petition and earlier supplements, you did not explain the criteria you used

for defining rhabdomyolysis in evaluating the adverse event reports, and you did not state whether you corrected for duplicative reporting. The differences in reporting periods and uncertainties regarding your definition of cases do not allow us to directly compare your latest findings to ours. Nevertheless, we do not believe that the adverse event reports on Crestor indicate that the drug poses an unacceptable risk of rhabdomyolysis. Moreover, as stated above, there are several reasons why conclusions about a drug's safety should not be based entirely on postmarketing adverse event reports, and the data from the preapproval and postmarketing clinical studies on Crestor do not suggest that the drug poses a greater risk of rhabdomyolysis compared to other statins, particularly considering its effectiveness in lowering LDL.

As is not uncommon for adverse events reported to FDA, review of the cases reveals that prescribers are not prescribing rosuvastatin in accordance with the approved labeling in certain instances. For example, two cases included patients co-prescribed cyclosporine and rosuvastatin 40 mg (the label recommends that only the 5-mg dose be used). One patient was started on therapy at the 40-mg dose (not a recommended start dose) and one patient with chronic renal failure was started on therapy at the 20-mg dose (the label recommends a 5-mg start dose with a 10-mg maximum daily dose). In both instances, an increased risk of myopathy with rosuvastatin is presumed and the existence of these reports may reasonably be interpreted as demonstrative of that risk.

In conclusion, based on the reporting rates for myopathy and rhabdomyolysis, there is no evidence that the risk of myopathy or rhabdomyolysis with rosuvastatin is similar to that of cerivastatin. Although estimates of the reporting rate for rosuvastatin are higher than those of the other marketed statins, the time period in which these reports were made (post-cerivastatin withdrawal) conceivably contributed to enhanced reporting of incident cases due to increased publicity about this adverse event. Finally, taking into consideration the extensive preapproval and ongoing clinical trial safety experience, the muscle safety of rosuvastatin appears comparable to that of other marketed statins. Given that the approved doses of rosuvastatin provide greater LDL-lowering efficacy than the approved doses of other statins, this comparable safety profile relative to greater efficacy offers reassurance that rosuvastatin does not have a less favorable benefit-risk profile compared to currently marketed statins. We will continue to monitor postmarketing reports of rhabdomyolysis in patients receiving Crestor and will consider future regulatory action should this risk-benefit profile change.

B. Crestor and Renal Insufficiency or Failure

You state that you have obtained information from FDA and health agencies in Canada and the United Kingdom concerning nine cases of kidney failure or kidney damage in patients mostly using lower doses of rosuvastatin (Petition at 1). In your May 2004 supplement, you refer to three additional cases of renal failure or renal insufficiency associated with the use of Crestor in this country (May 2004 Supplement at 1-2). You also claim that primary renal toxicity (separate from the secondary renal damage done as a consequence of rhabdomyolysis) is unique to rosuvastatin (May 2004 Supplement at 2).

In your October 2004 supplement, you state that you have found that the rate of adverse event reports of acute renal failure or renal insufficiency per million prescriptions in patients using Crestor (a total of 29 reports) is approximately 75 times higher than the rate of reports for all other statin drugs combined. You reviewed reports for statins other than Crestor submitted between January 1, 2001, through September 30, 2003, and reports for Crestor from its approval in August 2003 through August 26, 2004. You state that there were 29 reported cases of acute renal failure or insufficiency out of 4.5 million prescriptions for Crestor, which is a rate of 6.4 reports per million prescriptions. You state that there were 27 reported cases of acute renal failure or insufficiency out of 314 million prescriptions for all other statins, which is a rate of 0.085 reports per million prescriptions (October 2004 Supplement at 1-2).

As discussed below, based on our review of data from the clinical trials supporting the approval of Crestor, Phase 4 studies, and postmarketing adverse event reports, there is insufficient evidence that Crestor causes serious renal problems warranting withdrawal of the drug from the market.

1. Renal Insufficiency/Failure in Crestor Clinical Trial Database

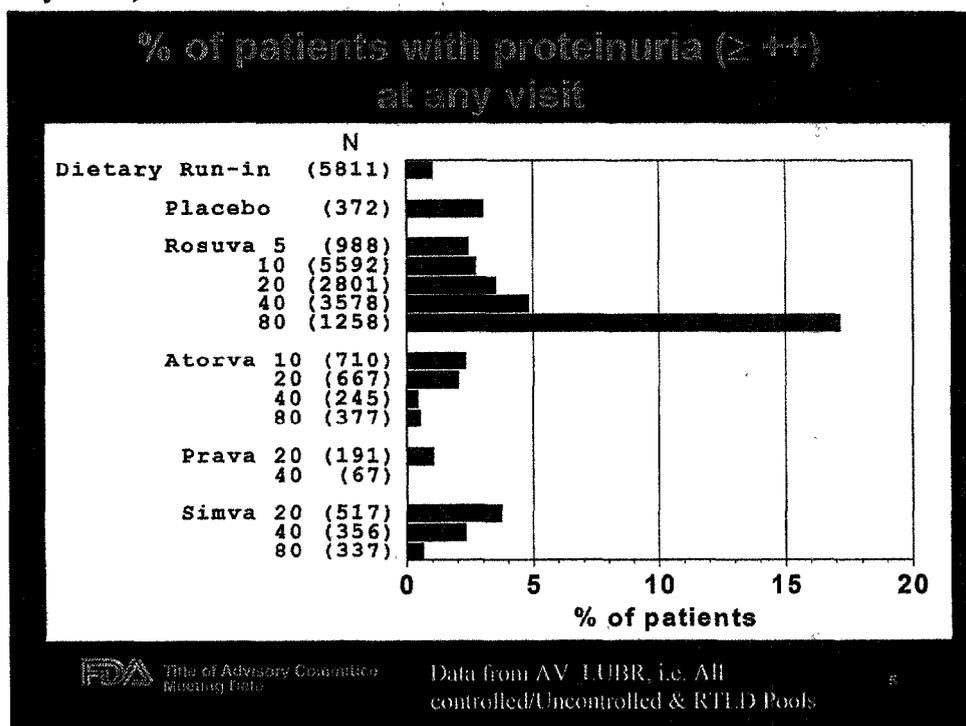
In the initial NDA submission for Crestor, the primary reviewing medical officer noted proteinuria with and without hematuria in some patients treated with rosuvastatin, with incidence increasing as the dose increased. These findings were based on dipstick assays on random urine samples, which are crudely quantitative and make no adjustment for urine osmolality. For the most part, the analyses did not contain data from patients on placebo because much of the data came from open-label safety studies. By far the most common urine abnormality observed was proteinuria alone, and this was observed more often at higher doses of rosuvastatin. Indeed, this dose-related increase in frequency does suggest a true drug effect of causing proteinuria.

The NDA resubmission in February 2003 provided additional renal safety data on rosuvastatin that were derived primarily from open-label extension studies. Chemical (electrophoretic) analysis and quantitation (< 1 gm per 24 hours) of urine protein in a subset of patients developing proteinuria treated with rosuvastatin 80 mg defined a tubular, rather than glomerular, origin. Even in some patients on rosuvastatin who did not have elevated urine protein excretion, electrophoretic analysis was consistent with tubular proteinuria. In addition, an evaluation of the effects of rosuvastatin and other statins in an opossum proximal tubular epithelial kidney cell line in culture was conducted to further elucidate the mechanism of proteinuria. This study demonstrated that the inhibition of HMG-CoA reductase in the renal tubular cells resulted in the blockade of the protein (albumin) uptake by rosuvastatin and four other statins (atorvastatin, simvastatin, pravastatin, and fluvastatin). This blockade was concentration-dependent (i.e., greater inhibition of the enzyme resulted in more blockade of protein uptake). Furthermore, this effect of statins on renal tubular protein uptake was corrected

when mevalonate was added.¹⁴ These observations, taken together, support a class pharmacological effect of statins on proximal tubular protein reabsorption not previously described. Therefore, these observations might explain the observation of proteinuria in patients treated with rosuvastatin and other statins in the rosuvastatin development program. As discussed later in this section of the response, the findings from this in vitro study and the clinical trials on Crestor suggest that the statin-associated proteinuria did not indicate a renal toxic effect either of statins generally or of rosuvastatin specifically.

In the original NDA review, the FDA reviewer made a comparison of the occurrence of dipstick proteinuria across all statins included in trials in the rosuvastatin clinical development program (i.e., rosuvastatin, atorvastatin, pravastatin, and simvastatin), as shown in Figure 2 below.

Figure 2. FDA Advisory Committee Presentation of Incidence of Proteinuria (at any Study Visit) in the Double-Blind Controlled Studies



The median duration of treatment with various doses of non-rosuvastatin statins in the controlled periods of these clinical trials was approximately 8 weeks. There was no baseline control for urine protein status. Upon completion of the controlled phase, patients treated with placebo and statins were permitted to enter an open-label extension study in which all received rosuvastatin. As a result, comparative analyses of the

¹⁴ Mevalonate is an intermediate in the metabolic pathway to cholesterol synthesis and is the direct product of the step that is inhibited by statins. Reversibility of an effect by addition of mevalonate confirms that the effect was caused by inhibition of HMG-CoA reductase and not by some other, unknown, effect of statin.

occurrences of proteinuria at *any* visit are potentially biased due to increased urine sampling over the longer course of therapy with rosuvastatin (up to 3.8 years).¹⁵

Setting aside these shortcomings, the data, taken at face value, lead to a conclusion that at doses of 40 mg and lower, the rate of proteinuria with rosuvastatin was within the range observed with several other statins and, notably, placebo. This bias in ascertainment would tend to inflate the rates observed with rosuvastatin. This assumes a transient, intermittent effect in at least some patients, as discussed further below. Therefore, any absolute differences between rosuvastatin and the other treatments (and between different doses of rosuvastatin), if indeed they exist, would likely be smaller than the data in Figure 2 suggest. Nevertheless, the data on the 80-mg dose of rosuvastatin suggests an apparent difference from the other treatment groups, because over 15 percent of the patients receiving 80 mg of rosuvastatin manifested proteinuria at some point during therapy, compared to less than 5 percent of those receiving any of the other statins or any other dose of rosuvastatin.¹⁶

Both AstraZeneca and FDA further analyzed the laboratory data available for doses of rosuvastatin up to 40 mg to examine whether urine dipstick abnormalities were associated with changes in renal function as measured by levels of serum creatinine¹⁷ (i.e., whether this was a pharmacologic effect of no clinical significance or represented a true toxic effect of rosuvastatin and perhaps other statins).¹⁸ AstraZeneca examined the rates of laboratory abnormalities at the *last* study visit, whereas the FDA reviewer analyzed the percent of patients with abnormalities at *any* visit. The available information relating to proteinuria precludes us from making definitive findings of toxicity.¹⁹ There were no

¹⁵ Because some placebo patients crossed over to receive rosuvastatin during the extension period, this analysis will result in more sampling in the rosuvastatin group and therefore increase the chances of observing proteinuria in rosuvastatin patients.

¹⁶ These data represent dipstick protein determinations on spot urine samples. Even if the sampling and laboratory methodologies are deemed reliable, from this analysis neither the percent manifesting proteinuria at any given point in time, nor the absolute differences between the rate with rosuvastatin 80 mg and the other treatments, is known.

¹⁷ Serum creatinine derives from muscle metabolism of creatinine. The concentration of creatinine in the serum is a surrogate measure of how well the glomeruli (the capillaries that serve as the “sieve” for the kidney) filter blood (the glomerular filtration rate (GFR)). In general, decreased GFR is marked by increased serum creatinine levels. Decreasing GFR is a manifestation of decline in renal function.

¹⁸ We were unable to obtain data on urine protein analyses from other recent statin trials. Specifically, there were no routine urinalyses conducted in the Heart Protection Study of simvastatin. In the Anglo-Scandinavian Cardiovascular Outcomes Trial of atorvastatin, no specific information on urine protein analyses was obtained, although cases of “renal failure” were collected as a study endpoint in the trial that enrolled a large number of patients with diabetes. In that trial, there was no statistical difference in the incidence of renal failure on treatment between atorvastatin-treated and placebo-treated groups.

¹⁹ Twenty-four-hour urine samples for creatinine clearance, which would have permitted precise quantitation of urine creatinine excretion, were not routinely collected. Instead, the criterion for defining a change in renal function was a single laboratory determination showing an increase in serum creatinine of > 30 percent from baseline. This criterion was essentially arbitrary and was not established based on a

data for placebo or for other statins because the data were derived from the open-label extension phase of the trials when all study subjects were switched to rosuvastatin. In the final analysis, none of the patients with proteinuria and these creatinine elevations manifested evidence of clinically serious renal functional deterioration during followup.

Table 3 below summarizes the data on creatinine increases in rosuvastatin-treated patients who had proteinuria.

Table 3. Frequency of > 30% Creatinine Elevations in Rosuvastatin-Treated Patients with Proteinuria from Combined All Controlled/Uncontrolled and RTL D Pools

| Sponsor's Analysis Based on Last Visit Data (Slide CS-33 from AC Meeting) | | | | FDA Analysis Based on Any Visit Data | | | |
|--|------|----------------------|-----------------------|--------------------------------------|------|--------------------|-----------------------|
| | N | Proteinuria n (%) | Cr >30% rise n (%) | | N | Proteinuria (%) | Cr >30% rise n (%) |
| 5 mg | 549 | 1 (0.2%) | 0 | 5 mg | 653 | 1.1% | 0 |
| 10 mg | 1822 | 10 (0.5%) | 0 | 5 mg OLE | 438 | 4.1% | 2 (0.5%) |
| 20 mg | 1253 | 11 (0.9%) | 2 (0.16%) | 10 mg | 1202 | 2.2% | 0 |
| 40 mg | 2824 | 32 (1.1%) | 0 | 10 mg OLE | 5011 | 2.7% | 6 (0.1%) |
| | | | | 20 mg | 1460 | 2.1% | 0 |
| | | | | 20 mg OLE | 1894 | 4.2% | 6 (0.3%) |
| | | | | 40 mg | 2384 | 3.8% | 9 (0.4%) |
| | | | | 40 mg OLE | 1684 | 5.0% | 6 (0.4%) |

Table 4 below summarizes the data on creatinine increases in rosuvastatin-treated patients who had *both* proteinuria and hematuria.

Table 4. Frequency of > 30% Creatinine Elevations in Rosuvastatin-Treated Patients with Combined Proteinuria/Hematuria from Combined All Controlled/Uncontrolled and RTL D Pools

| Sponsor's Analysis Based on Last Visit Data (Slide CS-34 from AC Meeting) | | | | FDA Analysis Based on Any Visit Data | | | |
|--|------|--------------------------------|-----------------------|--------------------------------------|------|--------------------------------|-----------------------|
| | N | Proteinuria/hematuria n (%) | Cr >30% rise n (%) | | N | Proteinuria/hematuria n (%) | Cr >30% rise n (%) |
| 5 mg | 493 | 0 | 0 | 5 mg | 653 | 0 | 0 |
| 10 mg | 1707 | 1 (0.1%) | 0 | 5 mg OLE | 438 | 7 (1.6%) | 0 |
| 20 mg | 1194 | 1 (0.1%) | 1 (0.08%) | 10 mg | 1202 | 4 (0.3%) | 0 |
| 40 mg | 2679 | 6 (0.2%) | 0 | 10 mg OLE | 5011 | 39 (0.8%) | 4 (0.1%) |
| | | | | 20 mg | 1460 | 5 (0.3%) | 0 |
| | | | | 20 mg OLE | 1894 | 13 (0.7%) | 3 (0.2%) |
| | | | | 40 mg | 2384 | 30 (1.3%) | 6 (0.3%) |
| | | | | 40 mg OLE | 1684 | 25 (1.5%) | 4 (0.2%) |

These data show that the frequency of proteinuria and the frequency of combined proteinuria and hematuria are both low. The analysis by *any* visit shows a higher rate of these laboratory abnormalities compared to the analysis by *last* visit, apparently as a

definition of a *clinically significant* increase in serum creatinine (e.g., one that might result in symptoms or clinical deterioration or one that might mark an increased risk for progression to severe renal dysfunction).

result of more sampling of individual patients. These data are consistent with a transient or an intermittent effect of the drug producing these abnormalities (although the absence of data from placebo patients makes reaching a definitive conclusion about the drug's role difficult). The rates of creatinine elevations in patients with proteinuria or combined proteinuria and hematuria in the *any visit* analyses are also very low, although detectable. Most important, the *last visit* analyses show not only very few patients with combined proteinuria and hematuria, but virtually no patients (a total of 3 out of approximately 6,000) with proteinuria and hematuria in concert with creatinine elevation. Moreover, as noted above, none of the patients with these laboratory abnormalities (either alone or in concert) developed kidney failure.

At the Advisory Committee meeting on rosuvastatin, AstraZeneca also presented data on patients treated long term with rosuvastatin in clinical trials, as shown in Table 5:

| | N | Proteinuria at any visit n (%) | Proteinuria at last visit n (%) | Cr >30% at last visit n |
|---------|-----|-----------------------------------|------------------------------------|----------------------------|
| 5mg | 261 | 3 (1.1%) | 0 | 0 |
| 10 mg | 838 | 17 (2.0%) | 4 (0.5%) | 0 |
| 20 mg | 112 | 5 (4.5%) | 1 (0.9%) | 0 |
| 40 mg | 100 | 4 (4.0%) | 2 (2.0%) | 0 |
| 80 mg | 590 | 99 (16.8%) | 37 (6.3%) | 7 |
| ≥40 mg* | 807 | 136 (16.9%) | 10 (1.2%) | 0 |

*Includes patients down-titrated from 80 mg

This analysis showed that no patients receiving rosuvastatin at doses from 5 mg to 40 mg for 2 years or more (≥ 96 weeks) had an increase in serum creatinine of greater than 30 percent. This means that no patient in this cohort developed significant renal functional deterioration. The analysis examined the frequency of proteinuria in the group of patients whose rosuvastatin was reduced from 80 mg to 40 mg. The frequency of proteinuria at the last visit decreased from 6.3 percent in the 80-mg group to 1.2 percent in the reduced-to-40-mg group. This decrease supports a conclusion that proteinuria is a reversible pharmacological effect of rosuvastatin.

AstraZeneca also examined the change in serum creatinine concentration from baseline to end of treatment in patients treated with at least 40 mg of rosuvastatin daily. The data showed an average *decrease* in serum creatinine among these patients, whether they had normal or impaired renal function when they entered the trial. Taken at face value, this outcome suggests that rosuvastatin might actually be *beneficial* to kidney function, although clearly such a hypothesis would need to be formally tested.

The overall available data (including data from in vitro studies and clinical trials) support an effect of rosuvastatin and other statins to induce tubular proteinuria. However, the existence of exceedingly small numbers of patients with combined proteinuria and hematuria at the last visit (and by extension at any visit) is far from definitive in supporting a dual effect on the kidney (i.e., causing both proteinuria and hematuria) of rosuvastatin specifically or statins in general. Indeed, a unifying renal pathology causing tubular proteinuria and hematuria (the latter more likely due to a glomerular lesion) is difficult to conceive. Moreover, intermittent, nonpathologic, dipstick-positive hematuria and low-level dipstick proteinuria are extremely common urinalysis findings, and the absence of a non-statin-treated control group makes reaching a definitive conclusion about rosuvastatin's role impossible.

With regard to the potential effects of rosuvastatin on renal function, no data on the co-occurrence of proteinuria, hematuria, and creatinine elevation were obtained and presented from patients taking placebo. This is particularly important in light of the low overall incidence rates for proteinuria at the last visit compared to at any visit (thus demonstrating the transient or intermittent nature of these events), the very small numbers of patients with combined proteinuria and hematuria at the last visit, and the virtual absence of patients with creatinine elevation of > 30 percent in combination with these urinary abnormalities at the last visit. Furthermore, use of high-dose rosuvastatin was shown to result in an average reduction in serum creatinine, which at least suggests the possibility of improved renal function. Thus, based on the existing data, the extent to which there is a renal effect of rosuvastatin or other statins beyond transient, intermittent tubular proteinuria is not clear. More precisely, the urine dipstick and serum chemistry data as well as the adverse event data from the clinical trials *do not* support a conclusion that any renal effect of rosuvastatin represents a signal of renal toxicity *per se* (i.e., leads to renal functional compromise). It is particularly significant that in the preapproval trials, no patient treated with Crestor 5 mg to 40 mg and manifesting proteinuria combined with hematuria developed renal insufficiency or renal failure.²⁰

In addition, in May 2004, AstraZeneca provided follow-up data of patients in the premarketing clinical database who had baseline proteinuria ($\geq 1+$) and were treated with rosuvastatin long term (mean 139 weeks). There were only 16, 45, 7, 7, and 43 patients with proteinuria at baseline at the 5-mg, 10-mg, 20-mg, 40-mg, and 80-mg doses, respectively, who received the drug for more than 2 years. No patient with baseline positive urine dipstick protein in the 10-mg, 20-mg, and 40-mg groups had a creatinine increase of > 30 percent. One patient in the 5-mg group and two in the 80-mg group had

²⁰ Two cases of renal failure and one case of renal insufficiency of unknown etiology were observed with rosuvastatin 80 mg in the original NDA. The patient with renal insufficiency had a positive rechallenge test to both rosuvastatin and atorvastatin. This suggests an effect/toxicity (apparently idiosyncratic) related to HMG-CoA reductase inhibition generally and not unique to rosuvastatin. Of the two patients who had renal failure, one had a renal scan showing multiple cystic masses in both kidneys and the second patient had a history of renal disease in childhood. In addition, in both cases, there was concomitant use of medications that have known adverse renal effects, as discussed in the WARNINGS or PRECAUTIONS sections of labeling for each (valsartan, rofecoxib, and candesartan). In short, neither of the two cases of renal failure was compelling with regard to a causative role of rosuvastatin, and certainly not a primary one.

a > 30 percent increase in serum creatinine. In this cohort, there were two patients who received the drug for > 48 weeks who experienced an adverse event of acute renal failure (ARF). Review of these case reports reveals the presence of medical illnesses as well as details of clinical management that conceivably contributed to the development of ARF. While a role for rosuvastatin in these cases obviously cannot be excluded, the information from these cases does not directly support primary causality by rosuvastatin.²¹

With regard to the clinical significance of these urinalysis findings, it is also important to note that renal disease of different types occurs in medical conditions that coexist with hypercholesterolemia, such as diabetes, hypertension, atherosclerosis, and congestive heart failure. In this clinical development program, approximately 39 percent of patients were \geq 65 years of age, 44.4 percent had mild renal impairment (CrCl 50-80 mL/min), 51.9 percent had hypertension, 36 percent had cardiovascular disease, and 16.5 percent had diabetes. Unlike rhabdomyolysis (an otherwise exceedingly rare event that, when it occurs in a statin-treated patient, is most likely due to statin), the few cases of serious renal disease observed in the rosuvastatin trials are confounded by multiple factors and have plausible or even likely explanations other than rosuvastatin itself. Furthermore, among the few cases of renal failure or insufficiency observed in these trials, no patterns emerge in the clinical or pathological presentations to clearly support a role of rosuvastatin.

In summary, regarding the renal safety data on Crestor from trials completed or ongoing at the time of approval, the following conclusions can be drawn:

- There appears to be a dose-related effect of Crestor (and likely other statins) causing mild, transient proteinuria, apparently due to a pharmacological effect of the drug on proximal renal tubular function. The effect appears to be on the order of 0.5 gm to 1 gm per 24 hours, consistent with tubular proteinuria.
- Consistent with a dose-related pharmacologic effect, this effect of rosuvastatin is also apparently reversible with a decrease in dose.
- The data are inadequate to conclude that there is a rosuvastatin-associated renal effect to cause proteinuria and hematuria in concert.
- The data do not support a rosuvastatin-associated renal effect to cause proteinuria, hematuria, and decreased glomerular filtration in concert.

²¹ Both patients were diabetic. One was a 59-year-old man treated with rosuvastatin 20 mg daily who had just undergone coronary artery bypass surgery and developed respiratory failure and hypotension requiring ventilation, sedation, and pressor therapy. The second patient was a 60-year-old man hospitalized with bilateral pleural effusions and pneumonia 3 months after beginning therapy with rosuvastatin 10 mg daily. His baseline creatinine was 1.7 mg/dL and peaked at 2.7 mg/dL while he was an in-patient.

- In preapproval clinical trials, no patients with proteinuria, or proteinuria with hematuria, treated with Crestor 5 mg to 40 mg developed renal insufficiency or renal failure.
- In a subgroup of patients treated for > 96 weeks with rosuvastatin, no patient who ever manifested combined proteinuria and hematuria had an increase in serum creatinine > 30 percent at the 10-mg to 40-mg doses.²²
- Although there were three patients in the preapproval studies and two in the postapproval studies who developed renal insufficiency/failure, all cases were confounded by co-morbid medical conditions that could contribute to the development of renal disease (e.g., critical illness requiring life-supportive measures, diabetes, recent major surgery).

2. *Renal Insufficiency/Failure in Crestor Phase 4 Studies Database*

The background on the ongoing Phase 4 clinical trials on Crestor is provided in section II.A.2 of this response. With respect to renal toxicity that might be associated with Crestor, the only clear renal signal from the NDA database and in ongoing studies is mild, transient and/or intermittent tubular proteinuria. The evidence does not suggest that Crestor causes tubular proteinuria, hematuria (more likely glomerular in origin), and decreased glomerular function in concert. Furthermore, the clinical renal adverse events are confounded by the presence of related pathologies and have occurred in a patient population in which risk factors for renal insufficiency and failure are prevalent. At present, there is insufficient evidence from clinical trials to conclude that rosuvastatin has a direct renal toxic effect or poses a greater risk of renal side effects than other marketed statins.

Among the 17,800 patients in postmarketing studies, there have been 12 cases of hematuria, 14 cases of ARF, 2 cases of chronic renal failure, 2 cases of renal impairment, 8 cases of renal insufficiency, 1 case of renal tubular necrosis, and 1 case of tubulointerstitial nephritis. The rates of renal failure and insufficiency are only 0.08 percent and 0.04 percent, respectively. For all of the listed conditions, there were *no* cases in which the investigator attributed the renal event to use of rosuvastatin. Our review of the case summaries confirms the presence of multiple, confounding clinical factors and the absence of any patterns of clinical or pathological presentation that would implicate rosuvastatin as the primary cause or even as a clear contributor.

3. *Adverse Event Reports on Crestor Concerning Renal Insufficiency or Failure*

Section II.A.3 of this response discusses several factors affecting the interpretation of adverse event reports, including the quality of information in the reports, the lack of a

²² There were no cases of combined proteinuria and hematuria at the 5-mg dose.

control group, and public awareness of potential adverse reactions. With respect to reports for rosuvastatin concerning renal insufficiency or failure, it is worth noting that rosuvastatin is the first statin labeled as having potential renal side effects,²³ and the Advisory Committee meeting on Crestor focused considerable attention on renal problems. These factors might have tended to increase the reporting of renal adverse events in association with rosuvastatin use compared to renal problems with other statins. This warrants caution in comparing reporting rates for renal-related adverse events between rosuvastatin and other statins.

We evaluated the adverse event reports for Crestor on renal insufficiency/failure reported between August 12, 2003, and October 31, 2004. A search of AERS for cases of renal injury in association with Crestor use included the following search criteria: ARF, acute tubular necrosis, and glomerulonephritis.

Among the cases of renal failure/insufficiency, most if not all patients had risk factors for renal failure/insufficiency. These included diabetes, warfarin coagulopathy resulting in renal hemorrhage, dehydration, preexisting renal disease, and concomitant drugs with potential renal adverse events. Indeed, renal disease is a relatively common complication of several medical conditions that occur alone or in combination in the target population for statins, which suggests that caution be used in attributing renal failure or insufficiency to the statin.²⁴ In patients for whom information was available, discontinuation of one or another drug (sometimes multiple drugs in addition to Crestor) was followed in some cases by clinical improvement or apparent recovery of renal function.

We identified a total of 38 cases; 30 were domestic. Table 6 below summarizes the proportion of domestic cases, by dose, compared to proportion of prescriptions dispensed, by dose:

Table 6. Renal Failure/Insufficiency Cases Associated With Crestor: Proportion of Cases by Dose Compared to Proportion of Use by Dose

| Dose | Cases, n (%) | Percent of Total Rxs |
|---------|--------------|----------------------|
| 5 mg | 1 (3.3) | 3.6 |
| 10 mg | 20 (66.7) | 77.1 |
| 20 mg | 2 (6.7) | 15.4 |
| 40 mg | 2 (6.7) | 3.8 |
| Unknown | 5 (16.6) | --- |

As shown, a majority of the cases reported were observed at the 10-mg dose. Whether or not any or all of the cases are related to the use of rosuvastatin, this finding is consistent with the fact that far greater numbers of patients were treated with this dose than any other dose.

²³ Crestor labeling refers to renal laboratory abnormalities in the PRECAUTIONS section.

²⁴ See Brewer, T. et al., Postmarketing surveillance and adverse drug reactions: current perspectives and future needs, *JAMA* 1990; 281(9):824-899.

We compared the adverse event reports on renal insufficiency/failure for Crestor to those for atorvastatin, another potent statin and the market leader for several years. This comparison also was analogous to one we conducted during the investigation of cerivastatin myotoxicity. For the period from August 2003 through October 2004, there were 30 domestic reports for rosuvastatin involving renal damage out of an estimated 6,071,000 prescriptions, for a reporting rate of 0.5/100,000. By comparison, in the same time period, there were 6 reports on renal damage for atorvastatin out of an estimated 13,300,000 prescriptions, for a reporting rate of 0.04/100,000. Thus, the reporting rate for renal injury with rosuvastatin was 12 times higher than the rate for atorvastatin.

As noted above, you claim that the rate of adverse event reports of acute renal failure or renal insufficiency per million prescriptions in patients using Crestor is approximately 75 times higher than the rate of reports for all other statin drugs combined. It is difficult to compare your findings on renal insufficiency/failure reporting rates with ours. Your analysis of renal adverse event reports includes statins with marketing periods beginning in 1987 and the early 1990s. It is possible that increased reporting of adverse events under the MedWatch program, which we established in 1993, might account for some of the differences in the two analyses. Moreover, as discussed in this section and in section II.A.3 of this response, assessing the data is further hindered due to (1) uncertainties about the actual number of events and the extent of population exposures, (2) the prevalence of other risk factors for renal compromise in patients treated with statins, (3) the fact that the adverse event is not otherwise unusual in the target population, and (4) the labeling and other publicity about the drugs being compared are distinctly different. Nevertheless, the results of both analyses are, on their face, cause for concern and are among the findings that have prompted us to further examine the renal effects of Crestor. As part of this effort, we reviewed the 38 individual (nonduplicated) cases of renal failure in association with rosuvastatin use for the August 2003 through October 2004 period.

- ***Clinical Review of Adverse Event Reports of Renal Insufficiency/Failure in Association with Crestor Use***

In reviewing the individual adverse event reports on renal insufficiency or failure, we focused on assessing evidence of potential causation by Crestor and considered whether there was compelling evidence of a pathognomonic renal “syndrome” associated with Crestor use. Two experienced FDA medical officers conducted independent reviews of the individual cases. The cases were grouped as follows:

- Group 1: Unrelated to Crestor use (Reviewer #1: 2 cases; Reviewer # 2: 3 cases)
- Group 2: Insufficient information (lack of historical detail, dose, dates, etc.) (Reviewer #1: 10 cases; Reviewer #2: 9 cases)

- Group 3: Confounded by other plausible causes or contributors or potentially related to rhabdomyolysis, thus low probability for primary, direct causation by Crestor (Reviewer #1: 11 cases; Reviewer #2: 19 cases)
- Group 4: Confounded, but history supporting possible direct causation by Crestor (Reviewer #1: 15 cases; Reviewer #2: 7 cases)

The difference between the assessments of the two reviewers lies mainly in cases included in Groups 3 and 4. One reviewer (#2) labeled more cases as overly confounded, by definition lacking sufficient evidence of direct causation (thus, Group 3). In contrast, the other reviewer (#1), while acknowledging these multiple confounding factors, nevertheless concluded that many of these cases should be classified in Group 4, in most instances because the temporal sequences of events supported a judgment that Crestor could have been causative. For completeness and transparency with regard to process and results, we have identified by reviewer the number of cases assigned to each group. The discussion that follows describes the panoply of confounding factors and temporal relationships, and examines the cases collectively for evidence of patterns of clinical or pathological presentation. This discussion is not impacted by the specific differences in the Group 3 and 4 categorizations of individual cases because confounding factors were identified across the cases included in these groups by both reviewers.

Among the Group 1 (unrelated) cases were two with negative rechallenges after dechallenge. The third case, included by reviewer # 2, was a clear case of contrast-induced acute tubular necrosis (ATN). Reviewer #1 had placed this case in Group 2 (insufficient information).

Among the Group 3 (confounded) cases, confounding factors that individually or together constituted likely contributing factors or plausible causes included the following: age, chronic illness (diabetes mellitus (DM), hypertension (HTN), history of chronic renal failure, ASCVD, CHF, atrial fibrillation, monoclonal gammopathy, hyperuricemia, COPD, biliary tract disease), multiple drugs (ACE/ARB, diuretics, allopurinol, NSAID), acute illness (hepatitis, myositis, Stevens Johnson Syndrome, sepsis, hypotension, vomiting, diarrhea, dehydration, post-surgery, pneumonia, s/p renal transplant, warfarin-related renal hemorrhage, small-bowel ileus, and recent open heart surgery). Examples of Group 3 cases include:

- A case of minimal change nephropathy by biopsy associated with massive proteinuria (12 g/day) in a patient with psoriasis, which did not respond to dechallenge
- A case of possible rhabdomyolysis in a longstanding diabetic with HTN, CHF, on multiple meds (including diuretics and ARB/ACE) with renal failure preceded by a 3-4 week history of nausea, vomiting, diarrhea, and muscle aches

- An elderly female with a history of hypertension with massive, progressive weight loss, abnormal liver function tests during the course of therapy with Crestor, and a creatinine clearance of 7 mL/minute 5 months after discontinuing Crestor

Among the Group 4 (confounded but history supporting possible direct causation) cases were several instances where there was an apparent positive dechallenge (i.e., the condition improved after discontinuation of Crestor — and often other medications as well), although no rechallenge was documented in any of these cases. Though cases in Group 4 were deemed potentially related by one or both reviewers, all cases included in Group 4 (regardless of reviewer) were still significantly confounded by preexisting risk factors for renal failure, including advanced age, DM, HTN, chronic renal failure, history of hyperkalemia prior to Crestor therapy, concomitant medications, and acute presentations suggesting other possible causes or contributors (e.g., hepatitis and hyperbilirubinemia in a patient with a history of biliary tract disease; hives, eosinophilia, and hypoalbuminemia in an elderly male with DM, HTN; chronic renal failure).

No clear patterns of clinical presentation of renal failure are apparent from these data. Conditions co-occurring with dyslipidemia (including advanced age, DM, HTN, ASCVD, CHF, and chronic renal insufficiency) occur, singly or multiply, in the majority of the cases for which sufficient information is reported. Further, as expected given these coexisting conditions, use of concomitant medications with known renal or prerenal effects was also reported.²⁵

With regard to patterns of pathological presentation, we note that in four cases, a diagnosis of acute tubular necrosis was cited. These cases are summarized briefly below to illustrate both the confounded nature of the cases and the absence of clinical patterns linking the cases, even though they share a related pathology (albeit a pathology with a known extensive list of possible causes).

- One case was an elderly female with a history of HTN on diuretics with unexplained massive, progressive weight loss (>50 pounds), abnormal liver function tests during the course of therapy with Crestor, and a creatinine clearance of 7 mL/minute 5 months after discontinuing Crestor.
- Another was a 62-year-old male with DM1, CAD, on multiple medications (including lasix) who developed abdominal pain, metabolic acidosis, and ATN 10 days after switching from Lipitor to Crestor. An exploratory laparoscopy was negative and a renal scan showed enlarged kidneys and increased uptake. Multiple medications, including Crestor, were discontinued, and the patient recovered.

²⁵ Use of diuretics, ACE/ARB, beta blockers, and NSAIDS also was reported, singly or multiply, in the majority of cases for which sufficient information was provided.

- A third case involved a 66-year-old female with hypothyroidism and hypertension who presented in DKA approximately 7 weeks after starting Crestor 10 mg. She had developed nephrotic syndrome during therapy with Crestor, with workup for other causes negative, which then resolved off Crestor.
- The fourth case did not include sufficient information beyond the diagnosis of ATN.

We also note that there were three cases of renal failure in association with hepatitis, again without clear clinical similarities:

- A 51-year-old female with no history given on ACE/HCTZ presenting with hepatitis, nausea, vomiting, and creatinine elevation/renal failure 3 months after starting Crestor. Resolved after discontinuation of Crestor.
- A 66-year-old male with history of cholecystectomy in the distant past, CAD s/p PTCA, aortic valve replacement, on coumadin, Celebrex, ASA, metoprolol presented with hepatitis, jaundice, and renal failure 3 weeks after starting Crestor. No follow-up information given.
- A 71-year-old black male with DM, HTN, and CRI on ACE presented with hives, fatigue, weakness, eosinophilia, and hepatitis with hyperbilirubinemia. The patient was treated with prednisone, antihistamines, and supportive measures and discontinuation of Crestor. Condition resolved.

The majority of these adverse event reports involved patients receiving the 10-mg dose, which is consistent with the usage pattern for Crestor and not necessarily indicative of causation.

There are several important findings from this case-by-case analysis of the adverse event reports on renal insufficiency/failure for Crestor. First, there are two or three cases (depending on the reviewer) in which one can, with reasonable confidence, exclude Crestor from having a role in the genesis of the renal failure. Among the 25 or 26 cases where there is sufficient information to conduct a meaningful case review, the vast majority of cases are confounded by concomitant conditions and medications that suggest at least potential alternative contributors or causative factors in the presentation of renal failure. However, there are a number of cases in which withdrawal of Crestor, with or without reported withdrawal of other medications, was followed by apparent partial or full resolution of renal failure. In none of these cases was rechallenge reported. Among cases rated as possibly related to Crestor use (Group 4) by one or another of the two reviewers, there were no evident patterns of clinical presentation, save for the preponderance of multiple conditions coexisting with dyslipidemia and themselves constituting risk factors for renal compromise. Likewise, there were no consistent

patterns of pathological presentation, with diagnoses including ATN, nephrotic syndrome, and minimal change nephropathy. Across the four cases in which there was a diagnosis of ATN, there were no compelling clinical similarities with regard to presentation that would permit tentative description of a “Crestor-related renal syndrome.”

In sum, the specifics of the cases reported to AERS thus far do not reveal a pattern of clinical or pathological presentation marking a potential Crestor-associated renal injury syndrome. However, neither does a review of the cases fully dispel concerns of possible renal effects of Crestor that might, in some instances, result in renal insufficiency or failure. Therefore, we will continue to monitor all available information concerning renal insufficiency and failure. At present, though, given the weight of evidence from preclinical data, premarketing and postmarketing controlled clinical studies, and spontaneous postmarketing adverse event reports, there is insufficient evidence to conclude that there is a direct renal toxic effect associated with rosuvastatin use. In light of the demonstrated LDL-lowering benefits, the current level of evidence for a possible renal effect does not constitute a basis for withdrawing Crestor from marketing.

III. SAFETY CONCLUSIONS AND FDA/SPONSOR ACTIONS

As with any drug, in evaluating the safety of rosuvastatin, it is essential to consider the totality of evidence from animal studies, preapproval controlled clinical trials, ongoing clinical trials, and postmarketing adverse event reports. With respect to the reports on Crestor concerning myopathy/rhabdomyolysis and renal insufficiency/failure, there are several factors that are relevant to assessing the seriousness of the risk and Crestor’s causative role. As discussed in sections II.A.3 and II.B.3 of this response, these include, among other things:

- uncertainties about the actual number of events and the extent of population exposures,
- variation in the level of detail in case reports,
- the lack of a control group with similar underlying risks,
- heightened awareness of rosuvastatin safety concerns due to product labeling and the withdrawal of cerivastatin, and
- the presence of confounding factors (drugs, risk factors, intercurrent illness).

Regarding Crestor and muscle toxicity, after careful examination of the available information we see no compelling evidence to date of clinical risks of rosuvastatin that distinguish it from other approved statins. In fact, some evidence suggests a lower risk when comparing across doses with similar cholesterol-lowering effects. Furthermore, there is substantial evidence to suggest that rosuvastatin is, counter to your contention, far safer with regard to muscle toxicity than cerivastatin. To the extent that there are risks of muscle injury associated with rosuvastatin therapy, as there are for all statins, use of the drug according to labeling is paramount to reducing those risks, though some individuals will inevitably have muscle side effects, ranging from mild aches to severe muscle

damage, the latter occurring extremely rarely. Because postmarketing reports suggest some inappropriate use of the 40-mg dose potentially contributing to occurrences of muscle toxicity, further revisions to the labeling to ensure that the 40-mg dose is used only in appropriate patients is warranted. To that end, AstraZeneca has agreed to further revisions to labeling, as discussed below.

With respect to Crestor and renal toxicity, while there is evidence of a renal effect of rosuvastatin (and other statins) to cause tubular proteinuria, there is no convincing evidence of a risk of serious renal injury from rosuvastatin. The data indicate that rosuvastatin can have minor, apparently transient and/or intermittent effects on renal tubular function in some individuals, but they do not constitute evidence of serious drug toxicity *per se*. On the contrary, recent data suggest that this renal effect is one that is shared across the statin class as a result of inhibition of renal tubular HMG-CoA reductase enzyme activity. Because rosuvastatin is more potent in that regard on a per-mg basis, given the doses studied, it is understandable that these renal effects might first be noticed in the clinical program for this drug. For renal adverse events, which occur commonly in the statin-eligible population regardless of statin exposure, the spontaneous adverse event reports are confounded, the diagnoses are incomplete, and there are no evident patterns of clinical or pathological presentation that clearly define a syndrome of Crestor renal injury. Unfortunately, although comparisons of reporting rates for renal failure between rosuvastatin and other marketed statins might be the only way we can evaluate such postmarketing data for inferences of causality, such assessments are fundamentally unreliable, for the reasons discussed earlier.

We will continue to evaluate the evidence concerning renal effects of Crestor. As always, particularly given the multiple risk factors for renal disease in patients with dyslipidemia and atherosclerosis who are candidates for statin therapy, ongoing vigilance concerning changes in clinical status in such patients is critical to effective management and disease prevention, whether patients are treated with Crestor, other statins, or neither.

Given the lack of a clear, monotonic signal for a particular adverse renal effect of Crestor arising from the AERS data, and given the fact that comparisons of reporting rates are fraught with potential biases, we need other means of assessments to further address Crestor renal effects. Ongoing controlled clinical trials of Crestor and of other statins, epidemiological studies of the safety and side effects of these drugs, and continuing pharmacovigilance by FDA will provide additional information on the safety and efficacy of Crestor and of other members of this generally safe, important class of drugs. We are working with AstraZeneca to insure that these studies are properly designed, expeditiously undertaken, and fully reported. We will make this information available to the public and, if necessary, take appropriate regulatory action.

Our review of the adverse event reports on rosuvastatin reveals use of the drug that is not consistent with its labeling. To address certain concerns regarding this use, AstraZeneca has agreed to make several changes to Crestor labeling. The sponsor is also revising the labeling to provide important information obtained from a Phase 4 pharmacokinetic study

in Asian Americans. These changes, which we approved on March 2, 2005, are intended to better communicate risks of rosuvastatin therapy to prescribers and pharmacists in order to promote, to the greatest extent possible, safe as well as effective use of the drug. In addition to FDA announcements regarding Crestor, AstraZeneca has agreed to issue a "Dear Healthcare Professional" letter describing these changes to labeling.

Following is a discussion of the specific changes to Crestor labeling:

1. Drug Exposure to Asian Americans: As part of the approval of Crestor, AstraZeneca agreed to conduct a Phase 4 study evaluating the pharmacokinetics of rosuvastatin in Asians residing in the United States. This Phase 4 study was prompted by findings from previously conducted pharmacokinetic studies in Asians residing in Singapore and Japan that suggested a two-fold increase in drug levels relative to Caucasians. As it was not clear at the time of approval whether this difference related to ethnic, genetic, or environmental differences, AstraZeneca agreed to conduct a clinical study that evaluated a diverse Asian-American patient population to determine the relevance of these findings to this group of patients in the United States. The preliminary findings of this study support earlier findings in Asians. As a result, AstraZeneca has revised Crestor labeling to describe the study and its results and has made dosing recommendations to address greater drug exposures in Asian Americans. The dosing recommendations are recognized as important information for the safe use of this product in this subpopulation because statins have adverse events (i.e., myopathy/rhabdomyolysis) whose risk appears to increase with increases in blood levels of the drug. The following are the Crestor labeling changes concerning the Asian-American population:

CLINICAL PHARMACOLOGY; Special Populations

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the U.S., have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group. (See WARNINGS, Myopathy/Rhabdomyolysis, PRECAUTIONS, General and DOSAGE AND ADMINISTRATION).

PRECAUTIONS; General

...The result of a large pharmacokinetic study conducted in the U.S. demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/ Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION; Dosage in Asian Patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS,

Myopathy/Rhabdomyolysis, CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General).

2. Increased Emphasis on Dose-Related Risks and Appropriate Dosing: Our review of postmarketing adverse event reports for myopathy/rhabdomyolysis revealed that physicians were prescribing Crestor in a manner inconsistent with labeling in certain instances. For example, two cases included patients co-prescribed cyclosporine and rosuvastatin 40 mg (the labeling recommends that only the 5-mg dose be used). Another patient was started on therapy at the 40-mg dose (not a recommended start dose). Consequently, AstraZeneca has revised several sections of the Crestor labeling to remind prescribers of the risk of myopathy associated with rosuvastatin therapy and that this risk increases with increasing doses and in special populations. There is emphasis on not initiating therapy with the 40-mg dose because it is not an approved start dose. This emphasis, which occurs in the DOSAGE AND ADMINISTRATION section, is a bolded statement, as shown below.

WARNINGS; Myopathy/Rhabdomyolysis section

...In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In post-marketing experience, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥ 65 years), hypothyroidism, and renal insufficiency.

...

The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION; Hypercholesterolemia (Heterozygous Familial and Nonfamilial and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

The dose range for CRESTOR is 5 to 40 mg once daily. Therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions. For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose

should first be utilized, and only then titrated according to the patient's individualized goal of therapy.

3. Jaundice: Rare cases of jaundice have been observed among the adverse event reports, although causality could not be established given other medical illnesses. These reports, however, warrant an update to the ADVERSE REACTIONS; Postmarketing Experience section of labeling to include the following:

In addition to the events reported above, as with other drugs in this class, the following event has been reported during postmarketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice.

IV. CONCLUSION

For the reasons stated above, we do not agree with your view that concerns about rhabdomyolysis and renal insufficiency/failure warrant the withdrawal of Crestor from the market. Our review of all of the available evidence (including preclinical data, premarketing clinical studies, Phase 4 clinical studies, and postmarketing adverse event reports) indicates that Crestor does not pose a risk of muscle toxicity greater than that of other approved statins. With respect to renal toxicity, there is no convincing evidence that Crestor poses a risk of serious renal injury. Therefore, your request that we withdraw Crestor from the market is denied. However, to help ensure the safe and effective use of Crestor, AstraZeneca has revised the labeling to address certain concerns regarding dose-related risks, proper dosing, and other matters related to information from adverse event reports and Phase 4 studies. In addition, we will continue to seek and evaluate information involving Crestor and muscle and renal toxicities, and we will take any appropriate action to protect patients who use this drug.

Sincerely,



Steven K. Galson, M.D., M.P.H
Acting Director
Center for Drug Evaluation and Research

APPENDIX

Table A1. Patient Exposures for Rosuvastatin in NDA Submission

| Maximum continuous duration of treatment for each dose of rosuvastatin in the Combined All Controlled/Uncontrolled and RTLD Pool* | | | | | | | | |
|---|----------------|-----------------|-----------------|--------------------------------------|---------------------------------|--------------------------|-----------------|--------------------------------|
| Duration of Tx | 5 mg N=1325 | 10 mg N=7819 | 20 mg N=3939 | not down-titrated to 40 mg N=3742 | down-titrated to 40 mg N=825 | total at 40 mg N=4007 | 80 mg N=1583 | total rosuvastatin N=12,569 |
| ≥ 6 wks | 1234 | 7467 | 3582 | 3381 | 820 | 3705 | 1417 | 12049 |
| ≥ 12 wks | 995 | 6219 | 2143 | 2001 | 803 | 2758 | 1055 | 10603 |
| ≥ 24 wks | 647 | 5041 | 1353 | 1227 | 686 | 1893 | 971 | 8860 |
| ≥ 48 wks | 542 | 4055 | 545 | 276 | 0 | 276 | 891 | 6646 |
| ≥ 72 wks | 324 | 1546 | 235 | 159 | 0 | 159 | 783 | 3423 |
| ≥ 96 wks | 283 | 903 | 120 | 110 | 0 | 110 | 642 | 2356 |
| Mean duration of treatment (days) | 362.8 | 348.6 | 167.8 | 142.9 | 211.8 | 169.5 | 450.5 | 413.6 |
| Pt-yrs of tx | 1315 | 7458 | 1800 | 1461 | 477 | 1857 | 1944 | 14231 |

*This database included all controlled and uncontrolled studies that had real-time laboratory data (RTLD).
Cut-off date for this summary was prior to June 2003.

Table A2. Incidence of Myopathy with Rosuvastatin in Pooled Analysis of All Controlled Studies

| Rosuvastatin | N | Percent of patients reported with CK > 10x ULN and Muscle Pain |
|--------------|------|--|
| 5 mg | 833 | 0.4% |
| 10 mg | 3193 | 0.1% |
| 20 mg | 2113 | 0.1% |
| 40 mg | 2804 | 0.4% |
| 80 mg | 988 | 0.9% |

Table A3: Muscle Toxicity in the Crestor Clinical Trials for Approved Daily Doses of 5 to 40 mg (Data Through December 2003)

| Dose (mg) | Patient number | CK> 10xULN & Muscle Symptoms (Myopathy) | | CK> 10xULN & Muscle Symptoms & Hospitalization | | Rhabdomyolysis ACC/AHA definition | |
|----------------|----------------|---|------|--|------|-----------------------------------|------|
| | | Number | % | Number | % | Number | % |
| 5 | 1,324 | 3 | 0.2 | 0 | 0 | 0 | 0 |
| 10 | 8,325 | 10* | 0.1* | 0* | 0* | 0* | 0* |
| 20 | 4,651 | 8 | 0.2 | 1 | 0.02 | 1 | 0.02 |
| 40 | 4,450 | 8 | 0.2 | 1 | 0.02 | 0 | 0 |
| All doses 5-40 | 13,395 | 29 | 0.2 | 2 | 0.01 | 1 | 0.01 |

*These data do not include two cases of rhabdomyolysis in patients treated with rosuvastatin 10 mg. One suspected case of rhabdomyolysis was later attributed to septic shock by the clinical investigator. This patient was enrolled in the GISSI HF trial in Italy which was not sponsored by AstraZeneca, so AstraZeneca did not have access to the data. The other case of rhabdomyolysis was in a 63 y/o with end stage renal failure on chronic dialysis. This patient was not included in this data set because he was identified after the cutoff date of Dec. 31, 2003. The inclusion of these 2 cases out of > 8,300 patients would represent a frequency of 0.02% or less, similar to the rate seen at the 20-mg dose.