approving the drug after a comprehensive review, determined CRESTOR to be safe and effective.

III. THE PETITION MISREPRESENTS THE SAFETY OF CRESTOR.

HRG presents a selective and misleading review of the clinical and post-marketing safety surveillance data. The clinical studies have confirmed that CRESTOR is safe and effective when used according to the prescribing information, and nothing in the post-marketing experience contradicts that conclusion. CRESTOR is now approved in more than 60 countries, and it is estimated that more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with the pre-approval experience as reflected in CRESTOR's prescribing information.

A. CLINICAL TRIALS ESTABLISHED AND POST-MARKETING EXPERIENCE CONFIRMS THE SAFETY OF CRESTOR.

The FDA requires that a product's underlying risks and benefits must be adequately assessed during the premarketing period, adding that "sponsors should provide a body of evidence from the clinical trials that adequately characterizes the product's safety profile."[50] The FDA has confirmed that "the larger and more comprehensive a preapproval database, the more likely it is that serious adverse events will be detected."[51] The FDA has advised that premarketing safety databases should include a diverse population to allow for "the development of safety data in a broader population, including patients previously excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking usual concomitant medications."[52]

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50 FDA Draft Guidance for Industry, "Premarketing Risk Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

51 *Id.*

52 *Id.*

At the time of FDA approval, the safety of CRESTOR had been evaluated in more than 10,000 patients,[53] with more than 1,500 patients treated for at least two years.[54] Currently more than 40,000 patients are being or have been treated with CRESTOR in controlled clinical trials. The most frequently observed adverse events thought to be related to CRESTOR include myalgia, constipation, asthenia, abdominal pain, and nausea; these adverse events were usually mild and transient.[55] Overall, CRESTOR was generally well tolerated in clinical trials.[56] The overall incidence of adverse events reported with CRESTOR was similar to placebo.[57] The overall frequency of adverse events was similar with CRESTOR doses of 5 mg to 40 mg.[58]

The safety and tolerability of CRESTOR have been assessed using data from the largest pre-approval clinical trial program for any statin approved to date. As every effort was made to recruit patients who would resemble, as closely as possible, individuals who would be candidates for statin therapy in clinical practice, the populations studied included patients with various forms of dyslipidemia, including heterozygous or homozygous familial hypercholesterolemia and the Fredrickson classifications of Type IIa or IIb hypercholesterolemia and Type IV hypertriglyceridemia.[59] In addition, in phase III trials, there was no upper age limit for entry, and patients with mild-to-moderate renal impairment with creatinine levels up to 2.5 mg/dl were enrolled, as were those with stable concomitant illnesses that are

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53 CRESTOR Prescribing Information.

54 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

55 CRESTOR Prescribing Information.

56 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.* 2003;92(suppl):23K-29K; CRESTOR Prescribing Information.

57 CRESTOR Prescribing Information; Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

58 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

59 *Id.*

commonly associated with dyslipidemia (e.g., hypertension, diabetes mellitus, and cardiovascular disease).[60]

As shown in Table IX (Appendix), in fixed-dose trials with comparator statins, CRESTOR 5 to 40 mg showed a similar adverse event profile to those for atorvastatin 10 to 80 mg, simvastatin 10 to 80 mg, and pravastatin 10 to 40 mg, with the most common adverse events across statin-treated groups being pharyngitis, headache, pain, myalgia, diarrhea, and abdominal pain.[61] Overall, the occurrence of treatment-related adverse events was low.

During the pre-approval clinical trials, there were no deaths attributed to CRESTOR. In controlled trials, clinically significant elevations of ALT (>3 x upper limit of normal at 2 consecutive treatments) occurred in a similar proportion of patients in each statin group (0.2%).[62] Myopathy possibly related to CRESTOR during the clinical trial program evaluating CRESTOR 5-40 mg was rare and occurred in ≤0.03% of patients.[63] There were no reports of rhabdomyolysis attributed to CRESTOR 5-40 mg.[64]

Proteinuria was seen in <1.0% of patients receiving CRESTOR 5, 10, or 20 mg and in those patients receiving placebo, atorvastatin 10 to 80 mg, simvastatin 10, 40, and 80 mg, or pravastatin 10 to 40 mg.[65] Proteinuria was seen in 1.2% of patients receiving CRESTOR 40 mg and 1.1% of patients receiving simvastatin 20 mg.[66] These findings of proteinuria were transient in many cases, reversible, and not associated with long-term detrimental effects on renal function. Importantly, renal function, assessed

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60 *Id.*

61 *Id.*

62 *Id.*

63 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.*2003;92(suppl):23K-29K.

64 *Id.*

65 Vidt DG et al. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology* 2004;102:52-60.

66 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

by mean glomerular filtration rates predicted from the Modification of Diet in Renal Disease (MDRD) equation, did not deteriorate in patients receiving long-term (≥96 weeks) CRESTOR therapy at any dose, irrespective of age, sex, hypertensive or diabetic status, level of renal function at baseline (glomerular filtration rates ≥60 versus <60 ml/min/1.72 m^2) or presence or absence of urine dipstick protein before or during treatment.[67]

In summary, the 5 - 40 mg dose range for CRESTOR provides greater lipid modification when compared with other marketed statins. The LDL-C benefits with CRESTOR translated to a greater number of patients achieving NCEP ATP III goals at the 10 mg/day start dose, thereby reducing the need to titrate to higher doses. CRESTOR also allowed many patients to increase their HDL-C and reduce non-HDL-C and triglycerides. This is achieved with a safety profile that is similar to other currently marketed statins. At doses up to and including 40 mg, CRESTOR was generally well tolerated. Thus, the clinical trial data establish the positive benefit-risk profile for CRESTOR when used according to the prescribing information. CRESTOR offers an important option for patients and their healthcare professionals for the treatment of dyslipidemia.

B. HRG REJECTS SCIENTIFIC ANALYSIS IN FAVOR OF SPECULATION REGARDING THE SAFETY OF CRESTOR BASED SOLELY UPON UNVERIFIED AND LIMITED DATA.

The petition bases its request that CRESTOR be "immediately removed" from the market on essentially two lines of alleged evidence. The first is a selective presentation of opinions not related to the safety and efficacy of CRESTOR, but rather in the nature of business decisions. Specifically, HRG notes that two insurance companies do not, at this time, reimburse their insureds for CRESTOR prescriptions. What HRG fails to mention is that the overwhelming majority of insurers and managed care organizations in the United States have added CRESTOR to their formularies. HRG

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67 *Id.*

also claims that "[i]n Sweden, regional government drug advisors recommended against the use of the drug." This is simply incorrect. In truth, the referenced board recommended reimbursement for CRESTOR, but only for patients who failed to reach lipid goals with generic drugs in the statin class. Thus, the decision was driven by economic interests and not safety or efficacy concerns. Moreover, since its approval on April 4, 2003 by the Medical Products Agency, CRESTOR remains available for prescription in Sweden. That HRG opts to rely upon such unsubstantiated information reveals the weakness of its entire position.

HRG's second line of alleged evidence is based upon a number of unverified, unidentified spontaneous post-approval adverse event reports, all of which have been appropriately reported to, and evaluated by, the FDA. This is not the first time HRG has attacked an FDA-approved medicine based upon such information. In denying previous HRG petitions, the FDA often has had to remind Public Citizen about the significant limitations on the use of adverse event reporting data and the dangers of its misuse.[68]

That adverse event reports can play a role in the identification of a safety signal is well-recognized.[69] Signals are hypothesis-generating and generally require further investigation, that, in turn, may or may not lead to the conclusion that the events were product-related.[70] The identification of a signal, however, demands careful case assessment of individual reports, including an evaluation of clinical content and completeness, as the quality of the reports is critical for appropriate evaluation of the relationship, if any, between the product and the adverse event.[71] Detailed case

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68 *See, e.g.*, Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking to ban the use of Feldene (prioxicam) in people aged 60 and over (July 7, 1986); Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking withdrawal of Arava (leflunomide) (Mar. 23, 2004).

69 FDA Draft Guidance for Industry, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

70 *Id.*

71 *Id.*

assessment is especially important with an event such as rhabdomyolysis, as the criteria used for its diagnosis can vary tremendously.

The outcome of a thorough case assessment must then be compared with other relevant safety information, such as results from preclinical, clinical, pharmacoepidemiologic, or other available studies, and placed into context by determining the extent of patient exposure.[72] Additionally, as many factors can affect the reporting of adverse events (*e.g.*, publicity and newness of the product), these factors must be considered in interpreting any results.[73]

HRG has performed none of these steps. Instead it relies solely on the fact that a number of adverse events labeled as rhabdomyolysis have been reported for CRESTOR. The numerous flaws to this approach are discussed below. Moreover, that there have been reports of rhabdomyolysis in patients using CRESTOR comes as no great surprise, as rhabdomyolysis is a labeled and well-known, although rare, risk of all the currently marketed members of the statin class.

1. HRG misuses adverse event reports.

The FDA is fully aware that adverse event reports alone can only provide limited information, at best, about the safety of a medicine. In fact, the FDA has published guidelines identifying at least some of the limitations on the use of adverse event reports:[74]

> Reports contain only those reactions voluntarily submitted either to the FDA or to the drug manufacturer by consumers and/or members of the health profession....
>
> The information contained in the reports has not been scientifically or otherwise verified.

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72 *Id.*

73 *Id.*

74 FDA, Office of Postmarketing Drug Risk Assessment, "Brief Description with Caveats of System" (Oct. 18, 1999).

> For any given report, there is no certainty that the suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions.
>
> Accumulated case reports cannot be used to calculate incidence or estimates of drug risk.

HRG, however, ignores these well-known limitations and, without the full facts, attempts to use adverse event reports in a manner that the FDA has criticized. For example, the FDA has recognized that an adverse event report cannot be interpreted as evidence that the medicine caused the event, stating affirmatively that "there is no certainty that the suspected drug caused the reaction":

> [A] possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure.[75]

A fair understanding of an adverse event report and its significance can be obtained only by a careful medical review. In the absence of a thorough examination, a causal connection cannot be inferred; even when the medical records are available, it is often difficult or impossible to assess causality.

HRG commits precisely the "serious error" identified by the FDA - it wrongly uses an adverse event report to claim that CRESTOR caused fatal rhabdomyolysis. HRG cites a report of "a 39-year-old woman, taking only 20 milligrams a day, [who] died of rhabdomyolysis and renal insufficiency." That is how the report initially came to AstraZeneca and how it was initially submitted to the FDA. However, as the FDA knows, subsequent investigation revealed autopsy records for

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[75] 62 Fed. Reg. 30678, 30689-90 (June 4, 1997) (proposed rule for dietary supplements containing ephedrine alkaloids); *see also* FDA, "Postmarketing Safety of Sildenafil Citrate (Viagra)," March 3, 2001, *available at* www.fda.gov/cder/consumerinfo/viagra/safety3.htm ("An accumulation of adverse event reports does not necessarily indicate that the adverse event was caused by the

this patient, establishing that she died of an acute myocardial infarction. At autopsy, there was no evidence of rhabdomyolysis, and the death had nothing to do with CRESTOR. This is an example of why adverse event reports cannot be used to establish a link between a medicine and the event, and it is wrong for HRG to attempt to do so in its petition.

Additionally, spontaneous adverse event reporting systems are voluntary. Thus, reporting is susceptible to a wide range of factors that may stimulate or discourage voluntary reporting, including:

- Adverse publicity: lay and medical reporting of serious events with a product will stimulate reports;[76]
- Number of years that the drug has been on the market: events are more likely to be reported in the first 2 years of marketing than in later years (the "Weber effect");[77]
- Seriousness of the adverse event: deaths and life-threatening reactions are more likely to be reported than mild or transient side effects.[78]

Clearly, several of these variables, especially the first in the wake of HRG's petition, may be at play with respect to CRESTOR.

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drug; rather, the event may be due to an underlying disease or some other factor(s).").

[76] Faich GA, Moseley RH. Troglitazone (Rezulin) and Hepatic Injury. *Pharmacoepidemiology and Drug Safety.* 2001;10:537-47; Meinzinger MS, Barry WS. Prospective Study of the Influence of the Media on Reporting Medical Events. *Drug Inf J.* 1990;24: 575-77; Rossi AC et al. The Importance of Adverse Reaction Reporting By Physicians: Suprofen and the Flank Pain Syndrome. *JAMA.* 1988;259:1203-04.

[77] Wallenstein EJ, Fife D. Temporal Patterns of NSAID Spontaneous Adverse Event Reports: the Weber Effect Revisited. *Drug Safety.* 2001;24:233-37; Tsong Y. Comparing Reporting Rates of Adverse Events Between Drugs with Adjustment for Year of Marketing and Secular Trends in Total Reporting. *J Biopharm Stat.* 1995;5:95-114; Sachs RM, Bortnichak EA. An Evaluation of Spontaneous Adverse Drug Reaction Monitoring Systems. *Am J Med.* 1986;81:49-55; Weber JCP. Epidemiology of Adverse Reactions to Nonsteroidal Antiinflammatory Drugs. In: Rainsford KD, Velo GP, eds. *Advances in Inflammatory Research.* Vol. 6. New York: Raven Press, 1984:1-7.

[78] Piazza-Hepp TD, Kennedy DL Reporting of adverse events to MedWatch. *Am J Health-Syst Pharm.* 1995;52:1436-39; Milstien JB et al. Factors Affecting Physician Reporting of Adverse Drug Reactions. *Drug Inf J.* 1986;20:157-64.

Additional problems with HRG's use of adverse event reports arise from the medical conditions HRG has raised, namely rhabdomyolysis and kidney damage. Neither has a standard medical definition,[79] further confounding the interpretation of spontaneous adverse event reports. Specifically, one consequence of not having standard medical definitions is that physicians may diagnose different events as "rhabdomyolysis" or "acute renal failure."

Moreover, HRG fails to provide any context for the adverse event reports it cites. HRG makes no attempt to reconcile the number of reports against the backdrop of ever-increasing use of CRESTOR in the United States. Nor does HRG attempt to reconcile the number of reports against the background rate of such adverse events in hypercholesterolemic patients. Absent such an analysis, the number of adverse event reports alone is meaningless.

In conclusion, HRG has simply failed to perform any of the basic and necessary steps in safety signal identification. On the other hand, AstraZeneca, the FDA and the MEB are continually evaluating the available post-marketing data and agree that CRESTOR is safe and effective when used in accordance with its product labeling. Despite the increased attention and publicity surrounding CRESTOR, its adverse event reporting experience has been stable and in line with that of the other currently marketed statins.

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[79] Thompson PD et al. Statin-Associated Myopathy. *JAMA*. 2003;289:1681-1690 ("The literature on skeletal muscle complaints with statins is confusing, in part because of a lack of clear definitions."); Thadhani Ret al. Acute Renal Failure. *NEJM*. 1996; 334:1448-1460 ("When one attempts to review the subject of acute renal failure, one is immediately struck by the confusion in terminology and the wide disparity in the definitions of terms. Notably, in a recent review of 26 studies on postoperative renal failure, no 2 studies used the same definition of acute renal failure.").

2. AstraZeneca diligently monitors reports of adverse drug events and shares all such information with the FDA in accordance with applicable regulations.

There is nothing new in the HRG petition. HRG simply reargues the same points it made over a year ago at the FDA Advisory Committee meeting regarding the approval of CRESTOR. Despite HRG's claims of an increased risk of rhabdomyolysis and kidney toxicity, the Advisory Committee unanimously recommended approval. Fully aware of the adverse events discussed in HRG's petition, the FDA, and numerous other regulatory agencies, have agreed and have properly concluded that the benefits of CRESTOR outweigh its risk when prescribed and used in accordance with its labeling.

AstraZeneca's highest priority is patient safety. AstraZeneca monitors and assesses reports of adverse events to identify and mitigate any safety risks. Through its monitoring efforts, AstraZeneca ensures that the FDA, other regulatory authorities, and prescribing physicians receive complete, up-to-date information about the safety of CRESTOR. Indeed, the adverse event reports cited by HRG already were brought to the FDA's attention. As the FDA and as the MEB concluded most recently, in response to Mr. Wolfe's Letter to the Lancet on June 25, 2004, CRESTOR is safe and effective when prescribed and used in accordance with its labeling.[80]

IV. THE STANDARD FOR WITHDRAWAL CANNOT BE MET.

CRESTOR is a "new drug" as defined under section 201(p) of the FFDCA, 21 U.S.C. § 321, and is the subject of an approved New Drug Application, 21 U.S.C. § 355. The Secretary is authorized to withdraw approval of a new drug only under extremely limited circumstances, and only after giving due notice and an opportunity for hearing. To withdraw a New Drug Application, the Secretary must determine one of the following:

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[80] Marc Kaufman, *Crestor's Withdrawal Urged*, WASHINGTON POST, June 25, 2004, at A12; http://www.cbg-meb.nl/uk/nieuws/start.htm.

1. clinical or other experience, tests, or other scientific data show that a drug is unsafe for use under the conditions of use that formed the basis for approval of its application;

2. new evidence of clinical experience evaluated together with the evidence available when the application was approved, shows that a drug is not shown to be safe for use under the conditions of use that formed the basis for approval of the application; or

3. new information evaluated together with the evidence available when a drug was approved, shows that there is a lack of substantial evidence that it will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[81]

None of these facts is present here. As demonstrated above, HRG has failed to prove any of the bases for withdrawal. CRESTOR is not "unsafe," and it has a proven safety profile. There is no new evidence of clinical experience warranting its withdrawal. Nor is there new information suggesting that CRESTOR does not have the effect it purports to have. Indeed, the overwhelming weight of reliable scientific data provides further evidence of the positive benefit-risk profile of CRESTOR.

HRG's demands that the Secretary "immediately remove" CRESTOR from the market is likewise meritless. The Secretary can take such action only if "there is an imminent hazard to the public health,"[82] and "only in the exceptional case of an emergency, which does not permit the Secretary to correct it by other means."[83] No "imminent hazard" to the public health amounting to an emergency exists. To the contrary, CRESTOR presents a positive benefit-risk profile. The petition is unsupported and unsupportable and must be denied.

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81 21 U.S.C. § 355(e).

82 *Id.* This authority cannot be delegated.

83 Sen. Rep. No. 1744 at 7, 87th Cong., 2d Sess. (1962).

V. CONCLUSION

The safety and efficacy of CRESTOR are well documented and were confirmed last summer when an FDA Advisory Committee, comprised of independent medical and scientific experts, unanimously recommended that CRESTOR be approved. In fact, the safety of CRESTOR was evaluated in more than 10,000 patients, more than any other statin prior to approval. The FDA agreed and approved CRESTOR on August 12, 2003. CRESTOR is now approved in more than 60 countries, and more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with its pre-approval experience as reflected in its prescribing information. Moreover, it has been shown that CRESTOR offers lipid modifying effects unique among the currently marketed statins, including the greatest efficacy for lowering serum LDL cholesterol and significant increases in HDL cholesterol. CRESTOR also provides the significant clinical advantages of allowing approximately 80% of patients to reach their LDL cholesterol goal on the usual starting dose of 10 mg/day, while providing the option of higher doses for those who do not achieve their desired goal with either lower doses or other current statin monotherapies. Nothing that HRG has submitted demonstrates otherwise. The legal standard applicable to withdrawal of an NDA has not been and cannot be met by HRG, and its petition must be denied.

APPENDIX

CLINICAL TRIAL EFFICACY AND SAFETY TABLES

TABLE I: Least-squares Mean Percentage Change from Baseline in LDL-C.
Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	**Atorvastatin**	**Simvastatin**	**Pravastatin**
10 mg				
n	156	158	165	160
Baseline (mg/dL)±SD	188 ± 19	189 ± 18	189 ± 19	189 ± 18
% Change	-45.8	-36.8	-28.3	-20.1
P Value vs CRESTOR 10 mg		<0.001	<0.001	<0.001
20 mg				
n	160	155	162	164
Baseline (mg/dL))±SD	187 ± 18	190 ± 20	189 ± 19	187 ± 17
% Change	-52.4	-42.6	-35.0	-24.4
P Value vs CRESTOR 10 mg		0.026	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.001	<0.001	<0.001
40 mg				
n	157	156	158	161
Baseline (mg/dL))±SD	194 ± 19	189 ± 20	187 ± 16	190 ± 19
% Change	-55.0	-47.8	-38.8	-29.7
P Value vs CRESTOR 10 mg		0.164	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.002	<0.001	<0.001
P Value vs CRESTOR 40 mg		<0.001	<0.001	<0.001
80 mg				
n		165	163	
Baseline (mg/dL))±SD	NA	190 ± 20	190 ± 19	NA
% Change	NA	-51.1	-45.8	NA
P Value vs CRESTOR 20 mg		0.363	<0.001	
P Value vs CRESTOR 40 mg		0.006	<0.001	

P<0.002 are statistically significant.

TABLE II: Least-squares Mean Percentage Changes from Baseline in HDL-C. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	Atorvastatin	Simvastatin	Pravastatin
10 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	51 ± 12	50 ± 13
% Change	+7.7	+5.7	+5.3	+3.2*
20 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	50 ± 12	49 ± 11
% Change	+9.5	+4.8+	+6.0	+4.4+
40 mg				
Baseline (mg/dL))±SD	50 ± 12	50 ± 11	51 ± 11	50 ± 10
% Change	+9.6	+4.4+#	+5.2+#	+5.6+#
80 mg				
Baseline (mg/dL))±SD	NA	51 ± 13	51 ± 12	NA
% Change	NA	+2.1+#	+6.8	NA

*p<0.002 vs CRESTOR 10 mg; +p<0.002 vs CRESTOR 20 mg; #p<0.002 vs CRESTOR 40 mg

TABLE III: Effects of CRESTOR 10 mg on LDL-C and Achievement of NCEP ATP III LDL-C Goals at 12 Weeks (Pooled Data from 5 Trials). Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=615)
Effect on LDL-C	
Mean Baseline LDL-C	186 mg/dL
Mean LDL-C at 12 Weeks	98 mg/dL
Mean % Change in LDL-C from Baseline	-47%
Patients who achieved ATP III LDL-C Goals	
All Goals	80% (491/615)
<100 mg/dL	61% (161/264)
<130 mg/dL	89% (119/134)
<160 mg/dL	97% (211/217)

TABLE IV: Percent Change from Baseline at 12 Weeks Compared with Atorvastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C and Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=390)		**CRESTOR 10 mg (n=389)**		**Atorvastatin 10 mg (n=393)**	
	Baseline mg/dL	**% Change**	**Baseline mg/dL**	**% Change**	**Baseline mg/dL**	**% Change**
LDL-C	188	-41.9[a]	185	-46.7[a]	187	-36.4
HDL-C	51.1	+8.2[c]	50.8	+8.9[b]	50.4	+5.5
TG	179	-16.4	176	-19.2	181	-17.6
Total-C	275	-29.6[a]	271	-33.0[a]	274	-26.7
Non-HDL-C	224	-38.2[a]	221	-42.6[a]	223	-33.9
ApoB	179	-32.7[a]	175	-36.5[a]	179	-29.0
ApoA-I	151	+6.0[b]	149	+7.3[a]	149	+4.1
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-31
LDL-C/HDL-C	-	-	3.9	-51[a]	3.9	-39
Total-C/HDL-C	-	-	5.6	-38[a]	5.7	-30
NonHDL-C/HDL-C	-	-	4.6	-47[a]	4.7	-37

[a] $p<0.001$ vs atorvastatin; [b] $p<0.05$ vs atorvastatin; [c] $p<0.01$ vs atorvastatin

TABLE V: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Atorvastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=389)	**Atorvastatin 10 mg (n=393)**
All Goals	76% (297/389)	53%[a] (210/393)
<100 mg/dL	60% (120/199)	19%[a] (35/189)
<130 mg/dL	88% (61/69)	80% (70/88)
<160 mg/dL	96% (116/121)	91% (105/116)

[a] $p<0.001$ vs CRESTOR

TABLE VI: Percent Change from Baseline at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C; Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=240)		**CRESTOR 10 mg (n=226)**		**Simvastatin 20 mg (n=249)**		**Pravastatin 20 mg (n=252)**	
	Baseline mg/dL	**% Change**	**Baseline** mg/dL	**% Change**	**Baseline** mg/dL	**% Change**	**Baseline** mg/dL	**% Change**
LDL-C	189	-40.6[a]	187	-48.1[a]	188	-35.7	189	-27.1
HDL-C	51	+6.9	51	+9.1[b]	53	+6.2	52	+6.2
TG	181	-14.9	170	-20.2[c]	166	-12.2	169	-12.4
Total-C	275	-29.1[a]	272	-34.0[a]	274	-25.1	275	-19.2
Non-HDL-C	225	-37.0[a]	221	-44.0[a]	221	-32.5	222	-25.0
ApoB	181	-32.3[a]	176	-37.9[a]	177	-28.0	177	-20.6
ApoA-I	151	+5.4	154	+5.3	155	+4.8	154	+4.2
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-30	1.2	-23
LDL-C/HDL-C	-	-	3.8	-52[a]	3.8	-39	3.8	-30
Total-C/HDL-C	-	-	5.5	-39[a]	5.4	-29	5.5	-23
Non-HDL-C/HDL-C	-	-	4.5	-48[a]	4.4	-36	4.5	-28

[a] $p<0.001$ vs simvastatin and pravastatin; [b] $p<0.05$ vs simvastatin and pravastatin; [c] $p<0.01$ vs simvastatin and pravastatin

TABLE VII: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=226)	**Simvastatin 20 mg (n=249)**	**Pravastatin 20 mg (n=252)**
All Goals	86% (194/226)	64%[a](159/249)	49%[a](124/252)
<100 mg/dL	63% (41/65)	22%[a](18/80)	5%[a](4/75)
<130 mg/dL	89% (58/65)	74%[b](51/69)	40%[a](30/75)
<160 mg/dL	99% (95/96)	90%[b](90/100)	88%[b](90/102)

[a] $p<0.001$ vs CRESTOR; [b] $p<0.05$ vs CRESTOR

TABLE VIII: Number of Patients Meeting NCEP ATP III LDL-C Goals. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	ROS	ATORV	SIMV	PRAV
10 mg	82.1% (128/156)	69.0% (109/158)	50.9% (84/165)[a]	31.3% (50/160)[a]
20 mg		74.7% (115/154)	63.0% (102/162)[a]	43.9% (72/164)[a]
40 mg		85.3% (133/156)	66.5% (105/158)	54.7% (88/161)[a]
20 mg	88.8% (142/160)	74.7% (115/154)[b]	63.0% (102/162)[b]	43.9% (72/164)[b]
40 mg		85.3% (133/156)	66.5% (105/158)[b]	54.7% (88/161)[b]
80 mg		82.4% (136/165)	82.2% (134/163)	
40 mg	89.2% (140/157)	85.3% (133/156)	66.5% (105/158)[c]	54.7% (88/161)[c]
80 mg		82.4% (136/165)	82.2% (134/163)	

[a]$p<0.001$ vs ROS 10 mg; [b]$p\leq0.001$ vs ROS 20 mg; [c]$p<0.001$ vs ROS 40 mg

TABLE IX: Number (Percentage) of Patients with Various Categories of Adverse Events (AEs) During the Treatment Period in Fixed-Dose Controlled Trials. Adapted from Shepherd J et al. The safety of CRESTOR. *Am J Cardiol.* In press, 2004.*

AE Category	ROS 5-40 mg (n=3912)	ATORV 10-80 mg (n=2899)	SIMV 10-80 mg (n=1457)	PRAV 10-40 mg (n=1278)	Total Statin Comparators† (n=5634)	Placebo (n=365)
Any AE	1988 (50.8%)	1247 (43.0%)	618 (42.4%)	523 (40.9%)	2388 (42.4%)	205 (56.2%)
AEs leading to withdrawal	127 (3.2%)	94 (3.2%)	37 (2.5%)	32 (2.5%)	163 (2.9%)	18 (4.9%)
Non-fatal serious AEs‡	73 (1.9%)	55 (1.9%)	27 (1.9%)	18 (1.4%)	100 (1.8%)	5 (1.4%)
AEs leading to death	5 (0.1%)	4 (0.1%)	3 (0.2%)	0	7 (0.1%)	1 (0.3%)
AEs attributed to study medication	579 (14.8%)	340 (11.7%)	126 (8.6%)	112 (8.8%)	578 (10.3%)	67 (18.4%)

*Patients are counted according to each treatment received; therefore, patients may be counted in more than 1 treatment group. Number of patients with adverse events based on actual treatment received at onset, death, or withdrawal. Patients may be included in more than 1 category.

†Refers to combined total for atorvastatin, pravastatin, and simvastatin.

‡A nonfatal serious AE was an event that satisfied 1 or more of the following criteria: was life threatening or a congenital abnormality, required prolonged hospitalization, required medical or surgical intervention to prevent permanent impairment or damage, or resulted in disability or incapacity.

AstraZeneca

July 20, 2004

The Honorable Tommy Thompson
Department of Health and Human Services
200 Independence Avenue SW
Washington, D.C. 20201

Re: CRESTOR® (rosuvastatin calcium) Tablets
Response to Citizen Petition (FDA Docket #2004-0113)

Dear Mr. Thompson:

Enclosed please find the response of AstraZeneca Pharmaceuticals LP (AstraZeneca) to Public Citizen Health Research Group's petition regarding CRESTOR® (rosuvastatin calcium) Tablets.

We are simultaneously forwarding the required copies of this response to the Dockets Management Brach of the Food and Drug Administration for filing.

Most sincerely,

Catherine M. Bonuccelli, MD

Catherine M. Bonuccelli, MD
Vice President, External Scientific Affairs
Telephone: (302) 886-7867
Fax: (302) 886-1889

AFR/giw
Enclosures

2004P-0113

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AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437

Tel 302 886 3000
www.astrazeneca-us.com

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

John Jenkins, New Drugs Director
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-020, Room 7220
5515 Security Lane
Rockville, MD 20852

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

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

Division of Dockets Management
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 208572

Docket No. 2004P-0113

RESPONSE OF ASTRAZENECA PHARMACEUTICALS LP TO PUBLIC CITIZEN HEALTH RESEARCH GROUP'S PETITION REGARDING CRESTOR®

Submitted by
AstraZeneca Pharmaceuticals LP
July 20, 2004

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EXECUTIVE SUMMARY

AstraZeneca Pharmaceuticals LP ("AstraZeneca"), as agent for IPR Pharmaceuticals, Inc., submits this response to the petition submitted by Public Citizen Health Research Group ("HRG") on March 4, 2004 requesting withdrawal of CRESTOR (rosuvastatin calcium) from the market. The petition is meritless and must be denied, as HRG's argument suffers from three fundamental flaws:

(1) There is nothing new about HRG's position. Instead, HRG recycles the very same unscientific arguments it made more than a year ago during CRESTOR's approval process - arguments that were subsequently rightfully rejected by a unanimous FDA Advisory Committee and the FDA.

(2) HRG ignores any consideration of the benefits of CRESTOR. The benefit-risk profile of CRESTOR is positive, as the FDA found when it approved the drug last year. HRG has offered no evidence to the contrary. The FDA has always interpreted the word "safe" to mean a judgment that the benefits offered by a therapeutic agent justify the risks associated with that agent. Thus, the fact that a drug presents risks does not automatically make it "unsafe."

(3) HRG incorrectly assumes every spontaneous adverse event report is accurate and reliable evidence that the reported event occurred and was caused by CRESTOR. This assumption ignores the FDA's express precautions regarding the use of such reports.

The Petition Recycles Rejected Arguments.

On July 9, 2003, HRG was afforded the opportunity to present its views about CRESTOR's approval at an FDA Advisory Committee meeting. HRG's presentation focused on claims of rhabdomyolysis and kidney toxicity, primarily at the 80 mg dose for which AstraZeneca did not seek marketing approval. Despite HRG's arguments, the Advisory Committee unanimously recommended that CRESTOR be approved and, on August 12, 2003, the FDA agreed. Almost a year later, HRG has repackaged these very same arguments in its petition, adding nothing new to its

one-sided attack other than further anecdote and speculation based on incomplete information.

The Petition Misuses and Misrepresents Limited Data.

As it has done previously with respect to other FDA-approved medicines, HRG ignores the compelling scientific and medical data establishing the safety and efficacy of CRESTOR. Instead, it selectively focuses on limited information from adverse event reports that have been appropriately submitted to and reviewed by the FDA and other health authorities. The FDA has previously warned that accurate evaluations of drug safety cannot be drawn solely from adverse event reports, and rightfully has criticized HRG in the past for using these reports in this fashion, noting that HRG "ignored all of the well-known limitations to use of FDA spontaneous reports."[1] HRG continues to ignore these warnings.

Moreover, in its zeal to have CRESTOR withdrawn, HRG not only has used unscientific information and unsound analysis, but has disseminated information that has proved to be incorrect. For example, HRG's petition claims that "a 39 year-old woman, taking only 20 milligrams a day [of CRESTOR], died of rhabdomyolysis and renal insufficiency." This statement is wrong and, like so many of HRG's statements, has precipitated unnecessary confusion and alarm. While the event initially was reported as a death caused by rhabdomyolysis, an autopsy ultimately determined that the woman died from myocardial infarction and had no evidence of rhabdomyolysis; her death had nothing to do with CRESTOR. This event exemplifies the problems with the unscientific and limited information underpinning HRG's petition.

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[1] FDA, Center for Drugs and Biologics, Recommendation in Piroxicam Imminent Hazard Proceeding (May 14, 1986) at 16, *attached to* Letter from Secretary of HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking to ban the use of Feldene (piroxicam) in people aged 60 and over (July 7, 1986).

The Petition Fails to Recognize the Positive Benefit-Risk Profile of CRESTOR.

The benefit-risk profile of a medicine cannot be determined by cursorily examining limited data from isolated spontaneous adverse event reports. Instead, a medication's benefit-risk profile can be evaluated only by thoroughly analyzing reliable medical data within the context of the disease the medication treats.

Coronary Heart Disease ("CHD") is a Serious and Prevalent Disease.

Cardiovascular disease is the world's leading cause of death for both men and women, accounting for almost one-third of all deaths globally – more than all cancers combined.[2] CHD is the most prevalent of the cardiovascular diseases. This widespread and effective killer is also stealthy: more than half of the people who die suddenly from CHD had no previous symptoms. Even those who survive have a significantly reduced life expectancy; an individual's risk of illness and death following a heart attack is up to 15 times greater than that of the general population. Additionally, the economic costs of cardiac morbidity are enormous, recently estimated to exceed $300 billion this year in the United States alone.

Statin Therapy Has Become the Standard of Care.

Elevated levels of LDL cholesterol are a major cause of CHD. Studies long have demonstrated that lowering LDL cholesterol levels significantly reduces the risk of CHD. Recently, the National Cholesterol Educational Program ("NCEP") has updated its clinical practice guidelines for the treatment of high blood cholesterol to recommend the use of more intensive LDL-lowering drug therapy for patients at high risk.

Statins have proven remarkably effective at lowering LDL cholesterol levels. Statin therapy also has been proven to be safe as well as effective. Although every statin has a recognized, but very low, risk for adverse events, including rhabdomyolysis, for the overwhelming majority of patients, the significant benefit of

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[2] WHO World Health Report, 2004 *available at* http://www.who.int/whr/en/.

statin medication in lowering cholesterol and reducing the risk of CHD substantially outweighs the risk of developing an adverse event.

Though all statins reduce LDL cholesterol, they differ in a number of important respects. Statins vary in terms of efficacy, drug-drug interactions, and pharmacokinetics, such as protein binding, metabolism, and elimination. Moreover, individual patients may respond differently to different statin medications, in terms of both efficacy and adverse events: what works well for one patient may work less well for another; similarly, what is tolerated perfectly by one patient may elicit an adverse event in another.

CRESTOR Has Clinically Proven Efficacy and Unique Lipid-Modifying Benefits.

Clinical studies have proved that CRESTOR is an effective lipid-modifying agent capable of providing significant improvements in lipid profile in a wide variety of adult patient populations. Indeed, clinical trials have established that CRESTOR reduces total cholesterol, LDL cholesterol, ApoB, non-HDL cholesterol, and triglycerides, and increases HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia. A therapeutic response is seen within one week; the maximum response is usually achieved within four weeks and maintained during long-term therapy.

In fact, studies have shown that CRESTOR offers lipid-modulating features unique among the currently marketed statins, including: (1) the greatest efficacy for lowering serum LDL cholesterol; and (2) significant increases in beneficial HDL-C. These pharmacologic features translate into two important clinical benefits. First, approximately 80% of patients using CRESTOR reach their LDL cholesterol goal on the usual starting dose of 10 mg/day. This is an important advantage because patients tend to remain on the dose with which therapy was initiated, even if their medical condition warrants a greater dose to achieve the desired result. Second, for the small number of patients with severe hypercholesterolemia who do not achieve their desired goal with the 10 mg/day dose or with other current monotherapies, higher

doses of CRESTOR are available. This option becomes even more important now that NCEP has established even more aggressive lipid-lowering goals for high risk patients.

CRESTOR's Benefits Far Outweigh Any Risks.

CRESTOR has a clearly demonstrated positive benefit-risk profile. At the time of FDA approval, the safety of CRESTOR was evaluated in more than 10,000 patients—more than any other marketed statin prior to approval—with more than 1,500 of those patients treated for at least 2 years. CRESTOR is now approved in more than 60 countries, and it is estimated that more than 2 million patients have been prescribed CRESTOR, with more than 6.5 million prescriptions dispensed. Additionally, more than 40,000 patients are being or have been treated with CRESTOR in controlled clinical trials. The totality of these data confirms that the FDA was correct in concluding that CRESTOR is safe and effective.

The clinical trial data demonstrate that CRESTOR is generally well tolerated, with an adverse event profile similar to that of other currently marketed statins. The most frequently observed adverse events with CRESTOR include myalgia, constipation, asthenia, abdominal pain, and nausea. Like the other currently marketed statins, CRESTOR also had a very low risk for rhabdomyolysis in clinical trials. These events are clearly noted in the prescribing information. Moreover, in addition to the clinical trials and as part of a comprehensive program to assure continued safety, AstraZeneca also monitors and assesses post-marketing reports of adverse events to identify and mitigate any risks they might uncover. Despite the increased attention and publicity surrounding CRESTOR, its adverse event reporting experience has been stable and in line with that of the other currently marketed statins. The FDA and myriad other regulatory agencies also independently have evaluated and continue to evaluate CRESTOR's safety.

Considering CRESTOR's clinically proven efficacy and unique lipid-modifying benefits and that a thorough review of clinical trial and post-marketing data confirms CRESTOR's safety, it is little wonder that the FDA and other countries'

regulatory agencies have concluded, and continue to conclude, that CRESTOR is safe and effective when used according to its labeling. Indeed, the Medicines Evaluation Board ("MEB"), for example, recently posted on its website a response to HRG stating that "Crestor is an effective and safe cholesterol-lowering agent provided that it is used at the recommended dosage and that the precautions stated in the product information are taken into consideration."[3] HRG's petition provides no scientific basis for challenging these conclusions, as discussed in more detail below.

In short, because HRG presents no new arguments, omits any consideration of CRESTOR's benefits, misuses limited and unverified data, and fails to show that CRESTOR does not have a positive benefit-risk profile, the legal standard applicable to the withdrawal of an NDA has not been and cannot be met by HRG, and its petition must be denied.

I. CHD IS THE LEADING CAUSE OF DEATH OF ADULTS IN THE U.S., YET REMAINS AN UNDERTREATED DISEASE.

A. CHD IS A SERIOUS AND PREVALENT DISEASE WITH SIGNIFICANT ECONOMIC AND PERSONAL CONSEQUENCES.

In order to evaluate the unique lipid-modifying benefits that CRESTOR offers to patients and their healthcare professionals, it is important to understand cardiovascular disease. In the United States, cardiovascular disease is the leading cause of death for both men and women, accounting for approximately 38.5 percent of all deaths.[4] With the exception of one year during World War I (1918), cardiovascular disease has remained the leading cause of death in the United States since 1900 – more than the next five leading causes of death (*i.e.*, cancer, chronic lower respiratory diseases, accidents, diabetes mellitus, and influenza/pneumonia) combined.[5] Declines

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3 *Available at* http://www.cbg-meb.nl/uk/nieuws/start.htm

4 American Heart Association. *Heart Disease and Stroke Statistics – 2004 Update.* Dallas, Tex.: American Heart Association; 2003.

5 *Id.*

in death rates from cardiovascular diseases are largely responsible for the increases in life expectancy in the United States during the twentieth century.[6]

CHD is the most prevalent of the cardiovascular diseases, causing more than twenty percent of all deaths in the United States.[7] More than half of the people who die suddenly from CHD had no previous symptoms.[8] Even those who survive have substantially reduced life expectancy - the risk of illness and death in individuals following a heart attack is up to 15 times greater than in the general population.[9] The economic cost of cardiovascular disease in the United States, estimated at $368.4 billion in 2004, is staggering and is nearly twice the cost of all cancers combined.[10]

B. CHD IS A TREATABLE YET UNDERTREATED DISEASE.

1. Statin therapy has become the standard of care.

Elevated levels of LDL cholesterol are a major cause of CHD.[11] Specifically, LDL cholesterol contributes to the development of coronary plaque, and recent studies have indicated that it contributes to plaque instability as well, which in turn results in heart disease.[12] Studies have long shown that lowering LDL cholesterol demonstrably reduces the mortality and morbidity associated with CHD.[13] As a result,

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6 *Id.*

7 *Id.*

8 *Id.*

9 *Id.*

10 *Id.*

11 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106:3143-3421.

12 *Id.*

13 *See, e.g.,* Cannon CP et al. Comparison of intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM.* 2004;350 (15):1495-1504; Wilson PWF et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837-47; Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I: Reduction in the incidence of coronary heart disease. *JAMA.* 1984;251:351-64; Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship

clinical treatment of CHD has focused on reducing the level of LDL cholesterol.[14] In fact, recent research studies evaluating LDL-C lowering have shown not only reductions in atherosclerosis, but also decreases in cardiovascular mortality.[15] This has resulted in the NCEP recently updating its clinical practice guidelines for the treatment of high blood cholesterol to recommend the use of more intensive LDL-lowering drug therapy for patients at high risk.[16]

Although many treatment methods are available - including diet and exercise - statins are currently the most effective treatment for reducing LDL cholesterol.[17] When studied, statins have been shown to substantially reduce CHD incidence and mortality over nearly every population group.[18] Additional studies

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of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA.* 1984;251:365-74; Pekkanen J et al. Ten year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *NEJM.* 1990;322:1700-7.

14 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Wood D et al. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J.* 1998;19:1434-1503.

15 Cannon CP et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM.* 2004;350(15):1495-1504; Nissen SE et al. REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004;291(9):1071-1080.

16 NCEP Report, Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation.* 2004;110:227-239.

17 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Wood, D et al. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J.* 1998;19:1434-1503.

18 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

indicate that the risk of developing CHD decreases the earlier LDL cholesterol-reducing therapy is started,[19] and that intensive therapy has a marked effect on the progression of coronary atherosclerosis.[20]

Statin therapy has thus become the standard of care, revolutionizing the treatment of high cholesterol.[21] Statins are easy to administer and have become widely accepted among patients.[22] Although every currently available statin has a recognized, but very low, risk for adverse events, for the overwhelming majority of patients, the significant benefit of statin therapy in reducing cholesterol and reducing the risk of CHD substantially outweighs the risk of developing an adverse event and clearly outweighs the risk of not being treated.[23]

Given the significant personal and economic impact of cardiovascular disease, and the ready availability of an effective medication, it is troubling that, although treatable, CHD is an undertreated disease.[24] Fewer than half of the people

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19 Law MR et al. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischemic heart disease? *BMJ.* 1994;308:367-72. Law MR. Lowering heart disease risk with cholesterol reduction: evidence from observational studies and clinical trials. *Eur Heart J Suppl.* 1999;(suppl. S):S3-S8.

20 Nissen SE et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA.* 2004;291:1071-1080.

21 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Evans M et al. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Safety.* 2002;25(9):649-663.

22 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

23 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Pasternak RC et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *J Am Coll Cardiol.* 2002;40:563-79.

24 *See* Preventive cardiology: how can we do better? Presented at the 33rd Bethesda Conference, Bethesda, Maryland, December 18, 2001. *J Am Coll Cardiol.* 2002;40:579-651.

who should be treated with cholesterol-reducing therapy are being treated.[25] Of those who are taking statin medications, many are not being titrated to a dosage that will result in reaching their recommended cholesterol goals.[26] In addition, and largely due to noncompliance, patients are simply not maintaining their lipid-reducing therapy over the long run.[27] As a result, the medical community is becoming increasingly aware of the need to screen for and treat high cholesterol and to follow patients more closely. Physicians also are prescribing statins earlier, and more aggressively, to close the gap of undertreatment.

2. Patients benefit from having several types of statin therapies available.

Currently, there are six statins available for treatment of high cholesterol. They are not the same. For example, although all the statins reduce LDL cholesterol via the same mechanism, that effect can vary considerably depending on the statin and dose used.[28] Moreover, despite this common effect of LDL reduction, there is considerable variation in the pharmacokinetic properties (*i.e.*, protein binding, metabolism, and elimination) of various statins after oral administration.[29] Additionally, drug-drug interactions vary among statins.[30]

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25 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 2002;106: 3143-3421.

26 *See, e.g.*, Sueta CA et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1999; 83:1303-1307.

27 *Id.*

28 CRESTOR Prescribing Information; Lescol Precribing Information; Lipitor Precribing Information; Mevacor Prescribing Information; Pravachol Prescribing Information; Zocor Prescribing Information.

29 *Id.*; Evans M et al. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Safety*. 2002;25(9):649-663.

30 *See* Moghadasian MH. A safety look at currently available statins. *Expert Opin Drug Saf*. 2002;1(3):269-74.

The availability of different statins and dosages is thus essential for the success of lipid-reduction therapy. Patients are individuals, and not all of them respond the same to any one statin medication, either in terms of efficacy or adverse events.[31] As a result, it is important for physicians to monitor an individual patient's response to the statin medication prescribed and to modify or change the medication, or its dosage, for the best results.[32] Choice among statins is essential to effective treatment of high cholesterol.

II. CRESTOR PROVIDES EFFECTIVE THERAPY FOR THE TREATMENT OF DYSLIPIDEMIA, OFFERING UNIQUE LIPID-MODIFYING BENEFITS IN THE STATIN CLASS.

CRESTOR is a selective, potent, and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. [33] CRESTOR reduces total-cholesterol, LDL-cholesterol, ApoB, non-HDL-cholesterol, and triglycerides, and increases HDL-cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia.[34] Therapeutic response is usually seen within one week and maximum response is usually achieved within four weeks and maintained during long-term therapy.[35]

CRESTOR is an effective statin delivering significant reductions in LDL cholesterol at all doses studied along with important modifications in the atherogenic lipid profile. Approximately 80% of patients can reach their LDL cholesterol goal on the

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31 Davidson MH. Controversy surrounding the safety of cerivastatin. *Expert Opin Drug Saf.* 2002;1(3):207-212; Thompson PD et al. Statin-associated myopathy. *JAMA.* 2003;289:1681-90.

32 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

33 CRESTOR Prescribing Information.

34 *Id.*

35 *Id.*

usual starting dose of 10 mg/day.[36] Additionally, for the small number of patients with particularly severe hypercholesterolemia who are inadequately treated with current monotherapies, titration to higher doses of CRESTOR offers an important therapeutic option to physicians. A 5 mg dose is also available for patients who require less aggressive LDL-C reduction or who have predisposing factors for myopathy.

CRESTOR is an effective lipid-modifying agent capable of providing significant improvements in the lipid profile in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age, and in special populations such as diabetics or patients with heterozygous or homozygous familial hypercholesterolemia.[37] CRESTOR is thus an important addition to the medical community's arsenal in its war against dyslipidemia.

A. EXTENSIVE CLINICAL TRIALS HAVE ESTABLISHED CRESTOR'S EFFICACY.

1. CRESTOR is a highly effective statin for reducing serum LDL cholesterol and increasing HDL cholesterol.

In its petition, HRG claims that CRESTOR offers no benefits different from other statins. As the data from the clinical studies prove, HRG is clearly wrong. In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hypercholesterolemia, CRESTOR significantly reduced LDL-C from 45 - 63% (vs 7% with placebo) across the 5 - 40 mg dose range and increased HDL-C between 8 - 14% (vs 3% with placebo) across that same dose range.[38]

Importantly, CRESTOR was compared with atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study analyzing 2,240 patients

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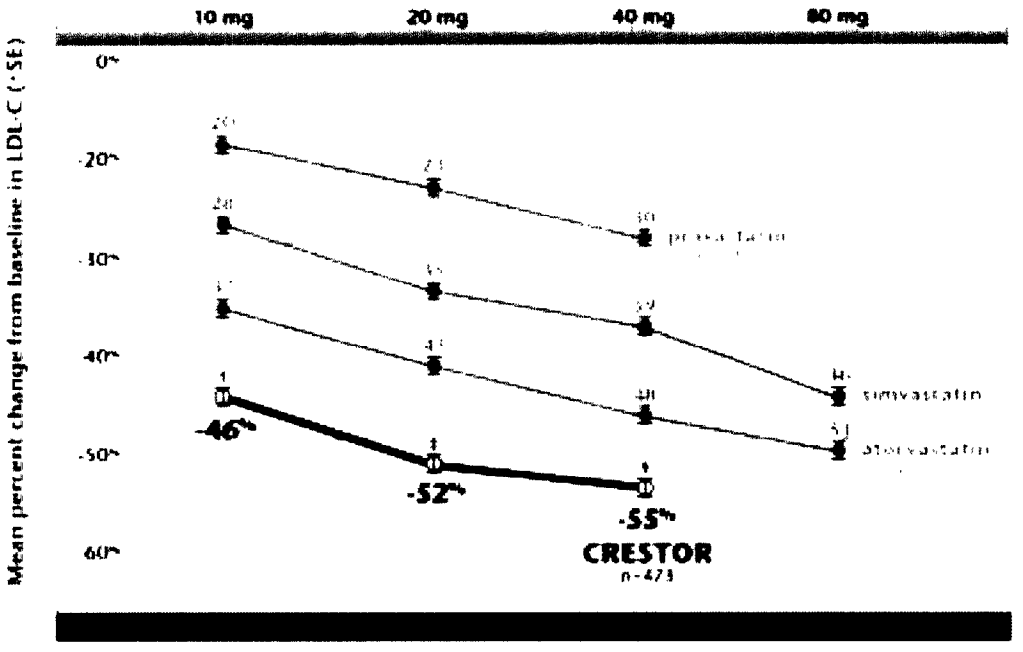
36 Shepherd J et al. *Am J Cardiol.* 2003;91(Suppl):11C-19C; Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160.

37 CRESTOR Prescribing Information.

38 *Id.*

with Fredrickson Type IIa and IIb hypercholesterolemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin. The dose response of CRESTOR (10 - 40 mg) reduced LDL-C significantly more than atorvastatin (10 - 80 mg), simvastatin (10 - 80 mg), and pravastatin (10 - 40 mg) across the studied dose range.[39] The usual starting dose of CRESTOR 10 mg provided significantly greater decreases in LDL-C than atorvastatin 10 mg, simvastatin 10, 20, and 40 mg and pravastatin 10, 20, and 40 mg.[40] (See Figure 1, below.)

Figure 1: LDL-C REDUCTION BY DOSE



[1] P<.002 vs atorvastatin 10 mg; simvastatin 10 mg, 20 mg, 40 mg; pravastatin 10 mg, 20 mg, 40 mg.
[1] P<.002 vs atorvastatin 20 mg, 40 mg; simvastatin 20 mg, 40 mg, 80 mg; pravastatin 20 mg, 40 mg.
[1] P<.002 vs atorvastatin 40 mg; simvastatin 40 mg, 80 mg; pravastatin 40 mg.
Mean baseline LDL-C: 189 mg/dl.

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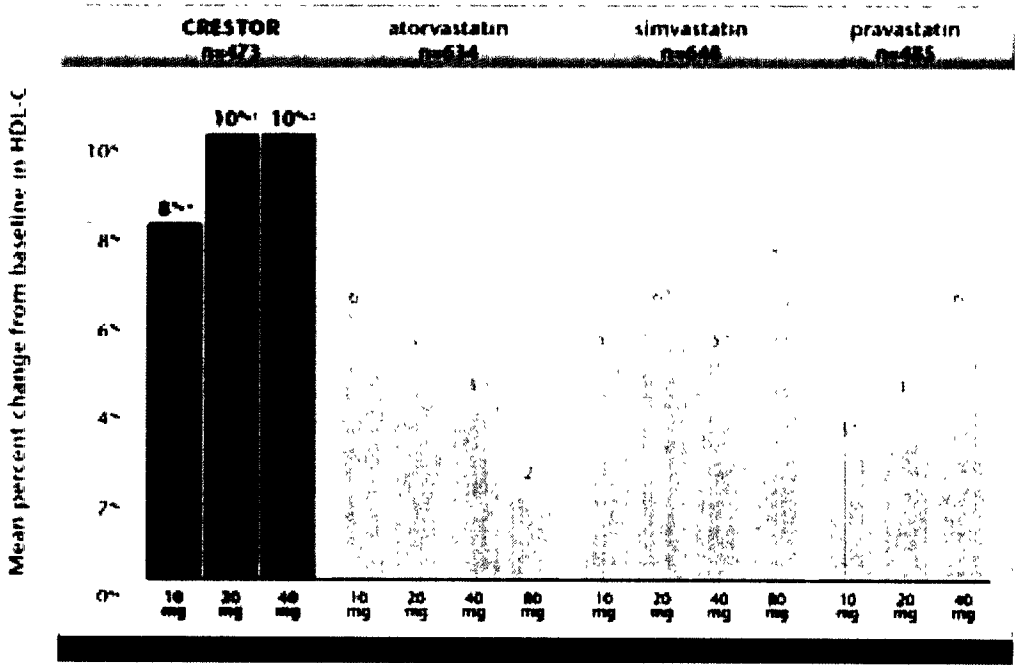
39 Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160; CRESTOR Prescribing Information; Data on File.

40 *Id.* The pairwise, dose-to-dose comparisons for LDL-C are provided in Table I in the Appendix.

The investigators concluded that CRESTOR was more effective in reducing LDL-C across the dose ranges when compared with atorvastatin, simvastatin, and pravastatin, supporting the conclusion that CRESTOR meets an important unmet clinical need. In addition, for the patients with particularly severe hypercholesterolemia who are inadequately treated with current statin monotherapy, titration to CRESTOR 40 mg offers an important therapeutic option. This option has become particularly important now that NCEP has recommended even more stringent lipid-lowering goals for high risk patients.

CRESTOR also consistently increased HDL-C across the 10 – 40 mg dose range, with no decrease in effect at higher doses.[41] (See Figure 2, below.)

Figure 2: HDL-C INCREASE BY DRUG



*P<.002 vs pravastatin 10 mg.
†P<.002 vs atorvastatin 20 mg, 40 mg, 80 mg; simvastatin 40 mg; pravastatin 20 mg, 40 mg.
‡P<.002 vs atorvastatin 40 mg, 80 mg; simvastatin 40 mg; pravastatin 40 mg.
Mean baseline HDL-C: 50 mg/dL

41 *Id.* The pairwise, dose-to-dose comparisons for HDL-C are provided in Table II in the Appendix.

2. Approximately 80% of patients using CRESTOR can reach their LDL cholesterol goal on the usual starting dose of 10 mg/day.

Another benefit ignored by HRG is that the majority of patients can reach their LDL cholesterol goal on the usual starting dose of CRESTOR.[42] Experience with medical practice has revealed that, despite recommendations about titration upward to reach LDL-C targets, patients are in fact not titrated but tend to remain on the dose with which therapy was initiated.[43] Accordingly, there is a clinical benefit to having a starting dose that is effective in a majority of patients. The results of multiple Phase III clinical trials involving various patient populations demonstrate that the starting 10 mg dose of CRESTOR allows significantly more of these patients to reach their LDL-C goals, thereby reducing the need to titrate to higher doses.

A prospectively-planned, pooled analysis of the first 12 weeks of 5 randomized, double-blind, parallel-group, comparator-controlled, multicenter studies was performed to compare the effects of CRESTOR 5 mg and 10 mg with atorvastatin 10 mg (3 studies) and simvastatin 20 mg and pravastatin 20 mg (2 studies) on lipid parameters.[44] Patients from all risk categories were included, with 43% of patients having an LDL-C goal < 100 mg/dL. All trials included in the pooled analyses were prospectively designed so that the data from the first 12 weeks of treatment could be pooled. Effects on lipid parameters and goal attainment at 12 weeks are presented in Table III for CRESTOR 10 mg in all 5 studies, Tables IV and V for CRESTOR and

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42 Shepherd J et al. *Am J Cardiol.* 2003;91(Suppl):11C-19C.

43 Sueta CA et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1999;83:1303-1307.

44 Blasetto JW et al. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C; Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of rosuvastatin compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C; Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

atorvastatin and Tables VI and VII for CRESTOR, simvastatin, and pravastatin (Appendix).

The authors concluded that treatment with CRESTOR 10 mg for 12 weeks resulted in significantly greater improvements in lipid parameters and allowed more patients to attain NCEP ATP III goals than atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg. A similar effect was observed by others, with reductions in LDL-C resulting in a higher percentage of patients reaching their NCEP ATP III LDL-C goals (Appendix—Table VIII).[45] CRESTOR thus presents unique lipid-modifying benefits consistent with its proven positive benefit-risk profile.

3. Additional studies in special populations further support CRESTOR's highly effective lipid-lowering profile.

- Heterozygous Familial Hypercholesterolemia: In an 18-week study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased at 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups, with CRESTOR producing significantly greater improvements in LDL-C, HDL-C, and total-C than atorvastatin and helping more patients achieve their target LDL-C goals.[46]

- Hypertriglyceridemia (Fredrickson Type IIb & IV): In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels from -18% to - 40%.[47]

- Homozygous Familial Hypercholesterolemia: This group of patients represented a group with very severe and difficult to treat hypercholesterolemia and at high risk for developing CHD. In an open-label,

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[45] Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160.

[46] Stein EA et al. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol.* 2003;92:1287-1293; CRESTOR Prescribing Information.

[47] Hunninghake DB, Stein EA, Bays HE, et al. Rosuvastatin improves the atherogenic and atheroprotective lipid profiles in patients with hypertriglyceridemia. Coron Artery Dis. 2004;15(2):115-123; CRESTOR Prescribing Information.

> forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL reduction of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, only 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.[48]
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> * * * * *

Thus, the results of these clinical studies prove CRESTOR to be an effective lipid-modifying agent capable of providing significant improvements in the atherogenic lipid profile in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age. CRESTOR also has proven efficacy in special populations such as diabetics and patients with heterozygous or homozygous familial hypercholesterolemia.

B. THE PETITION IGNORES THE EFFICACY OF CRESTOR AS DEMONSTRATED IN ITS CLINICAL TRIALS.

The HRG petition requests that the FDA take action under section 355(e)(3) of the Federal Food, Drug, and Cosmetic Act ("FFDCA").[49] This section requires a finding that there is a lack of substantial evidence demonstrating that the drug is effective for its intended uses. The HRG petition, however, does not and cannot challenge the efficacy of CRESTOR in reducing LDL-C and triglycerides and in increasing HDL-C. Moreover, the HRG petition simply ignores that the FDA, in

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[48] Marais D et al. Effect of rosuvastatin on LDL-cholesterol, mevalonic acid and other lipid measurements in patients with homozygous familial hypercholesterolemia [poster]. Presented at the 73rd European Atherosclerosis Society Congress; July 7-10, 2002; Salzburg, Austria; CRESTOR Prescribing Information.

[49] 21 U.S.C. 355(e)(3). *See* opening sentence of the HRG letter dated March 4, 2004.

approving the drug after a comprehensive review, determined CRESTOR to be safe and effective.

III. THE PETITION MISREPRESENTS THE SAFETY OF CRESTOR.

HRG presents a selective and misleading review of the clinical and post-marketing safety surveillance data. The clinical studies have confirmed that CRESTOR is safe and effective when used according to the prescribing information, and nothing in the post-marketing experience contradicts that conclusion. CRESTOR is now approved in more than 60 countries, and it is estimated that more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with the pre-approval experience as reflected in CRESTOR's prescribing information.

A. CLINICAL TRIALS ESTABLISHED AND POST-MARKETING EXPERIENCE CONFIRMS THE SAFETY OF CRESTOR.

The FDA requires that a product's underlying risks and benefits must be adequately assessed during the premarketing period, adding that "sponsors should provide a body of evidence from the clinical trials that adequately characterizes the product's safety profile."[50] The FDA has confirmed that "the larger and more comprehensive a preapproval database, the more likely it is that serious adverse events will be detected."[51] The FDA has advised that premarketing safety databases should include a diverse population to allow for "the development of safety data in a broader population, including patients previously excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking usual concomitant medications."[52]

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50 FDA Draft Guidance for Industry, "Premarketing Risk Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

51 *Id.*

52 *Id.*

At the time of FDA approval, the safety of CRESTOR had been evaluated in more than 10,000 patients,[53] with more than 1,500 patients treated for at least two years.[54] Currently more than 40,000 patients are being or have been treated with CRESTOR in controlled clinical trials. The most frequently observed adverse events thought to be related to CRESTOR include myalgia, constipation, asthenia, abdominal pain, and nausea; these adverse events were usually mild and transient.[55] Overall, CRESTOR was generally well tolerated in clinical trials.[56] The overall incidence of adverse events reported with CRESTOR was similar to placebo.[57] The overall frequency of adverse events was similar with CRESTOR doses of 5 mg to 40 mg.[58]

The safety and tolerability of CRESTOR have been assessed using data from the largest pre-approval clinical trial program for any statin approved to date. As every effort was made to recruit patients who would resemble, as closely as possible, individuals who would be candidates for statin therapy in clinical practice, the populations studied included patients with various forms of dyslipidemia, including heterozygous or homozygous familial hypercholesterolemia and the Fredrickson classifications of Type IIa or IIb hypercholesterolemia and Type IV hypertriglyceridemia.[59] In addition, in phase III trials, there was no upper age limit for entry, and patients with mild-to-moderate renal impairment with creatinine levels up to 2.5 mg/dl were enrolled, as were those with stable concomitant illnesses that are

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53 CRESTOR Prescribing Information.

54 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

55 CRESTOR Prescribing Information.

56 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.* 2003;92(suppl):23K-29K; CRESTOR Prescribing Information.

57 CRESTOR Prescribing Information; Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

58 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

59 *Id.*

commonly associated with dyslipidemia (e.g., hypertension, diabetes mellitus, and cardiovascular disease).[60]

As shown in Table IX (Appendix), in fixed-dose trials with comparator statins, CRESTOR 5 to 40 mg showed a similar adverse event profile to those for atorvastatin 10 to 80 mg, simvastatin 10 to 80 mg, and pravastatin 10 to 40 mg, with the most common adverse events across statin-treated groups being pharyngitis, headache, pain, myalgia, diarrhea, and abdominal pain.[61] Overall, the occurrence of treatment-related adverse events was low.

During the pre-approval clinical trials, there were no deaths attributed to CRESTOR. In controlled trials, clinically significant elevations of ALT (>3 x upper limit of normal at 2 consecutive treatments) occurred in a similar proportion of patients in each statin group (0.2%).[62] Myopathy possibly related to CRESTOR during the clinical trial program evaluating CRESTOR 5-40 mg was rare and occurred in ≤0.03% of patients.[63] There were no reports of rhabdomyolysis attributed to CRESTOR 5-40 mg.[64]

Proteinuria was seen in <1.0% of patients receiving CRESTOR 5, 10, or 20 mg and in those patients receiving placebo, atorvastatin 10 to 80 mg, simvastatin 10, 40, and 80 mg, or pravastatin 10 to 40 mg.[65] Proteinuria was seen in 1.2% of patients receiving CRESTOR 40 mg and 1.1% of patients receiving simvastatin 20 mg.[66] These findings of proteinuria were transient in many cases, reversible, and not associated with long-term detrimental effects on renal function. Importantly, renal function, assessed

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60 *Id.*

61 *Id.*

62 *Id.*

63 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.*2003;92(suppl):23K-29K.

64 *Id.*

65 Vidt DG et al. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology* 2004;102:52-60.

66 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

by mean glomerular filtration rates predicted from the Modification of Diet in Renal Disease (MDRD) equation, did not deteriorate in patients receiving long-term (≥96 weeks) CRESTOR therapy at any dose, irrespective of age, sex, hypertensive or diabetic status, level of renal function at baseline (glomerular filtration rates ≥60 versus <60 ml/min/1.72 m^2) or presence or absence of urine dipstick protein before or during treatment.[67]

In summary, the 5 - 40 mg dose range for CRESTOR provides greater lipid modification when compared with other marketed statins. The LDL-C benefits with CRESTOR translated to a greater number of patients achieving NCEP ATP III goals at the 10 mg/day start dose, thereby reducing the need to titrate to higher doses. CRESTOR also allowed many patients to increase their HDL-C and reduce non-HDL-C and triglycerides. This is achieved with a safety profile that is similar to other currently marketed statins. At doses up to and including 40 mg, CRESTOR was generally well tolerated. Thus, the clinical trial data establish the positive benefit-risk profile for CRESTOR when used according to the prescribing information. CRESTOR offers an important option for patients and their healthcare professionals for the treatment of dyslipidemia.

B. HRG REJECTS SCIENTIFIC ANALYSIS IN FAVOR OF SPECULATION REGARDING THE SAFETY OF CRESTOR BASED SOLELY UPON UNVERIFIED AND LIMITED DATA.

The petition bases its request that CRESTOR be "immediately removed" from the market on essentially two lines of alleged evidence. The first is a selective presentation of opinions not related to the safety and efficacy of CRESTOR, but rather in the nature of business decisions. Specifically, HRG notes that two insurance companies do not, at this time, reimburse their insureds for CRESTOR prescriptions. What HRG fails to mention is that the overwhelming majority of insurers and managed care organizations in the United States have added CRESTOR to their formularies. HRG

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67 *Id.*

also claims that "[i]n Sweden, regional government drug advisors recommended against the use of the drug." This is simply incorrect. In truth, the referenced board recommended reimbursement for CRESTOR, but only for patients who failed to reach lipid goals with generic drugs in the statin class. Thus, the decision was driven by economic interests and not safety or efficacy concerns. Moreover, since its approval on April 4, 2003 by the Medical Products Agency, CRESTOR remains available for prescription in Sweden. That HRG opts to rely upon such unsubstantiated information reveals the weakness of its entire position.

HRG's second line of alleged evidence is based upon a number of unverified, unidentified spontaneous post-approval adverse event reports, all of which have been appropriately reported to, and evaluated by, the FDA. This is not the first time HRG has attacked an FDA-approved medicine based upon such information. In denying previous HRG petitions, the FDA often has had to remind Public Citizen about the significant limitations on the use of adverse event reporting data and the dangers of its misuse.[68]

That adverse event reports can play a role in the identification of a safety signal is well-recognized.[69] Signals are hypothesis-generating and generally require further investigation, that, in turn, may or may not lead to the conclusion that the events were product-related.[70] The identification of a signal, however, demands careful case assessment of individual reports, including an evaluation of clinical content and completeness, as the quality of the reports is critical for appropriate evaluation of the relationship, if any, between the product and the adverse event.[71] Detailed case

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68 *See, e.g.*, Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking to ban the use of Feldene (prioxicam) in people aged 60 and over (July 7, 1986); Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking withdrawal of Arava (leflunomide) (Mar. 23, 2004).

69 FDA Draft Guidance for Industry, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

70 *Id.*

71 *Id.*

assessment is especially important with an event such as rhabdomyolysis, as the criteria used for its diagnosis can vary tremendously.

The outcome of a thorough case assessment must then be compared with other relevant safety information, such as results from preclinical, clinical, pharmacoepidemiologic, or other available studies, and placed into context by determining the extent of patient exposure.[72] Additionally, as many factors can affect the reporting of adverse events (*e.g.*, publicity and newness of the product), these factors must be considered in interpreting any results.[73]

HRG has performed none of these steps. Instead it relies solely on the fact that a number of adverse events labeled as rhabdomyolysis have been reported for CRESTOR. The numerous flaws to this approach are discussed below. Moreover, that there have been reports of rhabdomyolysis in patients using CRESTOR comes as no great surprise, as rhabdomyolysis is a labeled and well-known, although rare, risk of all the currently marketed members of the statin class.

1. HRG misuses adverse event reports.

The FDA is fully aware that adverse event reports alone can only provide limited information, at best, about the safety of a medicine. In fact, the FDA has published guidelines identifying at least some of the limitations on the use of adverse event reports:[74]

> Reports contain only those reactions voluntarily submitted either to the FDA or to the drug manufacturer by consumers and/or members of the health profession....
>
> The information contained in the reports has not been scientifically or otherwise verified.

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72 *Id.*

73 *Id.*

74 FDA, Office of Postmarketing Drug Risk Assessment, "Brief Description with Caveats of System" (Oct. 18, 1999).

> For any given report, there is no certainty that the suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions.
>
> Accumulated case reports cannot be used to calculate incidence or estimates of drug risk.

HRG, however, ignores these well-known limitations and, without the full facts, attempts to use adverse event reports in a manner that the FDA has criticized. For example, the FDA has recognized that an adverse event report cannot be interpreted as evidence that the medicine caused the event, stating affirmatively that "there is no certainty that the suspected drug caused the reaction":

> [A] possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure.[75]

A fair understanding of an adverse event report and its significance can be obtained only by a careful medical review. In the absence of a thorough examination, a causal connection cannot be inferred; even when the medical records are available, it is often difficult or impossible to assess causality.

HRG commits precisely the "serious error" identified by the FDA - it wrongly uses an adverse event report to claim that CRESTOR caused fatal rhabdomyolysis. HRG cites a report of "a 39-year-old woman, taking only 20 milligrams a day, [who] died of rhabdomyolysis and renal insufficiency." That is how the report initially came to AstraZeneca and how it was initially submitted to the FDA. However, as the FDA knows, subsequent investigation revealed autopsy records for

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[75] 62 Fed. Reg. 30678, 30689-90 (June 4, 1997) (proposed rule for dietary supplements containing ephedrine alkaloids); *see also* FDA, "Postmarketing Safety of Sildenafil Citrate (Viagra)," March 3, 2001, *available at* www.fda.gov/cder/consumerinfo/viagra/safety3.htm ("An accumulation of adverse event reports does not necessarily indicate that the adverse event was caused by the

this patient, establishing that she died of an acute myocardial infarction. At autopsy, there was no evidence of rhabdomyolysis, and the death had nothing to do with CRESTOR. This is an example of why adverse event reports cannot be used to establish a link between a medicine and the event, and it is wrong for HRG to attempt to do so in its petition.

Additionally, spontaneous adverse event reporting systems are voluntary. Thus, reporting is susceptible to a wide range of factors that may stimulate or discourage voluntary reporting, including:

- Adverse publicity: lay and medical reporting of serious events with a product will stimulate reports;[76]
- Number of years that the drug has been on the market: events are more likely to be reported in the first 2 years of marketing than in later years (the "Weber effect");[77]
- Seriousness of the adverse event: deaths and life-threatening reactions are more likely to be reported than mild or transient side effects.[78]

Clearly, several of these variables, especially the first in the wake of HRG's petition, may be at play with respect to CRESTOR.

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drug; rather, the event may be due to an underlying disease or some other factor(s).").

[76] Faich GA, Moseley RH. Troglitazone (Rezulin) and Hepatic Injury. *Pharmacoepidemiology and Drug Safety.* 2001;10:537-47; Meinzinger MS, Barry WS. Prospective Study of the Influence of the Media on Reporting Medical Events. *Drug Inf J.* 1990;24: 575-77; Rossi AC et al. The Importance of Adverse Reaction Reporting By Physicians: Suprofen and the Flank Pain Syndrome. *JAMA.* 1988;259:1203-04.

[77] Wallenstein EJ, Fife D. Temporal Patterns of NSAID Spontaneous Adverse Event Reports: the Weber Effect Revisited. *Drug Safety.* 2001;24:233-37; Tsong Y. Comparing Reporting Rates of Adverse Events Between Drugs with Adjustment for Year of Marketing and Secular Trends in Total Reporting. *J Biopharm Stat.* 1995;5:95-114; Sachs RM, Bortnichak EA. An Evaluation of Spontaneous Adverse Drug Reaction Monitoring Systems. *Am J Med.* 1986;81:49-55; Weber JCP. Epidemiology of Adverse Reactions to Nonsteroidal Antiinflammatory Drugs. In: Rainsford KD, Velo GP, eds. *Advances in Inflammatory Research.* Vol. 6. New York: Raven Press, 1984:1-7.

[78] Piazza-Hepp TD, Kennedy DL Reporting of adverse events to MedWatch. *Am J Health-Syst Pharm.* 1995;52:1436-39; Milstien JB et al. Factors Affecting Physician Reporting of Adverse Drug Reactions. *Drug Inf J.* 1986;20:157-64.

Additional problems with HRG's use of adverse event reports arise from the medical conditions HRG has raised, namely rhabdomyolysis and kidney damage. Neither has a standard medical definition,[79] further confounding the interpretation of spontaneous adverse event reports. Specifically, one consequence of not having standard medical definitions is that physicians may diagnose different events as "rhabdomyolysis" or "acute renal failure."

Moreover, HRG fails to provide any context for the adverse event reports it cites. HRG makes no attempt to reconcile the number of reports against the backdrop of ever-increasing use of CRESTOR in the United States. Nor does HRG attempt to reconcile the number of reports against the background rate of such adverse events in hypercholesterolemic patients. Absent such an analysis, the number of adverse event reports alone is meaningless.

In conclusion, HRG has simply failed to perform any of the basic and necessary steps in safety signal identification. On the other hand, AstraZeneca, the FDA and the MEB are continually evaluating the available post-marketing data and agree that CRESTOR is safe and effective when used in accordance with its product labeling. Despite the increased attention and publicity surrounding CRESTOR, its adverse event reporting experience has been stable and in line with that of the other currently marketed statins.

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[79] Thompson PD et al. Statin-Associated Myopathy. *JAMA*. 2003;289:1681-1690 ("The literature on skeletal muscle complaints with statins is confusing, in part because of a lack of clear definitions."); Thadhani Ret al. Acute Renal Failure. *NEJM*. 1996; 334:1448-1460 ("When one attempts to review the subject of acute renal failure, one is immediately struck by the confusion in terminology and the wide disparity in the definitions of terms. Notably, in a recent review of 26 studies on postoperative renal failure, no 2 studies used the same definition of acute renal failure.").

2. AstraZeneca diligently monitors reports of adverse drug events and shares all such information with the FDA in accordance with applicable regulations.

There is nothing new in the HRG petition. HRG simply reargues the same points it made over a year ago at the FDA Advisory Committee meeting regarding the approval of CRESTOR. Despite HRG's claims of an increased risk of rhabdomyolysis and kidney toxicity, the Advisory Committee unanimously recommended approval. Fully aware of the adverse events discussed in HRG's petition, the FDA, and numerous other regulatory agencies, have agreed and have properly concluded that the benefits of CRESTOR outweigh its risk when prescribed and used in accordance with its labeling.

AstraZeneca's highest priority is patient safety. AstraZeneca monitors and assesses reports of adverse events to identify and mitigate any safety risks. Through its monitoring efforts, AstraZeneca ensures that the FDA, other regulatory authorities, and prescribing physicians receive complete, up-to-date information about the safety of CRESTOR. Indeed, the adverse event reports cited by HRG already were brought to the FDA's attention. As the FDA and as the MEB concluded most recently, in response to Mr. Wolfe's Letter to the Lancet on June 25, 2004, CRESTOR is safe and effective when prescribed and used in accordance with its labeling.[80]

IV. THE STANDARD FOR WITHDRAWAL CANNOT BE MET.

CRESTOR is a "new drug" as defined under section 201(p) of the FFDCA, 21 U.S.C. § 321, and is the subject of an approved New Drug Application, 21 U.S.C. § 355. The Secretary is authorized to withdraw approval of a new drug only under extremely limited circumstances, and only after giving due notice and an opportunity for hearing. To withdraw a New Drug Application, the Secretary must determine one of the following:

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[80] Marc Kaufman, *Crestor's Withdrawal Urged*, WASHINGTON POST, June 25, 2004, at A12; http://www.cbg-meb.nl/uk/nieuws/start.htm.

1. clinical or other experience, tests, or other scientific data show that a drug is unsafe for use under the conditions of use that formed the basis for approval of its application;

2. new evidence of clinical experience evaluated together with the evidence available when the application was approved, shows that a drug is not shown to be safe for use under the conditions of use that formed the basis for approval of the application; or

3. new information evaluated together with the evidence available when a drug was approved, shows that there is a lack of substantial evidence that it will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[81]

None of these facts is present here. As demonstrated above, HRG has failed to prove any of the bases for withdrawal. CRESTOR is not "unsafe," and it has a proven safety profile. There is no new evidence of clinical experience warranting its withdrawal. Nor is there new information suggesting that CRESTOR does not have the effect it purports to have. Indeed, the overwhelming weight of reliable scientific data provides further evidence of the positive benefit-risk profile of CRESTOR.

HRG's demands that the Secretary "immediately remove" CRESTOR from the market is likewise meritless. The Secretary can take such action only if "there is an imminent hazard to the public health,"[82] and "only in the exceptional case of an emergency, which does not permit the Secretary to correct it by other means."[83] No "imminent hazard" to the public health amounting to an emergency exists. To the contrary, CRESTOR presents a positive benefit-risk profile. The petition is unsupported and unsupportable and must be denied.

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81 21 U.S.C. § 355(e).

82 *Id.* This authority cannot be delegated.

83 Sen. Rep. No. 1744 at 7, 87th Cong., 2d Sess. (1962).

V. CONCLUSION

The safety and efficacy of CRESTOR are well documented and were confirmed last summer when an FDA Advisory Committee, comprised of independent medical and scientific experts, unanimously recommended that CRESTOR be approved. In fact, the safety of CRESTOR was evaluated in more than 10,000 patients, more than any other statin prior to approval. The FDA agreed and approved CRESTOR on August 12, 2003. CRESTOR is now approved in more than 60 countries, and more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with its pre-approval experience as reflected in its prescribing information. Moreover, it has been shown that CRESTOR offers lipid modifying effects unique among the currently marketed statins, including the greatest efficacy for lowering serum LDL cholesterol and significant increases in HDL cholesterol. CRESTOR also provides the significant clinical advantages of allowing approximately 80% of patients to reach their LDL cholesterol goal on the usual starting dose of 10 mg/day, while providing the option of higher doses for those who do not achieve their desired goal with either lower doses or other current statin monotherapies. Nothing that HRG has submitted demonstrates otherwise. The legal standard applicable to withdrawal of an NDA has not been and cannot be met by HRG, and its petition must be denied.

APPENDIX

CLINICAL TRIAL EFFICACY AND SAFETY TABLES

TABLE I: Least-squares Mean Percentage Change from Baseline in LDL-C.
Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	Atorvastatin	Simvastatin	Pravastatin
10 mg				
n	156	158	165	160
Baseline (mg/dL)±SD	188 ± 19	189 ± 18	189 ± 19	189 ± 18
% Change	-45.8	-36.8	-28.3	-20.1
P Value vs CRESTOR 10 mg		<0.001	<0.001	<0.001
20 mg				
n	160	155	162	164
Baseline (mg/dL))±SD	187 ± 18	190 ± 20	189 ± 19	187 ± 17
% Change	-52.4	-42.6	-35.0	-24.4
P Value vs CRESTOR 10 mg		0.026	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.001	<0.001	<0.001
40 mg				
n	157	156	158	161
Baseline (mg/dL))±SD	194 ± 19	189 ± 20	187 ± 16	190 ± 19
% Change	-55.0	-47.8	-38.8	-29.7
P Value vs CRESTOR 10 mg		0.164	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.002	<0.001	<0.001
P Value vs CRESTOR 40 mg		<0.001	<0.001	<0.001
80 mg				
n		165	163	
Baseline (mg/dL))±SD	NA	190 ± 20	190 ± 19	NA
% Change	NA	-51.1	-45.8	NA
P Value vs CRESTOR 20 mg		0.363	<0.001	
P Value vs CRESTOR 40 mg		0.006	<0.001	

P<0.002 are statistically significant.

TABLE II: Least-squares Mean Percentage Changes from Baseline in HDL-C. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	Atorvastatin	Simvastatin	Pravastatin
10 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	51 ± 12	50 ± 13
% Change	+7.7	+5.7	+5.3	+3.2*
20 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	50 ± 12	49 ± 11
% Change	+9.5	+4.8+	+6.0	+4.4+
40 mg				
Baseline (mg/dL))±SD	50 ± 12	50 ± 11	51 ± 11	50 ± 10
% Change	+9.6	+4.4+#	+5.2+#	+5.6+#
80 mg				
Baseline (mg/dL))±SD	NA	51 ± 13	51 ± 12	NA
% Change	NA	+2.1+#	+6.8	NA

*p<0.002 vs CRESTOR 10 mg; +p<0.002 vs CRESTOR 20 mg; #p<0.002 vs CRESTOR 40 mg

TABLE III: Effects of CRESTOR 10 mg on LDL-C and Achievement of NCEP ATP III LDL-C Goals at 12 Weeks (Pooled Data from 5 Trials). Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=615)
Effect on LDL-C	
Mean Baseline LDL-C	186 mg/dL
Mean LDL-C at 12 Weeks	98 mg/dL
Mean % Change in LDL-C from Baseline	-47%
Patients who achieved ATP III LDL-C Goals	
All Goals	80% (491/615)
<100 mg/dL	61% (161/264)
<130 mg/dL	89% (119/134)
<160 mg/dL	97% (211/217)

TABLE IV: Percent Change from Baseline at 12 Weeks Compared with Atorvastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C and Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=390)		**CRESTOR 10 mg (n=389)**		**Atorvastatin 10 mg (n=393)**	
	Baseline mg/dL	**% Change**	**Baseline mg/dL**	**% Change**	**Baseline mg/dL**	**% Change**
LDL-C	188	-41.9[a]	185	-46.7[a]	187	-36.4
HDL-C	51.1	+8.2[c]	50.8	+8.9[b]	50.4	+5.5
TG	179	-16.4	176	-19.2	181	-17.6
Total-C	275	-29.6[a]	271	-33.0[a]	274	-26.7
Non-HDL-C	224	-38.2[a]	221	-42.6[a]	223	-33.9
ApoB	179	-32.7[a]	175	-36.5[a]	179	-29.0
ApoA-I	151	+6.0[b]	149	+7.3[a]	149	+4.1
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-31
LDL-C/HDL-C	-	-	3.9	-51[a]	3.9	-39
Total-C/HDL-C	-	-	5.6	-38[a]	5.7	-30
NonHDL-C/HDL-C	-	-	4.6	-47[a]	4.7	-37

[a] $p<0.001$ vs atorvastatin; [b] $p<0.05$ vs atorvastatin; [c] $p<0.01$ vs atorvastatin

TABLE V: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Atorvastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=389)	**Atorvastatin 10 mg (n=393)**
All Goals	76% (297/389)	53%[a] (210/393)
<100 mg/dL	60% (120/199)	19%[a] (35/189)
<130 mg/dL	88% (61/69)	80% (70/88)
<160 mg/dL	96% (116/121)	91% (105/116)

[a] $p<0.001$ vs CRESTOR

TABLE VI: Percent Change from Baseline at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C; Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=240)		**CRESTOR 10 mg (n=226)**		**Simvastatin 20 mg (n=249)**		**Pravastatin 20 mg (n=252)**	
	Baseline mg/dL	% **Change**	**Baseline** mg/dL	% **Change**	**Baseline** mg/dL	% **Change**	**Baseline** mg/dL	% **Change**
LDL-C	189	-40.6[a]	187	-48.1[a]	188	-35.7	189	-27.1
HDL-C	51	+6.9	51	+9.1[b]	53	+6.2	52	+6.2
TG	181	-14.9	170	-20.2[c]	166	-12.2	169	-12.4
Total-C	275	-29.1[a]	272	-34.0[a]	274	-25.1	275	-19.2
Non-HDL-C	225	-37.0[a]	221	-44.0[a]	221	-32.5	222	-25.0
ApoB	181	-32.3[a]	176	-37.9[a]	177	-28.0	177	-20.6
ApoA-I	151	+5.4	154	+5.3	155	+4.8	154	+4.2
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-30	1.2	-23
LDL-C/HDL-C	-	-	3.8	-52[a]	3.8	-39	3.8	-30
Total-C/HDL-C	-	-	5.5	-39[a]	5.4	-29	5.5	-23
Non-HDL-C/ HDL-C	-	-	4.5	-48[a]	4.4	-36	4.5	-28

[a] $p<0.001$ vs simvastatin and pravastatin; [b] $p<0.05$ vs simvastatin and pravastatin; [c] $p<0.01$ vs simvastatin and pravastatin

TABLE VII: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=226)	**Simvastatin 20 mg (n=249)**	**Pravastatin 20 mg (n=252)**
All Goals	86% (194/226)	64%[a](159/249)	49%[a](124/252)
<100 mg/dL	63% (41/65)	22%[a](18/80)	5%[a](4/75)
<130 mg/dL	89% (58/65)	74%[b](51/69)	40%[a](30/75)
<160 mg/dL	99% (95/96)	90%[b](90/100)	88%[b](90/102)

[a] $p<0.001$ vs CRESTOR; [b] $p<0.05$ vs CRESTOR

TABLE VIII: Number of Patients Meeting NCEP ATP III LDL-C Goals. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	ROS	ATORV	SIMV	PRAV
10 mg	82.1% (128/156)	69.0% (109/158)	50.9% (84/165)[a]	31.3% (50/160)[a]
20 mg		74.7% (115/154)	63.0% (102/162)[a]	43.9% (72/164)[a]
40 mg		85.3% (133/156)	66.5% (105/158)	54.7% (88/161)[a]
20 mg	88.8% (142/160)	74.7% (115/154)[b]	63.0% (102/162)[b]	43.9% (72/164)[b]
40 mg		85.3% (133/156)	66.5% (105/158)[b]	54.7% (88/161)[b]
80 mg		82.4% (136/165)	82.2% (134/163)	
40 mg	89.2% (140/157)	85.3% (133/156)	66.5% (105/158)[c]	54.7% (88/161)[c]
80 mg		82.4% (136/165)	82.2% (134/163)	

[a]$p<0.001$ vs ROS 10 mg; [b]$p\leq0.001$ vs ROS 20 mg; [c]$p<0.001$ vs ROS 40 mg

TABLE IX: Number (Percentage) of Patients with Various Categories of Adverse Events (AEs) During the Treatment Period in Fixed-Dose Controlled Trials. Adapted from Shepherd J et al. The safety of CRESTOR. *Am J Cardiol.* In press, 2004.*

AE Category	ROS 5-40 mg (n=3912)	ATORV 10-80 mg (n=2899)	SIMV 10-80 mg (n=1457)	PRAV 10-40 mg (n=1278)	Total Statin Comparators† (n=5634)	Placebo (n=365)
Any AE	1988 (50.8%)	1247 (43.0%)	618 (42.4%)	523 (40.9%)	2388 (42.4%)	205 (56.2%)
AEs leading to withdrawal	127 (3.2%)	94 (3.2%)	37 (2.5%)	32 (2.5%)	163 (2.9%)	18 (4.9%)
Non-fatal serious AEs‡	73 (1.9%)	55 (1.9%)	27 (1.9%)	18 (1.4%)	100 (1.8%)	5 (1.4%)
AEs leading to death	5 (0.1%)	4 (0.1%)	3 (0.2%)	0	7 (0.1%)	1 (0.3%)
AEs attributed to study medication	579 (14.8%)	340 (11.7%)	126 (8.6%)	112 (8.8%)	578 (10.3%)	67 (18.4%)

*Patients are counted according to each treatment received; therefore, patients may be counted in more than 1 treatment group. Number of patients with adverse events based on actual treatment received at onset, death, or withdrawal. Patients may be included in more than 1 category.

†Refers to combined total for atorvastatin, pravastatin, and simvastatin.

‡A nonfatal serious AE was an event that satisfied 1 or more of the following criteria: was life threatening or a congenital abnormality, required prolonged hospitalization, required medical or surgical intervention to prevent permanent impairment or damage, or resulted in disability or incapacity.

AstraZeneca

July 20, 2004

The Honorable Tommy Thompson
Department of Health and Human Services
200 Independence Avenue SW
Washington, D.C. 20201

Re: CRESTOR® (rosuvastatin calcium) Tablets
Response to Citizen Petition (FDA Docket #2004-0113)

Dear Mr. Thompson:

Enclosed please find the response of AstraZeneca Pharmaceuticals LP (AstraZeneca) to Public Citizen Health Research Group's petition regarding CRESTOR® (rosuvastatin calcium) Tablets.

We are simultaneously forwarding the required copies of this response to the Dockets Management Brach of the Food and Drug Administration for filing.

Most sincerely,

Catherine M. Bonuccelli, MD

Catherine M. Bonuccelli, MD
Vice President, External Scientific Affairs
Telephone: (302) 886-7867
Fax: (302) 886-1889

AFR/giw
Enclosures

2004P-0113 C2

AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 15437 Wilmington DE 19850-5437

Tel 302 886 3000
www.astrazeneca-us.com

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

John Jenkins, New Drugs Director
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-020, Room 7220
5515 Security Lane
Rockville, MD 20852

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

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

Division of Dockets Management
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 208572

Docket No. 2004P-0113

RESPONSE OF ASTRAZENECA PHARMACEUTICALS LP TO PUBLIC CITIZEN HEALTH RESEARCH GROUP'S PETITION REGARDING CRESTOR®

Submitted by
AstraZeneca Pharmaceuticals LP
July 20, 2004

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EXECUTIVE SUMMARY

AstraZeneca Pharmaceuticals LP ("AstraZeneca"), as agent for IPR Pharmaceuticals, Inc., submits this response to the petition submitted by Public Citizen Health Research Group ("HRG") on March 4, 2004 requesting withdrawal of CRESTOR (rosuvastatin calcium) from the market. The petition is meritless and must be denied, as HRG's argument suffers from three fundamental flaws:

(1) There is nothing new about HRG's position. Instead, HRG recycles the very same unscientific arguments it made more than a year ago during CRESTOR's approval process - arguments that were subsequently rightfully rejected by a unanimous FDA Advisory Committee and the FDA.

(2) HRG ignores any consideration of the benefits of CRESTOR. The benefit-risk profile of CRESTOR is positive, as the FDA found when it approved the drug last year. HRG has offered no evidence to the contrary. The FDA has always interpreted the word "safe" to mean a judgment that the benefits offered by a therapeutic agent justify the risks associated with that agent. Thus, the fact that a drug presents risks does not automatically make it "unsafe."

(3) HRG incorrectly assumes every spontaneous adverse event report is accurate and reliable evidence that the reported event occurred and was caused by CRESTOR. This assumption ignores the FDA's express precautions regarding the use of such reports.

The Petition Recycles Rejected Arguments.

On July 9, 2003, HRG was afforded the opportunity to present its views about CRESTOR's approval at an FDA Advisory Committee meeting. HRG's presentation focused on claims of rhabdomyolysis and kidney toxicity, primarily at the 80 mg dose for which AstraZeneca did not seek marketing approval. Despite HRG's arguments, the Advisory Committee unanimously recommended that CRESTOR be approved and, on August 12, 2003, the FDA agreed. Almost a year later, HRG has repackaged these very same arguments in its petition, adding nothing new to its

one-sided attack other than further anecdote and speculation based on incomplete information.

The Petition Misuses and Misrepresents Limited Data.

As it has done previously with respect to other FDA-approved medicines, HRG ignores the compelling scientific and medical data establishing the safety and efficacy of CRESTOR. Instead, it selectively focuses on limited information from adverse event reports that have been appropriately submitted to and reviewed by the FDA and other health authorities. The FDA has previously warned that accurate evaluations of drug safety cannot be drawn solely from adverse event reports, and rightfully has criticized HRG in the past for using these reports in this fashion, noting that HRG "ignored all of the well-known limitations to use of FDA spontaneous reports."[1] HRG continues to ignore these warnings.

Moreover, in its zeal to have CRESTOR withdrawn, HRG not only has used unscientific information and unsound analysis, but has disseminated information that has proved to be incorrect. For example, HRG's petition claims that "a 39 year-old woman, taking only 20 milligrams a day [of CRESTOR], died of rhabdomyolysis and renal insufficiency." This statement is wrong and, like so many of HRG's statements, has precipitated unnecessary confusion and alarm. While the event initially was reported as a death caused by rhabdomyolysis, an autopsy ultimately determined that the woman died from myocardial infarction and had no evidence of rhabdomyolysis; her death had nothing to do with CRESTOR. This event exemplifies the problems with the unscientific and limited information underpinning HRG's petition.

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[1] FDA, Center for Drugs and Biologics, Recommendation in Piroxicam Imminent Hazard Proceeding (May 14, 1986) at 16, *attached to* Letter from Secretary of HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking to ban the use of Feldene (piroxicam) in people aged 60 and over (July 7, 1986).

The Petition Fails to Recognize the Positive Benefit-Risk Profile of CRESTOR.

The benefit-risk profile of a medicine cannot be determined by cursorily examining limited data from isolated spontaneous adverse event reports. Instead, a medication's benefit-risk profile can be evaluated only by thoroughly analyzing reliable medical data within the context of the disease the medication treats.

Coronary Heart Disease ("CHD") is a Serious and Prevalent Disease.

Cardiovascular disease is the world's leading cause of death for both men and women, accounting for almost one-third of all deaths globally – more than all cancers combined.[2] CHD is the most prevalent of the cardiovascular diseases. This widespread and effective killer is also stealthy: more than half of the people who die suddenly from CHD had no previous symptoms. Even those who survive have a significantly reduced life expectancy; an individual's risk of illness and death following a heart attack is up to 15 times greater than that of the general population. Additionally, the economic costs of cardiac morbidity are enormous, recently estimated to exceed $300 billion this year in the United States alone.

Statin Therapy Has Become the Standard of Care.

Elevated levels of LDL cholesterol are a major cause of CHD. Studies long have demonstrated that lowering LDL cholesterol levels significantly reduces the risk of CHD. Recently, the National Cholesterol Educational Program ("NCEP") has updated its clinical practice guidelines for the treatment of high blood cholesterol to recommend the use of more intensive LDL-lowering drug therapy for patients at high risk.

Statins have proven remarkably effective at lowering LDL cholesterol levels. Statin therapy also has been proven to be safe as well as effective. Although every statin has a recognized, but very low, risk for adverse events, including rhabdomyolysis, for the overwhelming majority of patients, the significant benefit of

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[2] WHO World Health Report, 2004 *available at* http://www.who.int/whr/en/.

statin medication in lowering cholesterol and reducing the risk of CHD substantially outweighs the risk of developing an adverse event.

Though all statins reduce LDL cholesterol, they differ in a number of important respects. Statins vary in terms of efficacy, drug-drug interactions, and pharmacokinetics, such as protein binding, metabolism, and elimination. Moreover, individual patients may respond differently to different statin medications, in terms of both efficacy and adverse events: what works well for one patient may work less well for another; similarly, what is tolerated perfectly by one patient may elicit an adverse event in another.

CRESTOR Has Clinically Proven Efficacy and Unique Lipid-Modifying Benefits.

Clinical studies have proved that CRESTOR is an effective lipid-modifying agent capable of providing significant improvements in lipid profile in a wide variety of adult patient populations. Indeed, clinical trials have established that CRESTOR reduces total cholesterol, LDL cholesterol, ApoB, non-HDL cholesterol, and triglycerides, and increases HDL cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia. A therapeutic response is seen within one week; the maximum response is usually achieved within four weeks and maintained during long-term therapy.

In fact, studies have shown that CRESTOR offers lipid-modulating features unique among the currently marketed statins, including: (1) the greatest efficacy for lowering serum LDL cholesterol; and (2) significant increases in beneficial HDL-C. These pharmacologic features translate into two important clinical benefits. First, approximately 80% of patients using CRESTOR reach their LDL cholesterol goal on the usual starting dose of 10 mg/day. This is an important advantage because patients tend to remain on the dose with which therapy was initiated, even if their medical condition warrants a greater dose to achieve the desired result. Second, for the small number of patients with severe hypercholesterolemia who do not achieve their desired goal with the 10 mg/day dose or with other current monotherapies, higher

doses of CRESTOR are available. This option becomes even more important now that NCEP has established even more aggressive lipid-lowering goals for high risk patients.

CRESTOR's Benefits Far Outweigh Any Risks.

CRESTOR has a clearly demonstrated positive benefit-risk profile. At the time of FDA approval, the safety of CRESTOR was evaluated in more than 10,000 patients—more than any other marketed statin prior to approval—with more than 1,500 of those patients treated for at least 2 years. CRESTOR is now approved in more than 60 countries, and it is estimated that more than 2 million patients have been prescribed CRESTOR, with more than 6.5 million prescriptions dispensed. Additionally, more than 40,000 patients are being or have been treated with CRESTOR in controlled clinical trials. The totality of these data confirms that the FDA was correct in concluding that CRESTOR is safe and effective.

The clinical trial data demonstrate that CRESTOR is generally well tolerated, with an adverse event profile similar to that of other currently marketed statins. The most frequently observed adverse events with CRESTOR include myalgia, constipation, asthenia, abdominal pain, and nausea. Like the other currently marketed statins, CRESTOR also had a very low risk for rhabdomyolysis in clinical trials. These events are clearly noted in the prescribing information. Moreover, in addition to the clinical trials and as part of a comprehensive program to assure continued safety, AstraZeneca also monitors and assesses post-marketing reports of adverse events to identify and mitigate any risks they might uncover. Despite the increased attention and publicity surrounding CRESTOR, its adverse event reporting experience has been stable and in line with that of the other currently marketed statins. The FDA and myriad other regulatory agencies also independently have evaluated and continue to evaluate CRESTOR's safety.

Considering CRESTOR's clinically proven efficacy and unique lipid-modifying benefits and that a thorough review of clinical trial and post-marketing data confirms CRESTOR's safety, it is little wonder that the FDA and other countries'

regulatory agencies have concluded, and continue to conclude, that CRESTOR is safe and effective when used according to its labeling. Indeed, the Medicines Evaluation Board ("MEB"), for example, recently posted on its website a response to HRG stating that "Crestor is an effective and safe cholesterol-lowering agent provided that it is used at the recommended dosage and that the precautions stated in the product information are taken into consideration."[3] HRG's petition provides no scientific basis for challenging these conclusions, as discussed in more detail below.

In short, because HRG presents no new arguments, omits any consideration of CRESTOR's benefits, misuses limited and unverified data, and fails to show that CRESTOR does not have a positive benefit-risk profile, the legal standard applicable to the withdrawal of an NDA has not been and cannot be met by HRG, and its petition must be denied.

I. CHD IS THE LEADING CAUSE OF DEATH OF ADULTS IN THE U.S., YET REMAINS AN UNDERTREATED DISEASE.

A. CHD IS A SERIOUS AND PREVALENT DISEASE WITH SIGNIFICANT ECONOMIC AND PERSONAL CONSEQUENCES.

In order to evaluate the unique lipid-modifying benefits that CRESTOR offers to patients and their healthcare professionals, it is important to understand cardiovascular disease. In the United States, cardiovascular disease is the leading cause of death for both men and women, accounting for approximately 38.5 percent of all deaths.[4] With the exception of one year during World War I (1918), cardiovascular disease has remained the leading cause of death in the United States since 1900 - more than the next five leading causes of death (*i.e.*, cancer, chronic lower respiratory diseases, accidents, diabetes mellitus, and influenza/pneumonia) combined.[5] Declines

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3 *Available at* http://www.cbg-meb.nl/uk/nieuws/start.htm

4 American Heart Association. *Heart Disease and Stroke Statistics - 2004 Update.* Dallas, Tex.: American Heart Association; 2003.

5 *Id.*

in death rates from cardiovascular diseases are largely responsible for the increases in life expectancy in the United States during the twentieth century.[6]

CHD is the most prevalent of the cardiovascular diseases, causing more than twenty percent of all deaths in the United States.[7] More than half of the people who die suddenly from CHD had no previous symptoms.[8] Even those who survive have substantially reduced life expectancy - the risk of illness and death in individuals following a heart attack is up to 15 times greater than in the general population.[9] The economic cost of cardiovascular disease in the United States, estimated at $368.4 billion in 2004, is staggering and is nearly twice the cost of all cancers combined.[10]

B. CHD IS A TREATABLE YET UNDERTREATED DISEASE.

1. Statin therapy has become the standard of care.

Elevated levels of LDL cholesterol are a major cause of CHD.[11] Specifically, LDL cholesterol contributes to the development of coronary plaque, and recent studies have indicated that it contributes to plaque instability as well, which in turn results in heart disease.[12] Studies have long shown that lowering LDL cholesterol demonstrably reduces the mortality and morbidity associated with CHD.[13] As a result,

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6 *Id.*

7 *Id.*

8 *Id.*

9 *Id.*

10 *Id.*

11 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106:3143-3421.

12 *Id.*

13 *See, e.g.,* Cannon CP et al. Comparison of intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM.* 2004;350 (15):1495-1504; Wilson PWF et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97:1837-47; Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I: Reduction in the incidence of coronary heart disease. *JAMA.* 1984;251:351-64; Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. II: The relationship

clinical treatment of CHD has focused on reducing the level of LDL cholesterol.[14] In fact, recent research studies evaluating LDL-C lowering have shown not only reductions in atherosclerosis, but also decreases in cardiovascular mortality.[15] This has resulted in the NCEP recently updating its clinical practice guidelines for the treatment of high blood cholesterol to recommend the use of more intensive LDL-lowering drug therapy for patients at high risk.[16]

Although many treatment methods are available - including diet and exercise - statins are currently the most effective treatment for reducing LDL cholesterol.[17] When studied, statins have been shown to substantially reduce CHD incidence and mortality over nearly every population group.[18] Additional studies

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of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA.* 1984;251:365-74; Pekkanen J et al. Ten year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *NEJM.* 1990;322:1700-7.

14 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Wood D et al. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J.* 1998;19:1434-1503.

15 Cannon CP et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM.* 2004;350(15):1495-1504; Nissen SE et al. REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004;291(9):1071-1080.

16 NCEP Report, Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation.* 2004;110:227-239.

17 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Wood, D et al. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Eur Heart J.* 1998;19:1434-1503.

18 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

indicate that the risk of developing CHD decreases the earlier LDL cholesterol-reducing therapy is started,[19] and that intensive therapy has a marked effect on the progression of coronary atherosclerosis.[20]

Statin therapy has thus become the standard of care, revolutionizing the treatment of high cholesterol.[21] Statins are easy to administer and have become widely accepted among patients.[22] Although every currently available statin has a recognized, but very low, risk for adverse events, for the overwhelming majority of patients, the significant benefit of statin therapy in reducing cholesterol and reducing the risk of CHD substantially outweighs the risk of developing an adverse event and clearly outweighs the risk of not being treated.[23]

Given the significant personal and economic impact of cardiovascular disease, and the ready availability of an effective medication, it is troubling that, although treatable, CHD is an undertreated disease.[24] Fewer than half of the people

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19 Law MR et al. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischemic heart disease? *BMJ.* 1994;308:367-72. Law MR. Lowering heart disease risk with cholesterol reduction: evidence from observational studies and clinical trials. *Eur Heart J Suppl.* 1999;(suppl. S):S3-S8.

20 Nissen SE et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *JAMA.* 2004;291:1071-1080.

21 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Evans M et al. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Safety.* 2002;25(9):649-663.

22 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

23 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421; Pasternak RC et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. *J Am Coll Cardiol.* 2002;40:563-79.

24 *See* Preventive cardiology: how can we do better? Presented at the 33rd Bethesda Conference, Bethesda, Maryland, December 18, 2001. *J Am Coll Cardiol.* 2002;40:579-651.

who should be treated with cholesterol-reducing therapy are being treated.[25] Of those who are taking statin medications, many are not being titrated to a dosage that will result in reaching their recommended cholesterol goals.[26] In addition, and largely due to noncompliance, patients are simply not maintaining their lipid-reducing therapy over the long run.[27] As a result, the medical community is becoming increasingly aware of the need to screen for and treat high cholesterol and to follow patients more closely. Physicians also are prescribing statins earlier, and more aggressively, to close the gap of undertreatment.

2. Patients benefit from having several types of statin therapies available.

Currently, there are six statins available for treatment of high cholesterol. They are not the same. For example, although all the statins reduce LDL cholesterol via the same mechanism, that effect can vary considerably depending on the statin and dose used.[28] Moreover, despite this common effect of LDL reduction, there is considerable variation in the pharmacokinetic properties (*i.e.*, protein binding, metabolism, and elimination) of various statins after oral administration.[29] Additionally, drug-drug interactions vary among statins.[30]

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25 Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

26 *See, e.g.,* Sueta CA et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1999; 83:1303-1307.

27 *Id.*

28 CRESTOR Prescribing Information; Lescol Precribing Information; Lipitor Precribing Information; Mevacor Prescribing Information; Pravachol Prescribing Information; Zocor Prescribing Information.

29 *Id.*; Evans M et al. Effects of HMG-CoA reductase inhibitors on skeletal muscle: are all statins the same? *Drug Safety.* 2002;25(9):649-663.

30 *See* Moghadasian MH. A safety look at currently available statins. *Expert Opin Drug Saf.* 2002;1(3):269-74.

The availability of different statins and dosages is thus essential for the success of lipid-reduction therapy. Patients are individuals, and not all of them respond the same to any one statin medication, either in terms of efficacy or adverse events.[31] As a result, it is important for physicians to monitor an individual patient's response to the statin medication prescribed and to modify or change the medication, or its dosage, for the best results.[32] Choice among statins is essential to effective treatment of high cholesterol.

II. CRESTOR PROVIDES EFFECTIVE THERAPY FOR THE TREATMENT OF DYSLIPIDEMIA, OFFERING UNIQUE LIPID-MODIFYING BENEFITS IN THE STATIN CLASS.

CRESTOR is a selective, potent, and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. [33] CRESTOR reduces total-cholesterol, LDL-cholesterol, ApoB, non-HDL-cholesterol, and triglycerides, and increases HDL-cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia.[34] Therapeutic response is usually seen within one week and maximum response is usually achieved within four weeks and maintained during long-term therapy.[35]

CRESTOR is an effective statin delivering significant reductions in LDL cholesterol at all doses studied along with important modifications in the atherogenic lipid profile. Approximately 80% of patients can reach their LDL cholesterol goal on the

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31 Davidson MH. Controversy surrounding the safety of cerivastatin. *Expert Opin Drug Saf.* 2002;1(3):207-212; Thompson PD et al. Statin-associated myopathy. *JAMA.* 2003;289:1681-90.

32 *See* Third Report of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation.* 2002;106: 3143-3421.

33 CRESTOR Prescribing Information.

34 *Id.*

35 *Id.*

usual starting dose of 10 mg/day.[36] Additionally, for the small number of patients with particularly severe hypercholesterolemia who are inadequately treated with current monotherapies, titration to higher doses of CRESTOR offers an important therapeutic option to physicians. A 5 mg dose is also available for patients who require less aggressive LDL-C reduction or who have predisposing factors for myopathy.

CRESTOR is an effective lipid-modifying agent capable of providing significant improvements in the lipid profile in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age, and in special populations such as diabetics or patients with heterozygous or homozygous familial hypercholesterolemia.[37] CRESTOR is thus an important addition to the medical community's arsenal in its war against dyslipidemia.

A. EXTENSIVE CLINICAL TRIALS HAVE ESTABLISHED CRESTOR'S EFFICACY.

1. CRESTOR is a highly effective statin for reducing serum LDL cholesterol and increasing HDL cholesterol.

In its petition, HRG claims that CRESTOR offers no benefits different from other statins. As the data from the clinical studies prove, HRG is clearly wrong. In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hypercholesterolemia, CRESTOR significantly reduced LDL-C from 45 - 63% (vs 7% with placebo) across the 5 - 40 mg dose range and increased HDL-C between 8 - 14% (vs 3% with placebo) across that same dose range.[38]

Importantly, CRESTOR was compared with atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose-ranging study analyzing 2,240 patients

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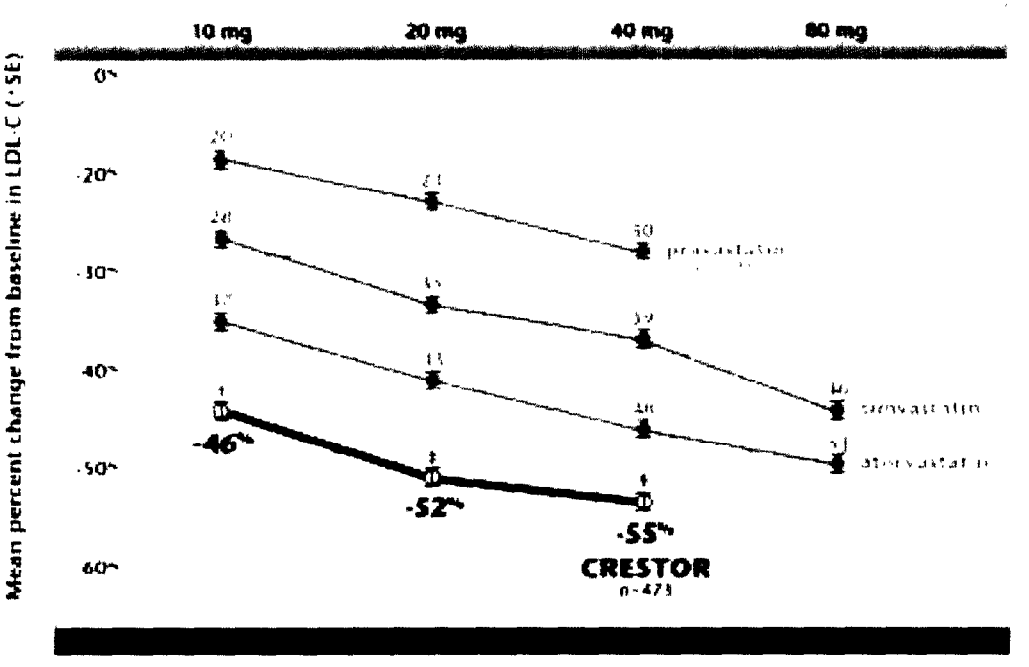
36 Shepherd J et al. *Am J Cardiol.* 2003;91(Suppl):11C-19C; Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160.

37 CRESTOR Prescribing Information.

38 *Id.*

with Fredrickson Type IIa and IIb hypercholesterolemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin. The dose response of CRESTOR (10 - 40 mg) reduced LDL-C significantly more than atorvastatin (10 - 80 mg), simvastatin (10 - 80 mg), and pravastatin (10 - 40 mg) across the studied dose range.[39] The usual starting dose of CRESTOR 10 mg provided significantly greater decreases in LDL-C than atorvastatin 10 mg, simvastatin 10, 20, and 40 mg and pravastatin 10, 20, and 40 mg.[40] (See Figure 1, below.)

Figure 1: LDL-C REDUCTION BY DOSE



[1] P<.002 vs atorvastatin 10 mg; simvastatin 10 mg, 20 mg, 40 mg; pravastatin 10 mg, 20 mg, 40 mg.
[2] P<.002 vs atorvastatin 20 mg, 40 mg; simvastatin 20 mg, 40 mg, 80 mg; pravastatin 20 mg, 40 mg.
[3] P<.002 vs atorvastatin 40 mg; simvastatin 40 mg, 80 mg; pravastatin 40 mg.
Mean baseline LDL-C: 189 mg/dL

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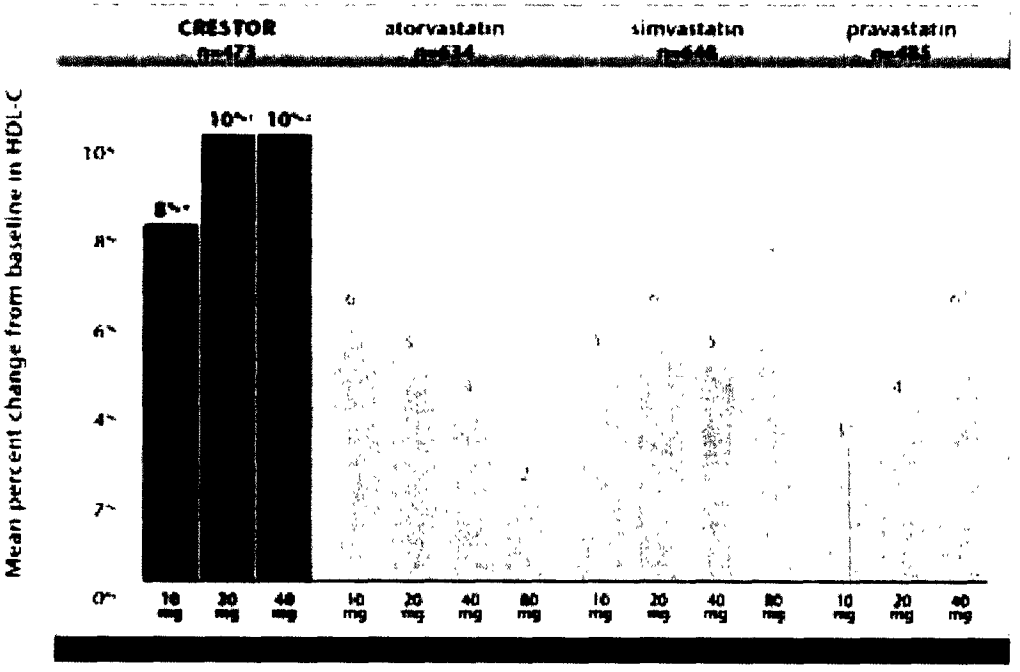
39 Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160; CRESTOR Prescribing Information; Data on File.

40 *Id.* The pairwise, dose-to-dose comparisons for LDL-C are provided in Table I in the Appendix.

The investigators concluded that CRESTOR was more effective in reducing LDL-C across the dose ranges when compared with atorvastatin, simvastatin, and pravastatin, supporting the conclusion that CRESTOR meets an important unmet clinical need. In addition, for the patients with particularly severe hypercholesterolemia who are inadequately treated with current statin monotherapy, titration to CRESTOR 40 mg offers an important therapeutic option. This option has become particularly important now that NCEP has recommended even more stringent lipid-lowering goals for high risk patients.

CRESTOR also consistently increased HDL-C across the 10 - 40 mg dose range, with no decrease in effect at higher doses.[41] (See Figure 2, below.)

Figure 2: HDL-C INCREASE BY DRUG



*P<.002 vs pravastatin 10 mg.
†P<.002 vs atorvastatin 20 mg, 40 mg, 80 mg; simvastatin 40 mg; pravastatin 20 mg, 40 mg.
‡P<.002 vs atorvastatin 40 mg, 80 mg; simvastatin 40 mg; pravastatin 40 mg.
Mean baseline HDL-C: 38 mg/dL.

41 *Id.* The pairwise, dose-to-dose comparisons for HDL-C are provided in Table II in the Appendix.

2. Approximately 80% of patients using CRESTOR can reach their LDL cholesterol goal on the usual starting dose of 10 mg/day.

Another benefit ignored by HRG is that the majority of patients can reach their LDL cholesterol goal on the usual starting dose of CRESTOR.[42] Experience with medical practice has revealed that, despite recommendations about titration upward to reach LDL-C targets, patients are in fact not titrated but tend to remain on the dose with which therapy was initiated.[43] Accordingly, there is a clinical benefit to having a starting dose that is effective in a majority of patients. The results of multiple Phase III clinical trials involving various patient populations demonstrate that the starting 10 mg dose of CRESTOR allows significantly more of these patients to reach their LDL-C goals, thereby reducing the need to titrate to higher doses.

A prospectively-planned, pooled analysis of the first 12 weeks of 5 randomized, double-blind, parallel-group, comparator-controlled, multicenter studies was performed to compare the effects of CRESTOR 5 mg and 10 mg with atorvastatin 10 mg (3 studies) and simvastatin 20 mg and pravastatin 20 mg (2 studies) on lipid parameters.[44] Patients from all risk categories were included, with 43% of patients having an LDL-C goal < 100 mg/dL. All trials included in the pooled analyses were prospectively designed so that the data from the first 12 weeks of treatment could be pooled. Effects on lipid parameters and goal attainment at 12 weeks are presented in Table III for CRESTOR 10 mg in all 5 studies, Tables IV and V for CRESTOR and

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42 Shepherd J et al. *Am J Cardiol.* 2003;91(Suppl):11C-19C.

43 Sueta CA et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *Am J Cardiol.* 1999;83:1303-1307.

44 Blasetto JW et al. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C; Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of rosuvastatin compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C; Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

atorvastatin and Tables VI and VII for CRESTOR, simvastatin, and pravastatin (Appendix).

The authors concluded that treatment with CRESTOR 10 mg for 12 weeks resulted in significantly greater improvements in lipid parameters and allowed more patients to attain NCEP ATP III goals than atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg. A similar effect was observed by others, with reductions in LDL-C resulting in a higher percentage of patients reaching their NCEP ATP III LDL-C goals (Appendix—Table VIII).[45] CRESTOR thus presents unique lipid-modifying benefits consistent with its proven positive benefit-risk profile.

3. Additional studies in special populations further support CRESTOR's highly effective lipid-lowering profile.

- Heterozygous Familial Hypercholesterolemia: In an 18-week study of patients with heterozygous FH (baseline mean LDL of 291), patients were randomized to CRESTOR 20 mg or atorvastatin 20 mg. The dose was increased at 6-week intervals. Significant LDL-C reductions from baseline were seen at each dose in both treatment groups, with CRESTOR producing significantly greater improvements in LDL-C, HDL-C, and total-C than atorvastatin and helping more patients achieve their target LDL-C goals.[46]

- Hypertriglyceridemia (Fredrickson Type IIb & IV): In a double-blind, placebo-controlled dose-response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels from -18% to - 40%.[47]

- Homozygous Familial Hypercholesterolemia: This group of patients represented a group with very severe and difficult to treat hypercholesterolemia and at high risk for developing CHD. In an open-label,

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45 Jones PH et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;93:152-160.

46 Stein EA et al. Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol.* 2003;92:1287-1293; CRESTOR Prescribing Information.

47 Hunninghake DB, Stein EA, Bays HE, et al. Rosuvastatin improves the atherogenic and atheroprotective lipid profiles in patients with hypertriglyceridemia. Coron Artery Dis. 2004;15(2):115-123; CRESTOR Prescribing Information.

forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL reduction of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, only 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.[48]

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Thus, the results of these clinical studies prove CRESTOR to be an effective lipid-modifying agent capable of providing significant improvements in the atherogenic lipid profile in a wide variety of adult patient populations with hypercholesterolemia, with and without hypertriglyceridemia, regardless of race, gender, or age. CRESTOR also has proven efficacy in special populations such as diabetics and patients with heterozygous or homozygous familial hypercholesterolemia.

B. THE PETITION IGNORES THE EFFICACY OF CRESTOR AS DEMONSTRATED IN ITS CLINICAL TRIALS.

The HRG petition requests that the FDA take action under section 355(e)(3) of the Federal Food, Drug, and Cosmetic Act ("FFDCA").[49] This section requires a finding that there is a lack of substantial evidence demonstrating that the drug is effective for its intended uses. The HRG petition, however, does not and cannot challenge the efficacy of CRESTOR in reducing LDL-C and triglycerides and in increasing HDL-C. Moreover, the HRG petition simply ignores that the FDA, in

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[48] Marais D et al. Effect of rosuvastatin on LDL-cholesterol, mevalonic acid and other lipid measurements in patients with homozygous familial hypercholesterolemia [poster]. Presented at the 73rd European Atherosclerosis Society Congress; July 7-10, 2002; Salzburg, Austria; CRESTOR Prescribing Information.

[49] 21 U.S.C. 355(e)(3). *See* opening sentence of the HRG letter dated March 4, 2004.

approving the drug after a comprehensive review, determined CRESTOR to be safe and effective.

III. THE PETITION MISREPRESENTS THE SAFETY OF CRESTOR.

HRG presents a selective and misleading review of the clinical and post-marketing safety surveillance data. The clinical studies have confirmed that CRESTOR is safe and effective when used according to the prescribing information, and nothing in the post-marketing experience contradicts that conclusion. CRESTOR is now approved in more than 60 countries, and it is estimated that more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with the pre-approval experience as reflected in CRESTOR's prescribing information.

A. CLINICAL TRIALS ESTABLISHED AND POST-MARKETING EXPERIENCE CONFIRMS THE SAFETY OF CRESTOR.

The FDA requires that a product's underlying risks and benefits must be adequately assessed during the premarketing period, adding that "sponsors should provide a body of evidence from the clinical trials that adequately characterizes the product's safety profile."[50] The FDA has confirmed that "the larger and more comprehensive a preapproval database, the more likely it is that serious adverse events will be detected."[51] The FDA has advised that premarketing safety databases should include a diverse population to allow for "the development of safety data in a broader population, including patients previously excluded from clinical trials, such as the elderly (particularly the very old), patients with concomitant diseases, and patients taking usual concomitant medications."[52]

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50 FDA Draft Guidance for Industry, "Premarketing Risk Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

51 *Id.*

52 *Id.*

At the time of FDA approval, the safety of CRESTOR had been evaluated in more than 10,000 patients,[53] with more than 1,500 patients treated for at least two years.[54] Currently more than 40,000 patients are being or have been treated with CRESTOR in controlled clinical trials. The most frequently observed adverse events thought to be related to CRESTOR include myalgia, constipation, asthenia, abdominal pain, and nausea; these adverse events were usually mild and transient.[55] Overall, CRESTOR was generally well tolerated in clinical trials.[56] The overall incidence of adverse events reported with CRESTOR was similar to placebo.[57] The overall frequency of adverse events was similar with CRESTOR doses of 5 mg to 40 mg.[58]

The safety and tolerability of CRESTOR have been assessed using data from the largest pre-approval clinical trial program for any statin approved to date. As every effort was made to recruit patients who would resemble, as closely as possible, individuals who would be candidates for statin therapy in clinical practice, the populations studied included patients with various forms of dyslipidemia, including heterozygous or homozygous familial hypercholesterolemia and the Fredrickson classifications of Type IIa or IIb hypercholesterolemia and Type IV hypertriglyceridemia.[59] In addition, in phase III trials, there was no upper age limit for entry, and patients with mild-to-moderate renal impairment with creatinine levels up to 2.5 mg/dl were enrolled, as were those with stable concomitant illnesses that are

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53 CRESTOR Prescribing Information.

54 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

55 CRESTOR Prescribing Information.

56 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.* 2003;92(suppl):23K-29K; CRESTOR Prescribing Information.

57 CRESTOR Prescribing Information; Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

58 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

59 *Id.*

commonly associated with dyslipidemia (e.g., hypertension, diabetes mellitus, and cardiovascular disease).[60]

As shown in Table IX (Appendix), in fixed-dose trials with comparator statins, CRESTOR 5 to 40 mg showed a similar adverse event profile to those for atorvastatin 10 to 80 mg, simvastatin 10 to 80 mg, and pravastatin 10 to 40 mg, with the most common adverse events across statin-treated groups being pharyngitis, headache, pain, myalgia, diarrhea, and abdominal pain.[61] Overall, the occurrence of treatment-related adverse events was low.

During the pre-approval clinical trials, there were no deaths attributed to CRESTOR. In controlled trials, clinically significant elevations of ALT (>3 x upper limit of normal at 2 consecutive treatments) occurred in a similar proportion of patients in each statin group (0.2%).[62] Myopathy possibly related to CRESTOR during the clinical trial program evaluating CRESTOR 5-40 mg was rare and occurred in ≤0.03% of patients.[63] There were no reports of rhabdomyolysis attributed to CRESTOR 5-40 mg.[64]

Proteinuria was seen in <1.0% of patients receiving CRESTOR 5, 10, or 20 mg and in those patients receiving placebo, atorvastatin 10 to 80 mg, simvastatin 10, 40, and 80 mg, or pravastatin 10 to 40 mg.[65] Proteinuria was seen in 1.2% of patients receiving CRESTOR 40 mg and 1.1% of patients receiving simvastatin 20 mg.[66] These findings of proteinuria were transient in many cases, reversible, and not associated with long-term detrimental effects on renal function. Importantly, renal function, assessed

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60 *Id.*

61 *Id.*

62 *Id.*

63 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004; Brewer HB. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. *Am J Cardiol.*2003;92(suppl):23K-29K.

64 *Id.*

65 Vidt DG et al. Rosuvastatin-induced arrest in progression of renal disease. *Cardiology* 2004;102:52-60.

66 Shepherd J et al. The safety of rosuvastatin. *Am J Cardiol.* In press, 2004.

by mean glomerular filtration rates predicted from the Modification of Diet in Renal Disease (MDRD) equation, did not deteriorate in patients receiving long-term (≥96 weeks) CRESTOR therapy at any dose, irrespective of age, sex, hypertensive or diabetic status, level of renal function at baseline (glomerular filtration rates ≥60 versus <60 ml/min/1.72 m^2) or presence or absence of urine dipstick protein before or during treatment.[67]

In summary, the 5 - 40 mg dose range for CRESTOR provides greater lipid modification when compared with other marketed statins. The LDL-C benefits with CRESTOR translated to a greater number of patients achieving NCEP ATP III goals at the 10 mg/day start dose, thereby reducing the need to titrate to higher doses. CRESTOR also allowed many patients to increase their HDL-C and reduce non-HDL-C and triglycerides. This is achieved with a safety profile that is similar to other currently marketed statins. At doses up to and including 40 mg, CRESTOR was generally well tolerated. Thus, the clinical trial data establish the positive benefit-risk profile for CRESTOR when used according to the prescribing information. CRESTOR offers an important option for patients and their healthcare professionals for the treatment of dyslipidemia.

B. HRG REJECTS SCIENTIFIC ANALYSIS IN FAVOR OF SPECULATION REGARDING THE SAFETY OF CRESTOR BASED SOLELY UPON UNVERIFIED AND LIMITED DATA.

The petition bases its request that CRESTOR be "immediately removed" from the market on essentially two lines of alleged evidence. The first is a selective presentation of opinions not related to the safety and efficacy of CRESTOR, but rather in the nature of business decisions. Specifically, HRG notes that two insurance companies do not, at this time, reimburse their insureds for CRESTOR prescriptions. What HRG fails to mention is that the overwhelming majority of insurers and managed care organizations in the United States have added CRESTOR to their formularies. HRG

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[67] *Id.*

also claims that "[i]n Sweden, regional government drug advisors recommended against the use of the drug." This is simply incorrect. In truth, the referenced board recommended reimbursement for CRESTOR, but only for patients who failed to reach lipid goals with generic drugs in the statin class. Thus, the decision was driven by economic interests and not safety or efficacy concerns. Moreover, since its approval on April 4, 2003 by the Medical Products Agency, CRESTOR remains available for prescription in Sweden. That HRG opts to rely upon such unsubstantiated information reveals the weakness of its entire position.

HRG's second line of alleged evidence is based upon a number of unverified, unidentified spontaneous post-approval adverse event reports, all of which have been appropriately reported to, and evaluated by, the FDA. This is not the first time HRG has attacked an FDA-approved medicine based upon such information. In denying previous HRG petitions, the FDA often has had to remind Public Citizen about the significant limitations on the use of adverse event reporting data and the dangers of its misuse.[68]

That adverse event reports can play a role in the identification of a safety signal is well-recognized.[69] Signals are hypothesis-generating and generally require further investigation, that, in turn, may or may not lead to the conclusion that the events were product-related.[70] The identification of a signal, however, demands careful case assessment of individual reports, including an evaluation of clinical content and completeness, as the quality of the reports is critical for appropriate evaluation of the relationship, if any, between the product and the adverse event.[71] Detailed case

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68 *See, e.g.*, Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking to ban the use of Feldene (prioxicam) in people aged 60 and over (July 7, 1986); Letter from HHS to Sidney Wolfe, M.D., Health Research Group, denying petition seeking withdrawal of Arava (leflunomide) (Mar. 23, 2004).

69 FDA Draft Guidance for Industry, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (May 2004), *available at* http://www.fda.gov/cder/guidance/index.htm.

70 *Id.*

71 *Id.*

assessment is especially important with an event such as rhabdomyolysis, as the criteria used for its diagnosis can vary tremendously.

The outcome of a thorough case assessment must then be compared with other relevant safety information, such as results from preclinical, clinical, pharmacoepidemiologic, or other available studies, and placed into context by determining the extent of patient exposure.[72] Additionally, as many factors can affect the reporting of adverse events (*e.g.*, publicity and newness of the product), these factors must be considered in interpreting any results.[73]

HRG has performed none of these steps. Instead it relies solely on the fact that a number of adverse events labeled as rhabdomyolysis have been reported for CRESTOR. The numerous flaws to this approach are discussed below. Moreover, that there have been reports of rhabdomyolysis in patients using CRESTOR comes as no great surprise, as rhabdomyolysis is a labeled and well-known, although rare, risk of all the currently marketed members of the statin class.

1. HRG misuses adverse event reports.

The FDA is fully aware that adverse event reports alone can only provide limited information, at best, about the safety of a medicine. In fact, the FDA has published guidelines identifying at least some of the limitations on the use of adverse event reports:[74]

> Reports contain only those reactions voluntarily submitted either to the FDA or to the drug manufacturer by consumers and/or members of the health profession....
>
> The information contained in the reports has not been scientifically or otherwise verified.

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72 *Id.*

73 *Id.*

74 FDA, Office of Postmarketing Drug Risk Assessment, "Brief Description with Caveats of System" (Oct. 18, 1999).

> For any given report, there is no certainty that the suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions.
>
> Accumulated case reports cannot be used to calculate incidence or estimates of drug risk.

HRG, however, ignores these well-known limitations and, without the full facts, attempts to use adverse event reports in a manner that the FDA has criticized. For example, the FDA has recognized that an adverse event report cannot be interpreted as evidence that the medicine caused the event, stating affirmatively that "there is no certainty that the suspected drug caused the reaction":

> [A] possible source of serious error in evaluating observational data, such as that found in FDA's postmarketing surveillance system, is the potential for inappropriately assuming that a cause and effect relationship exists between a particular exposure and a particular adverse event without evaluating the true relationship of the adverse event to the exposure.[75]

A fair understanding of an adverse event report and its significance can be obtained only by a careful medical review. In the absence of a thorough examination, a causal connection cannot be inferred; even when the medical records are available, it is often difficult or impossible to assess causality.

HRG commits precisely the "serious error" identified by the FDA - it wrongly uses an adverse event report to claim that CRESTOR caused fatal rhabdomyolysis. HRG cites a report of "a 39-year-old woman, taking only 20 milligrams a day, [who] died of rhabdomyolysis and renal insufficiency." That is how the report initially came to AstraZeneca and how it was initially submitted to the FDA. However, as the FDA knows, subsequent investigation revealed autopsy records for

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[75] 62 Fed. Reg. 30678, 30689-90 (June 4, 1997) (proposed rule for dietary supplements containing ephedrine alkaloids); *see also* FDA, "Postmarketing Safety of Sildenafil Citrate (Viagra)," March 3, 2001, *available at* www.fda.gov/cder/consumerinfo/viagra/safety3.htm ("An accumulation of adverse event reports does not necessarily indicate that the adverse event was caused by the

this patient, establishing that she died of an acute myocardial infarction. At autopsy, there was no evidence of rhabdomyolysis, and the death had nothing to do with CRESTOR. This is an example of why adverse event reports cannot be used to establish a link between a medicine and the event, and it is wrong for HRG to attempt to do so in its petition.

Additionally, spontaneous adverse event reporting systems are voluntary. Thus, reporting is susceptible to a wide range of factors that may stimulate or discourage voluntary reporting, including:

- Adverse publicity: lay and medical reporting of serious events with a product will stimulate reports;[76]
- Number of years that the drug has been on the market: events are more likely to be reported in the first 2 years of marketing than in later years (the "Weber effect");[77]
- Seriousness of the adverse event: deaths and life-threatening reactions are more likely to be reported than mild or transient side effects.[78]

Clearly, several of these variables, especially the first in the wake of HRG's petition, may be at play with respect to CRESTOR.

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drug; rather, the event may be due to an underlying disease or some other factor(s).").

[76] Faich GA, Moseley RH. Troglitazone (Rezulin) and Hepatic Injury. *Pharmacoepidemiology and Drug Safety.* 2001;10:537-47; Meinzinger MS, Barry WS. Prospective Study of the Influence of the Media on Reporting Medical Events. *Drug Inf J.* 1990;24: 575-77; Rossi AC et al. The Importance of Adverse Reaction Reporting By Physicians: Suprofen and the Flank Pain Syndrome. *JAMA.* 1988;259:1203-04.

[77] Wallenstein EJ, Fife D. Temporal Patterns of NSAID Spontaneous Adverse Event Reports: the Weber Effect Revisited. *Drug Safety.* 2001;24:233-37; Tsong Y. Comparing Reporting Rates of Adverse Events Between Drugs with Adjustment for Year of Marketing and Secular Trends in Total Reporting. *J Biopharm Stat.* 1995;5:95-114; Sachs RM, Bortnichak EA. An Evaluation of Spontaneous Adverse Drug Reaction Monitoring Systems. *Am J Med.* 1986;81:49-55; Weber JCP. Epidemiology of Adverse Reactions to Nonsteroidal Antiinflammatory Drugs. In: Rainsford KD, Velo GP, eds. *Advances in Inflammatory Research.* Vol. 6. New York: Raven Press, 1984:1-7.

[78] Piazza-Hepp TD, Kennedy DL Reporting of adverse events to MedWatch. *Am J Health-Syst Pharm.* 1995;52:1436-39; Milstien JB et al. Factors Affecting Physician Reporting of Adverse Drug Reactions. *Drug Inf J.* 1986;20:157-64.

Additional problems with HRG's use of adverse event reports arise from the medical conditions HRG has raised, namely rhabdomyolysis and kidney damage. Neither has a standard medical definition,[79] further confounding the interpretation of spontaneous adverse event reports. Specifically, one consequence of not having standard medical definitions is that physicians may diagnose different events as "rhabdomyolysis" or "acute renal failure."

Moreover, HRG fails to provide any context for the adverse event reports it cites. HRG makes no attempt to reconcile the number of reports against the backdrop of ever-increasing use of CRESTOR in the United States. Nor does HRG attempt to reconcile the number of reports against the background rate of such adverse events in hypercholesterolemic patients. Absent such an analysis, the number of adverse event reports alone is meaningless.

In conclusion, HRG has simply failed to perform any of the basic and necessary steps in safety signal identification. On the other hand, AstraZeneca, the FDA and the MEB are continually evaluating the available post-marketing data and agree that CRESTOR is safe and effective when used in accordance with its product labeling. Despite the increased attention and publicity surrounding CRESTOR, its adverse event reporting experience has been stable and in line with that of the other currently marketed statins.

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[79] Thompson PD et al. Statin-Associated Myopathy. *JAMA*. 2003;289:1681-1690 ("The literature on skeletal muscle complaints with statins is confusing, in part because of a lack of clear definitions."); Thadhani Ret al. Acute Renal Failure. *NEJM*. 1996; 334:1448-1460 ("When one attempts to review the subject of acute renal failure, one is immediately struck by the confusion in terminology and the wide disparity in the definitions of terms. Notably, in a recent review of 26 studies on postoperative renal failure, no 2 studies used the same definition of acute renal failure.").

2. AstraZeneca diligently monitors reports of adverse drug events and shares all such information with the FDA in accordance with applicable regulations.

There is nothing new in the HRG petition. HRG simply reargues the same points it made over a year ago at the FDA Advisory Committee meeting regarding the approval of CRESTOR. Despite HRG's claims of an increased risk of rhabdomyolysis and kidney toxicity, the Advisory Committee unanimously recommended approval. Fully aware of the adverse events discussed in HRG's petition, the FDA, and numerous other regulatory agencies, have agreed and have properly concluded that the benefits of CRESTOR outweigh its risk when prescribed and used in accordance with its labeling.

AstraZeneca's highest priority is patient safety. AstraZeneca monitors and assesses reports of adverse events to identify and mitigate any safety risks. Through its monitoring efforts, AstraZeneca ensures that the FDA, other regulatory authorities, and prescribing physicians receive complete, up-to-date information about the safety of CRESTOR. Indeed, the adverse event reports cited by HRG already were brought to the FDA's attention. As the FDA and as the MEB concluded most recently, in response to Mr. Wolfe's Letter to the Lancet on June 25, 2004, CRESTOR is safe and effective when prescribed and used in accordance with its labeling.[80]

IV. THE STANDARD FOR WITHDRAWAL CANNOT BE MET.

CRESTOR is a "new drug" as defined under section 201(p) of the FFDCA, 21 U.S.C. § 321, and is the subject of an approved New Drug Application, 21 U.S.C. § 355. The Secretary is authorized to withdraw approval of a new drug only under extremely limited circumstances, and only after giving due notice and an opportunity for hearing. To withdraw a New Drug Application, the Secretary must determine one of the following:

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[80] Marc Kaufman, *Crestor's Withdrawal Urged*, WASHINGTON POST, June 25, 2004, at A12; http://www.cbg-meb.nl/uk/nieuws/start.htm.

1. clinical or other experience, tests, or other scientific data show that a drug is unsafe for use under the conditions of use that formed the basis for approval of its application;

2. new evidence of clinical experience evaluated together with the evidence available when the application was approved, shows that a drug is not shown to be safe for use under the conditions of use that formed the basis for approval of the application; or

3. new information evaluated together with the evidence available when a drug was approved, shows that there is a lack of substantial evidence that it will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[81]

None of these facts is present here. As demonstrated above, HRG has failed to prove any of the bases for withdrawal. CRESTOR is not "unsafe," and it has a proven safety profile. There is no new evidence of clinical experience warranting its withdrawal. Nor is there new information suggesting that CRESTOR does not have the effect it purports to have. Indeed, the overwhelming weight of reliable scientific data provides further evidence of the positive benefit-risk profile of CRESTOR.

HRG's demands that the Secretary "immediately remove" CRESTOR from the market is likewise meritless. The Secretary can take such action only if "there is an imminent hazard to the public health,"[82] and "only in the exceptional case of an emergency, which does not permit the Secretary to correct it by other means."[83] No "imminent hazard" to the public health amounting to an emergency exists. To the contrary, CRESTOR presents a positive benefit-risk profile. The petition is unsupported and unsupportable and must be denied.

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81 21 U.S.C. § 355(e).

82 *Id.* This authority cannot be delegated.

83 Sen. Rep. No. 1744 at 7, 87th Cong., 2d Sess. (1962).

V. CONCLUSION

The safety and efficacy of CRESTOR are well documented and were confirmed last summer when an FDA Advisory Committee, comprised of independent medical and scientific experts, unanimously recommended that CRESTOR be approved. In fact, the safety of CRESTOR was evaluated in more than 10,000 patients, more than any other statin prior to approval. The FDA agreed and approved CRESTOR on August 12, 2003. CRESTOR is now approved in more than 60 countries, and more than 2 million patients have been prescribed CRESTOR with more than 6.5 million prescriptions dispensed. With this post-marketing experience, the safety profile of CRESTOR remains consistent with its pre-approval experience as reflected in its prescribing information. Moreover, it has been shown that CRESTOR offers lipid modifying effects unique among the currently marketed statins, including the greatest efficacy for lowering serum LDL cholesterol and significant increases in HDL cholesterol. CRESTOR also provides the significant clinical advantages of allowing approximately 80% of patients to reach their LDL cholesterol goal on the usual starting dose of 10 mg/day, while providing the option of higher doses for those who do not achieve their desired goal with either lower doses or other current statin monotherapies. Nothing that HRG has submitted demonstrates otherwise. The legal standard applicable to withdrawal of an NDA has not been and cannot be met by HRG, and its petition must be denied.

APPENDIX

CLINICAL TRIAL EFFICACY AND SAFETY TABLES

TABLE I: Least-squares Mean Percentage Change from Baseline in LDL-C.
Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	Atorvastatin	Simvastatin	Pravastatin
10 mg				
n	156	158	165	160
Baseline (mg/dL)±SD	188 ± 19	189 ± 18	189 ± 19	189 ± 18
% Change	-45.8	-36.8	-28.3	-20.1
P Value vs CRESTOR 10 mg		<0.001	<0.001	<0.001
20 mg				
n	160	155	162	164
Baseline (mg/dL))±SD	187 ± 18	190 ± 20	189 ± 19	187 ± 17
% Change	-52.4	-42.6	-35.0	-24.4
P Value vs CRESTOR 10 mg		0.026	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.001	<0.001	<0.001
40 mg				
n	157	156	158	161
Baseline (mg/dL))±SD	194 ± 19	189 ± 20	187 ± 16	190 ± 19
% Change	-55.0	-47.8	-38.8	-29.7
P Value vs CRESTOR 10 mg		0.164	<0.001	<0.001
P Value vs CRESTOR 20 mg		<0.002	<0.001	<0.001
P Value vs CRESTOR 40 mg		<0.001	<0.001	<0.001
80 mg				
n		165	163	
Baseline (mg/dL))±SD	NA	190 ± 20	190 ± 19	NA
% Change	NA	-51.1	-45.8	NA
P Value vs CRESTOR 20 mg		0.363	<0.001	
P Value vs CRESTOR 40 mg		0.006	<0.001	

P<0.002 are statistically significant.

TABLE II: Least-squares Mean Percentage Changes from Baseline in HDL-C. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	CRESTOR	Atorvastatin	Simvastatin	Pravastatin
10 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	51 ± 12	50 ± 13
% Change	+7.7	+5.7	+5.3	+3.2*
20 mg				
Baseline (mg/dL))±SD	51 ± 11	50 ± 12	50 ± 12	49 ± 11
% Change	+9.5	+4.8+	+6.0	+4.4+
40 mg				
Baseline (mg/dL))±SD	50 ± 12	50 ± 11	51 ± 11	50 ± 10
% Change	+9.6	+4.4+#	+5.2+#	+5.6+#
80 mg				
Baseline (mg/dL))±SD	NA	51 ± 13	51 ± 12	NA
% Change	NA	+2.1+#	+6.8	NA

*p<0.002 vs CRESTOR 10 mg; +p<0.002 vs CRESTOR 20 mg; #p<0.002 vs CRESTOR 40 mg

TABLE III: Effects of CRESTOR 10 mg on LDL-C and Achievement of NCEP ATP III LDL-C Goals at 12 Weeks (Pooled Data from 5 Trials). Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=615)
Effect on LDL-C	
Mean Baseline LDL-C	186 mg/dL
Mean LDL-C at 12 Weeks	98 mg/dL
Mean % Change in LDL-C from Baseline	-47%
Patients who achieved ATP III LDL-C Goals	
All Goals	80% (491/615)
<100 mg/dL	61% (161/264)
<130 mg/dL	89% (119/134)
<160 mg/dL	97% (211/217)

TABLE IV: Percent Change from Baseline at 12 Weeks Compared with Atorvastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C and Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=390)		**CRESTOR 10 mg (n=389)**		**Atorvastatin 10 mg (n=393)**	
	Baseline mg/dL	**% Change**	**Baseline mg/dL**	**% Change**	**Baseline mg/dL**	**% Change**
LDL-C	188	-41.9[a]	185	-46.7[a]	187	-36.4
HDL-C	51.1	+8.2[c]	50.8	+8.9[b]	50.4	+5.5
TG	179	-16.4	176	-19.2	181	-17.6
Total-C	275	-29.6[a]	271	-33.0[a]	274	-26.7
Non-HDL-C	224	-38.2[a]	221	-42.6[a]	223	-33.9
ApoB	179	-32.7[a]	175	-36.5[a]	179	-29.0
ApoA-I	151	+6.0[b]	149	+7.3[a]	149	+4.1
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-31
LDL-C/HDL-C	-	-	3.9	-51[a]	3.9	-39
Total-C/HDL-C	-	-	5.6	-38[a]	5.7	-30
NonHDL-C/HDL-C	-	-	4.6	-47[a]	4.7	-37

[a] $p<0.001$ vs atorvastatin; [b] $p<0.05$ vs atorvastatin; [c] $p<0.01$ vs atorvastatin

TABLE V: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Atorvastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=389)	**Atorvastatin 10 mg (n=393)**
All Goals	76% (297/389)	53%[a] (210/393)
<100 mg/dL	60% (120/199)	19%[a] (35/189)
<130 mg/dL	88% (61/69)	80% (70/88)
<160 mg/dL	96% (116/121)	91% (105/116)

[a] $p<0.001$ vs CRESTOR

TABLE VI: Percent Change from Baseline at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Blasetto JW et al. Efficacy of CRESTOR compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol.* 2003; 91(Suppl): 3C-10C; Rader DJ et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of CRESTOR compared with atorvastatin, pravastatin, and simvastatin. *Am J Cardiol.* 2003; 91(Suppl): 20C-24C.

	CRESTOR 5 mg (n=240)		**CRESTOR 10 mg (n=226)**		**Simvastatin 20 mg (n=249)**		**Pravastatin 20 mg (n=252)**	
	Baseline mg/dL	**% Change**	**Baseline** mg/dL	**% Change**	**Baseline** mg/dL	**% Change**	**Baseline** mg/dL	**% Change**
LDL-C	189	-40.6[a]	187	-48.1[a]	188	-35.7	189	-27.1
HDL-C	51	+6.9	51	+9.1[b]	53	+6.2	52	+6.2
TG	181	-14.9	170	-20.2[c]	166	-12.2	169	-12.4
Total-C	275	-29.1[a]	272	-34.0[a]	274	-25.1	275	-19.2
Non-HDL-C	225	-37.0[a]	221	-44.0[a]	221	-32.5	222	-25.0
ApoB	181	-32.3[a]	176	-37.9[a]	177	-28.0	177	-20.6
ApoA-I	151	+5.4	154	+5.3	155	+4.8	154	+4.2
ApoB/ApoA-I	-	-	1.2	-40[a]	1.2	-30	1.2	-23
LDL-C/HDL-C	-	-	3.8	-52[a]	3.8	-39	3.8	-30
Total-C/HDL-C	-	-	5.5	-39[a]	5.4	-29	5.5	-23
Non-HDL-C/ HDL-C	-	-	4.5	-48[a]	4.4	-36	4.5	-28

[a] $p<0.001$ vs simvastatin and pravastatin; [b] $p<0.05$ vs simvastatin and pravastatin; [c] $p<0.01$ vs simvastatin and pravastatin

TABLE VII: Percentage of Patients Achieving NCEP ATP III LDL-C Goals at 12 Weeks Compared with Simvastatin and Pravastatin. Adapted from Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of CRESTOR with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol.* 2003; 91(Suppl): 11C-19C.

	CRESTOR 10 mg (n=226)	**Simvastatin 20 mg (n=249)**	**Pravastatin 20 mg (n=252)**
All Goals	86% (194/226)	64%[a](159/249)	49%[a](124/252)
<100 mg/dL	63% (41/65)	22%[a](18/80)	5%[a](4/75)
<130 mg/dL	89% (58/65)	74%[b](51/69)	40%[a](30/75)
<160 mg/dL	99% (95/96)	90%[b](90/100)	88%[b](90/102)

[a] $p<0.001$ vs CRESTOR; [b] $p<0.05$ vs CRESTOR

TABLE VIII: Number of Patients Meeting NCEP ATP III LDL-C Goals. Adapted from Jones PH et al. Comparison of the efficacy and safety of CRESTOR versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). *Am J Cardiol.* 2003;92:152-160.

	ROS	ATORV	SIMV	PRAV
10 mg	82.1% (128/156)	69.0% (109/158)	50.9% (84/165)[a]	31.3% (50/160)[a]
20 mg		74.7% (115/154)	63.0% (102/162)[a]	43.9% (72/164)[a]
40 mg		85.3% (133/156)	66.5% (105/158)	54.7% (88/161)[a]
20 mg	88.8% (142/160)	74.7% (115/154)[b]	63.0% (102/162)[b]	43.9% (72/164)[b]
40 mg		85.3% (133/156)	66.5% (105/158)[b]	54.7% (88/161)[b]
80 mg		82.4% (136/165)	82.2% (134/163)	
40 mg	89.2% (140/157)	85.3% (133/156)	66.5% (105/158)[c]	54.7% (88/161)[c]
80 mg		82.4% (136/165)	82.2% (134/163)	

[a]$p<0.001$ vs ROS 10 mg; [b]$p\leq0.001$ vs ROS 20 mg; [c]$p<0.001$ vs ROS 40 mg

TABLE IX: Number (Percentage) of Patients with Various Categories of Adverse Events (AEs) During the Treatment Period in Fixed-Dose Controlled Trials. Adapted from Shepherd J et al. The safety of CRESTOR. *Am J Cardiol.* In press, 2004.*

AE Category	ROS 5-40 mg (n=3912)	ATORV 10-80 mg (n=2899)	SIMV 10-80 mg (n=1457)	PRAV 10-40 mg (n=1278)	Total Statin Comparators† (n=5634)	Placebo (n=365)
Any AE	1988 (50.8%)	1247 (43.0%)	618 (42.4%)	523 (40.9%)	2388 (42.4%)	205 (56.2%)
AEs leading to withdrawal	127 (3.2%)	94 (3.2%)	37 (2.5%)	32 (2.5%)	163 (2.9%)	18 (4.9%)
Non-fatal serious AEs‡	73 (1.9%)	55 (1.9%)	27 (1.9%)	18 (1.4%)	100 (1.8%)	5 (1.4%)
AEs leading to death	5 (0.1%)	4 (0.1%)	3 (0.2%)	0	7 (0.1%)	1 (0.3%)
AEs attributed to study medication	579 (14.8%)	340 (11.7%)	126 (8.6%)	112 (8.8%)	578 (10.3%)	67 (18.4%)

*Patients are counted according to each treatment received; therefore, patients may be counted in more than 1 treatment group. Number of patients with adverse events based on actual treatment received at onset, death, or withdrawal. Patients may be included in more than 1 category.

†Refers to combined total for atorvastatin, pravastatin, and simvastatin.

‡A nonfatal serious AE was an event that satisfied 1 or more of the following criteria: was life threatening or a congenital abnormality, required prolonged hospitalization, required medical or surgical intervention to prevent permanent impairment or damage, or resulted in disability or incapacity.