DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mark R. Szewczak, Ph.D.
Director, Promotional Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

RE: NDA # 21-366
Crestor® (rosuvastatin calcium) Tablets
MACMIS ID # 12979

Dear Dr. Szewczak:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the Food and Drug Administration ("FDA" or the "Agency"), in consultation with the FDA's Division of Metabolic and Endocrine Drug Products (DMEDP), has reviewed a direct-to-consumer (DTC) television advertisement (TV ad) and three DTC print ads ("STELLAR" print ads) for Crestor® (rosuvastatin calcium) Tablets (Crestor) submitted by AstraZeneca Pharmaceuticals LP (AstraZeneca) under cover of Form FDA 2253 (ID# 223151, 223444, 224174, and 225058).

The TV ad and the "STELLAR" print ads make false or misleading claims regarding the superiority of Crestor. The TV and print ads thus misbrand Crestor in violation of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 352 (n)); 21 CFR 202.1(e)(6) (ii).

Background: Approved Product Labeling

Indications and Usage

The indications in the approved product labeling (PI) for Crestor are as follows:

> CRESTOR is indicated:
>
> 1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb);

2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV);

3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Clinical Studies

The Clinical Studies section of the Crestor PI describes the STELLAR study, a 6-week open-label active-controlled study in which Crestor was compared to Lipitor (atorvastatin), Zocor (simvastatin), and Pravachol (pravastatin) in 2,240 patients with Type IIa/IIb hypercholesterolemia. Figure 1 and Table 2 in the Clinical Studies section show the percent LDL-C change from baseline of each of the drugs at week 6. Table 2 is reproduced below:

Table 2. Percent Change in LDL-C From Baseline to Week 6 (LS means[§]) by Treatment Group (sample sizes ranging from 156-167 patients per group)

Treatment	10 mg	20 mg	40 mg	80 mg
Crestor	-46*	-52†	-55‡	---
Atorvastatin	-37	-43	-48	-51
Pravastatin	-20	-24	-30	---
Simvastatin	-28	-35	-39	-46

* CRESTOR 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg….

† CRESTOR 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg….

‡ CRESTOR 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg….

§ Corresponding standard errors are approximately 1.00

Misleading Superiority Claims

Frames 10-14 of the TV ad and each of the "STELLAR" print ads present a bar graph purportedly based on the STELLAR study. In conjunction with the bar graph, the ads make the following comparative claims:

- "All cholesterol drugs simply aren't the same. When Crestor performed in a head to head test its lowering effect was clearly the best." (TV ad)

- "Cholesterol high? Trouble getting it low? Perhaps your answer is right here, below." (print ad)

- "Lowering cholesterol isn't a game. It's vital to know not all drugs are the same." (print ad)

- "Is your cholesterol treatment doing its share? Are you where you should be? If not, then compare." (print ad)

In the TV ad and "STELLAR" print ads, the graph is titled "THE STELLAR STUDY Bad cholesterol (LDL-C) lowering effect" and shows LDL-C lowering from baseline for Pravachol 40 mg (30%), Zocor 20 mg (35%), Lipitor 10 mg (37%), and Crestor 10 mg (46%). Below the graph in the TV ad are small SUPERs "Most commonly Rx'd doses (August 2003-July 2004)" and "Your results may vary." Below the graph in the "STELLAR" print ads is a small SUPER "Your results may vary" and the text below the graph states "In the STELLAR study, the usual starting dose of CRESTOR was more effective at lowering bad cholesterol than the most common doses of the other leading medications."

The presentation is a misleading comparison because it relies solely on data that are not relevant to comparisons of the drugs such as most common dose or starting dose, while ignoring data that do not support the claim of superiority made in the ads. Specifically, the comparison with Lipitor is misleading because it suggests that Crestor is superior to Lipitor when in fact none of the approved doses of Crestor was significantly superior to 80 mg of Lipitor in the STELLAR study. The STELLAR study itself states "The best LDL cholesterol reduction (55%) was achieved in the rosuvastatin 40-mg group and **was not significantly different**…from the next highest LDL cholesterol reduction (51%) observed in the atorvastatin [Lipitor] 80-mg group" (emphasis added).[1] Moreover, the 10 mg dose of Crestor was not statistically significantly more effective at LDL-C lowering than Lipitor 20 mg or 40 mg. Comparison of the most common doses or starting doses is irrelevant to the actual effectiveness of the drugs. Starting and common doses reflect a variety of influences, including doses studied in trials, commercial considerations, and toxicity concerns; however, they do not represent factors that are relevant for comparative effectiveness. Accordingly, your suggestion that Crestor is superior to Lipitor is therefore misleading. 21 CFR 202.1(e)(6)(ii).

We acknowledge receipt of your December 2, 2004, letter to Steven Galson. In this letter, you refer to an email from FDA's Division of Drug Information (DDI). This email states that "…Crestor lowered the LDL cholesterol more than other marketed statins, supporting the conclusion that a favorable risk vs. benefit profile was observed for Crestor." While the STELLAR data support this statement with respect to some statins, they do not with respect to Lipitor.

Conclusion and Requested Action

For the reasons discussed above, the TV ad and print ads misbrand Crestor in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. §§ 352 (n); 21 CFR 202.1(e)(6) (ii).

DDMAC requests that AstraZeneca immediately cease the dissemination of violative promotional materials for Crestor such as those described above. Please submit a written response to this letter on

[1] Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003; 92:152-60.

or before March 22, 2005, describing your intent to comply with this request, listing all violative promotional materials for Crestor the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6759. In all future correspondence regarding this matter, please refer to MACMIS ID #12979 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Crestor comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Christine Hemler Smith, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Smith
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