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 LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

RE: NDA # 21-366
Crestor® (rosuvastatin calcium) Tablets
MACMIS ID # 12779

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) print ad for Crestor entitled "You can be assured that at AstraZeneca, patient safety is our number one priority" that appeared in the November 23, 2004, edition of the *Washington Post* newspaper ("patient safety" print ad), and was submitted by AstraZeneca LP (AstraZeneca) under cover of Form FDA 2253 (ID# 224693).

The "patient safety" print ad makes false or misleading safety claims that minimize the risks associated with Crestor, thereby suggesting that Crestor is safer than has been demonstrated by substantial evidence or substantial clinical experience. The print ad thus misbrands Crestor in violation of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. § 352 n); 21 CFR 202.1(e)(6)(i).

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.

Pertinent Risk Information

According to the PI, the serious risks associated with Crestor include (original emphasis):

Contraindications

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases….

Warnings, Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively….Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended….Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease….

Warnings, Myopathy/Rhabdomyolysis

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

Uncomplicated myalgia has been reported in rosuvastatin-treated patients….Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. Rare cases of rhabdomyolysis were seen with higher than recommended doses (80 mg) of rosuvastatin in clinical trials.

Precautions, Laboratory Tests

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients, predominantly in patients dosed above the recommended dosage range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function.

Dosage and Administration

The 40-mg dose of CRESTOR should be reserved for those patients who have not achieved goal LDL-C at 20 mg (see WARNINGS, Myopathy/Rhabdomyolysis).

During the clinical trials, Crestor was shown to cause myopathy at the 40 mg dose. Prior to approval, the Agency recommended (and AstraZeneca agreed to) a risk management plan in which "[three] ongoing clinical studies with patients receiving long term treatment with 40 mg daily of Crestor…should have regular renal monitoring with urinalysis and serum creatinine measurements in order to better describe the clinical course of the renal findings."

As a consequence of the risks identified with the 40 mg dose, the August 12, 2003 approval letter for Crestor refers to a premarketing submission of July 18, 2003 in which AstraZeneca describes voluntary special distribution measures for the 40 mg dose of Crestor "to ensure that the 40-mg dose is available only to patients who truly need this dose." The special distribution measures were undertaken by AstraZeneca because the Medical Review concluded that the 40 mg dose was only appropriate for "patients with severe hypercholesterolemia who have not responded adequately to all other available forms of therapy."

Minimization of Risk /Misleading Safety Claims

The "patient safety" print ad presents false or misleading safety claims that minimize the risks associated with Crestor. The ad is headlined "You can be assured that at AstraZeneca, patient safety is our number one priority" and seeks to assure readers that Crestor is "more effective and just as safe" as "the leading medications in its class." These false or misleading claims include:

- "A medication <u>can</u> be more effective and just as safe."

This claim is misleading because it minimizes the risks associated with the 40 mg dose of Crestor. As discussed previously, these risks led to AstraZeneca agreeing to special distribution measures for Crestor 40 mg and to conduct three long-term post-marketing clinical trials to further assess the safety of the 40 mg dose. The PI reflects this concern, stating "The 40-mg dose of CRESTOR should be reserved for those patients who have not achieved goal LDL-C at 20 mg…." FDA is not aware of substantial evidence or substantial clinical experience demonstrating that all doses of Crestor are "just as safe" as other statins.

Similarly, we are concerned about the section of your ad entitled, "The FDA has confidence in the safety and efficacy of CRESTOR" in that it misleadingly suggests that the Agency does not believe that Crestor poses safety concerns. Specifically, your ad states:

- "The scientists at the FDA who are responsible for the approval and ongoing review of CRESTOR have, as recently as last Friday, publicly confirmed that CRESTOR is safe and effective; and that the concerns that have been raised have no medical or scientific basis."

The citation for this claim is "www.fda.gov accessed on 11/19/04." There is, however, no statement on the website by FDA concluding that "the concerns [about Crestor] that have been raised have no medical or scientific basis." In fact, recent public statements made by the Agency contradict that conclusion. For example, in an article entitled "Campaign Waged Against Crestor" appearing the previous week (on November 18, 2004) in the *Washington Post*, which discusses the safety concerns raised by the consumer advocacy group Public Citizen about Crestor, Dr. Steven Galson, Acting Director of the FDA's Center for Drug Evaluation and Research is quoted as saying:

- "[the Agency] has been very concerned about Crestor since the day it was approved, and we've been watching it very carefully." Dr. Galson further stated that the Agency is "concerned about the same issues with Crestor as Public Citizen."[1]

Conclusion and Requested Action

For the reasons discussed above, the "patient safety" print ad misbrands Crestor in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. §§ 352 (n); CFR 202.1(e)(6)(i.).

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 or before January 7, 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 #12779 in addition to the NDA number. We remind you that only written communications are considered official.

[1] The most recent information specific to CRESTOR on the www.fda.gov website is an "FDA Public Health Advisory for Crestor (rosuvastatin)" (posted on June 9, 2004) that alerts prescribers and consumers about the risks associated with Crestor.

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.
Consumer Promotion Analyst
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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