

FDA Warns Asians About Crestor

http://www.legalnewswatch.com/news_547.html

Source: U.S. Food and Drug Administration

Published: March 04, 2005

Asian American patients taking Crestor, a cholesterol-lowering drug made by AstraZeneca, may be at greater risk of muscle injury because of Crestor than the general public, the Food and Drug Administration warned on Tuesday.

The announcement comes after AstraZeneca revised the package insert for Crestor, advising physicians to consider using lower starting doses of the drug in some individuals as a means of reducing the risk of rhabdomyolysis. The revised label includes dosing instructions for Asian Americans, as well as patients on cyclosporine and patients with severe kidney disease.

Crestor is part of a class of drugs called statins that have been linked to rhabdomyolysis (serious muscle damage) and other types of kidney failure.

Despite the warning, the FDA said it "believes that potential benefits of statin drugs (including Crestor) when used as labeled and indicated for the treatment of elevated cholesterol (hypercholesterolemia) outweigh their potential risks and provide an important treatment option for millions of Americans at risk of heart disease."

<http://www.fda.gov/bbs/topics/news/2005/NEW01159.html>

Read Full Story at U.S. Food and Drug Administration

<http://my.webmd.com/content/article/101/106357.htm>

FDA Updates Crestor Warning Information

Asian-Americans Among Groups More at Risk of Serious Muscle Damage By

http://my.webmd.com/content/article/101//content/Biography/7/1756_53096.htm

Michael Smith, MD

WebMD Medical News Reviewed By

<http://my.webmd.com/content/article/101//content/Biography/7/40428.htm>

Brunilda Nazario, MD on Thursday, March 03, 2005

March 3, 2005 -- The FDA has issued a public health advisory to further explain the risks and benefits of the cholesterol-lowering drug Crestor. The drug will now carry a new label that includes new recommended doses for patients at a higher risk of muscle damage, including Asian patients.

"The FDA is committed to providing Americans with the latest and most comprehensive information on the medicines they use," says Steven Galson, MD, MPH, acting director of the Center for Drug Evaluation and Research (CDER), in a news release. "Today's FDA advisory on Crestor is part of an ongoing effort to notify the public of potentially significant emerging safety data so that they can make more informed choices about their medical care."

Serious Muscle Damage

The FDA is providing up-to-date information about the risk of serious muscle damage - called rhabdomyolysis -- in patients taking Crestor as well as similar drugs, called statins.

<http://my.webmd.com/content/article/101//content/article/98/104657.htm> similar drugs, called statins. This is a well-known, rare side effect of all statins, it says.

Rhabdomyolysis is a condition in which muscle cells break down. This floods the blood with muscle proteins, sometimes leading to fatal kidney failure.

In June 2004, the FDA advised doctors to be careful about how they prescribe Crestor.

<http://my.webmd.com/content/article/101//content/article/88/99939.htm> Careful about how they prescribe Crestor. And in January 2005, Crestor's manufacturer, AstraZeneca Pharmaceuticals, reported that a patient died while taking Crestor.

<http://my.webmd.com/content/article/101//content/article/99/105148.htm> Patient died while taking Crestor.

The FDA says extensive review of the large amount of available data indicates that patients taking recommended doses of Crestor have a similar risk of rhabdomyolysis as patients taking other statin drugs. Other available statins include Lipitor, Pravachol, and Zocor.

Crestor's manufacturer is also reminding doctors that they should consider using lower starting doses of Crestor in some individuals. AstraZeneca today revised the package insert to re-emphasize these recommendations.

3 Groups of Patients More at Risk

Data show that certain people may have higher drug levels and therefore be at greater risk for muscle injury due to Crestor. The drug's new label recommends that those at higher risk start with a dose of only 5 mg. The higher-risk groups include:

- * **Asian-Americans**
- * People taking the immune suppressing drug cyclosporine, such as organ transplant patients
- * Patients with severe kidney failure

Kidney failure of various types has also been reported in patients treated with Crestor, as well as other statins.

However, the FDA says it's difficult to establish the exact association between kidney failure and statins. People who often need statins to lower their cholesterol include patients with diabetes, high blood pressure, heart disease, and heart failure. These same people are already at a higher risk of developing kidney failure.

Therefore, the FDA says it cannot confirm that recommended doses of statins, including Crestor, can cause or worsen kidney failure. Overall, the FDA says the potential benefits of Crestor and other statin drugs when used as recommended outweigh their potential risks.

Statins provide an important treatment option for millions of Americans at risk of heart disease, it says.

SOURCE: News release, FDA.

<http://www.pharmalive.com/News/index.cfm?articleid=217585&categoryid=56>

FDA MedWatch - FDA Public Health Advisory issued for Crestor (rosuvastatin calcium)

MedWatch - The FDA Safety Information and Adverse Event Reporting Program

ROCKVILLE, Md., March 2, 2005--FDA issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling. The revisions include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information.

Read the complete MedWatch 2005 Safety Summary below. The revised label is attached.

FDA Public Health Advisory on Crestor (rosuvastatin)

Astra-Zeneca Pharmaceuticals today released a revised package insert for Crestor (rosuvastatin) (link to FDA approved labeling). The changes to the label include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy/rhabdomyolysis), especially at the highest approved dose of 40 mg. At this time, the FDA is also making statements about the muscle and kidney safety of Crestor based on extensive review of available information.

Background

Crestor, a member of a class of cholesterol-lowering drugs commonly referred to as "statins", was approved in the U.S. in August 2003, based on review of an extensive clinical database involving approximately 12,000 patients. These data supported the safety and efficacy of Crestor for use in lowering serum cholesterol, but also showed that Crestor, like all statins, rarely could cause serious muscle damage (myopathy and rhabdomyolysis). In the approved labeling, the FDA identified in the WARNINGS section of the product label those patients in whom more careful monitoring was warranted when prescribed Crestor. In a section titled: "Myopathy/Rhabdomyolysis", the label states that patients who are of advanced age (> 65 years), have hypothyroidism, and/or renal insufficiency should be considered to have a greater risk for developing myopathy while receiving a statin. Physicians are warned to prescribe Crestor with caution in these patients, particularly at higher doses, as the risk of myopathy increases with higher drug levels.

Based on these concerns, from the time of original approval, the FDA required Astra-Zeneca to make available in the U.S. a 5-mg dose that could be used in patients requiring less aggressive cholesterol-lowering or who were taking concurrent cyclosporine. The maximum recommended dose in the FDA-approved label is limited to 10 mg daily in patients with severe renal impairment or who are also taking gemfibrozil.

Description of current changes to the Crestor label

In a pharmacokinetic study involving a diverse population of Asians residing in the United States, rosuvastatin drug levels were found to be elevated approximately 2-fold compared with a Caucasian control group. As a result of these findings, the "Dosage and Administration" section of the label now states that the 5 mg dose of Crestor should be considered as the start dose for Asian patients and any increase in dose should take into consideration the increased drug exposure in this patient population. Results of this pharmacokinetic study are further discussed under the "Clinical Pharmacology" and "Precautions" section of labeling.

The "Warnings" and "Dosage and Administration" sections of the label have been revised to more strongly emphasize the risks of myopathy, particularly at the highest approved dose of 40 mg. In order to minimize risks of myopathy and rhabdomyolysis (the most severe form of statin muscle injury), the revised label now explicitly states that the 5 mg dose is available as a start dose for those individuals who do not require aggressive cholesterol reductions or who have predisposing factors for myopathy. This includes patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency. It also emphasizes that the 40 mg dose is not an appropriate start dose and should be reserved only for those patients who have not achieved their cholesterol goals with the 20 mg dose. This information is included in a bolded paragraph under the "Dosage and Administration" section that also reminds prescribers who switch patients from other statins to initiate therapy only with approved doses of Crestor and titrate according to the patient's individualized goal of therapy. Healthcare professionals are reminded of the following key safety messages from the Crestor label:

Start doses and maintenance doses of drug should be based on individual cholesterol goals and apparent risks for side-effects

All patients should be informed that statins can cause muscle injury, which in rare, severe cases, can cause kidney damage and organ failure that are potentially life-threatening

Patients should be told to promptly report to their healthcare provider signs or symptoms of muscle pain and weakness, malaise, fever, dark urine, nausea or vomiting

Review of Crestor muscle and kidney safety

Concerns have been raised about the possible increased muscle toxicity of Crestor compared to other statins on the market and about possible adverse effects on the kidney. The FDA has conducted an extensive review of Crestor data from pre-marketing and post-marketing clinical trials as well as adverse event reports submitted to the agency.

Muscle Crestor, like all statins, has been associated with a low incidence of rhabdomyolysis (severe muscle damage). Data available to date from controlled trials, as well as post-marketing safety information, indicate that the risk of serious muscle damage is similar with Crestor compared to other marketed statins. As with all statins, some individuals taking Crestor will experience muscle side effects, most commonly mild aches and very rarely severe muscle damage. Like all drugs in this class, risks of muscle injury can be minimized by adhering to labeled warnings and precautions, carefully following dosing instructions, and instructing patients to be aware of and to report possible side effects to the physician. Finally, like all statins, Crestor should be prescribed at the lowest dose that achieves the goals of therapy (e.g., target LDL-C level).

Kidney Various forms of kidney failure have been reported in patients taking Crestor, as well as with other statins. Renal failure due to other factors is known to occur at a higher rate in patients who are candidates for statin therapy (e.g., patients with diabetes, hypertension, atherosclerosis, heart failure). No consistent pattern of clinical presentation or of renal injury (i.e., pathology) is evident among the cases of renal failure reported to date that clearly indicate causation by Crestor or other statins.

Mild, transient proteinuria (or protein in the urine, usually from the tubules), with and without microscopic hematuria (minute amounts of blood in the urine), occurred with Crestor, as it has with other statins, in Crestor's pre-approval trials. The frequency of occurrence of proteinuria appeared dose-related. In clinical trials with doses from 5 to 40 mg daily, this effect was not associated with renal impairment or renal failure (i.e., damage to the kidneys). It is recommended, nevertheless, that a dose reduction and an investigation into other potential causes be considered if a patient on Crestor develops unexplained, persistent proteinuria.

Ongoing controlled clinical trials of Crestor and other statins, epidemiologic studies of the safety and side effects of Crestor, and ongoing pharmacovigilance by FDA will continue to provide information on the balance of risks and benefits of Crestor and other members of this important class of drugs. This information will be made available and, as appropriate, applied to drug labeling in a timely fashion.

Contacting MedWatch

U.S. Food and Drug Administration
MedWatch Office, 5600 Fishers Lane, HFD-410
Rockville, MD 20857
Fax: 301-827-7241