"The Pink Sheet" DAILY

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

Crestor May Be Safer Than Other Statins, FDA Tells Public Citizen

March 14, 2005

Number 004

AstraZeneca's ***Crestor*** (rosuvastatin) may be safer than other statins that have similar LDL-lowering efficacy, FDA said in rejecting Public Citizen's petition to withdraw Crestor.

"For any degree of LDL lowering, rosuvastatin is as safe, and may well be safer than, any other marketed statin with regard to muscle toxicity, particularly if rosuvastatin's nonsusceptibility to CYP 3A4-based drug interactions is considered," FDA said in its March 11 response to Public Citizen.

In March 2004, Public Citizen requested FDA pull Crestor off the market due to safety concerns, including kidney damage and rhabdomyolysis ("The Pink Sheet" DAILY, March 4, 2004).

Public Citizen maintains that Crestor's safety profile is similar to that of Bayer's ***Baycol*** (cerivastatin), which was withdrawn in 2001 due to safety concerns.

FDA disagreed, stating that for both the 0.4 mg and 0.8 mg doses of Baycol, "the observed rates of myopathy exceeded those with **all** marketed doses of **all** marketed statins."

"Moreover, the labeled LDL-lowering effects of cerivastatin 0.4 mg and 0.8 mg are inferior to all marketed doses of rosuvastatin," the agency said.

"By contrast, the observed absolute rates of marked [creatine kinase] elevations/myopathy in the extensive rosuvastatin trials program (for all marketed doses) were not different from those observed with other statins," FDA said.

Two cases of myopathy/rhabdomyolysis were observed in the rosuvastatin population (or 0.3 cases per 100,000 prescriptions) over a six-month interval post-approval, FDA noted.

By comparison, six-month post-approval reports show one case of myopathy/rhabdomyolysis for all doses of Pfizer's ***Lipitor*** (0.06 cases per 100,000 prescriptions), five cases for 0.4 mg

Baycol (two cases per 100,000 prescriptions) and 25 cases for 0. 8 mg Baycol (25 cases per 100,000 prescriptions).

A myopathy/rhabdomyolysis event rate of 0.18 per 100,000 prescriptions was observed overall in the class of statins using data from six-month post-approval intervals.

"One cannot conclude on the basis of these data that there is a greater risk of muscle toxicity for rosuvastatin given the very small number of cases contributing to these reporting rates," FDA said.

There appears to be a dose-related increase in frequency of proteinuria (renal toxicity) associated with Crestor, suggesting a drug effect, FDA said.

However, the agency added, risk of proteinuria is likely a class effect related to the renal tubular protein uptake.

There is evidence to "support a class pharmacological effect of statins on proximal tubular protein reabsorption," FDA said.

Clinical trial data, "taken at face value, lead to a conclusion that at doses of 40 mg and lower, the rate of proteinuria with rosuvastatin was within the range observed with several other statins and, notably, placebo," FDA said.

However, data on Crestor use at 80 mg "suggest an apparent difference with other treatment groups." Over 15% of patients receiving 80 mg Crestor developed proteinuria compared to less than 5% of those receiving other statins or other doses of rosuvastatin.

AstraZeneca halted development of the 80 mg rosuvastatin dose following reports of rhabdomyolysis and renal impairment.

In conclusion, FDA assessed that rosuvastatin's muscle and renal toxicity profiles do not warrant the withdrawal of Crestor.

"Crestor does not pose a risk of muscle toxicity greater than that of other approved statins. With respect to renal toxicity, there is no convincing evidence that Crestor poses a risk of serious renal injury."

"However, to help ensure the safe and effective use of Crestor, AstraZeneca has revised the labeling to address certain concerns regarding dose-related risks, proper dosing, and other matters related to information from adverse event reporting and *Phase IV* studies."

AstraZeneca received approval March 2 for a labeling revision that emphasizes the rhabdomyolysis risk associated with Crestor, particularly at the 40 mg dose. Labeling now states 40 mg is not an approved starting dose, and recommends that most Crestor patients start at 5 mg ("The Pink Sheet" DAILY, March 2, 2005).

– *Lee Kalowski*

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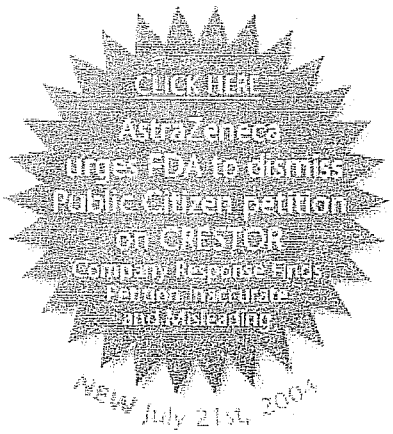

Get the facts

Recently, there has been a great deal of misinformation about the safety of the statin class of cholesterol-lowering medications and, specifically, CRESTOR® (rosuvastatin calcium). Make sure you have *all* the facts.

What you should know

- The safety of CRESTOR was evaluated in clinical trials with over 10,000 patients prior to FDA approval — more than any other statin. Learn more about CRESTOR safety
- CRESTOR has been approved in over 60 countries around the world
- More than 5 million prescriptions for CRESTOR have been written by doctors worldwide
- CRESTOR is very effective for lowering "bad" cholesterol when combined with a healthy diet. Learn more about how CRESTOR works

What you should do

Make sure you have all the facts. Discuss them with your doctor. Any treatment decisions regarding your health should be made between you and your doctor based on medical fact and your doctor's advice, not on information in the media. If you still have questions that you need answered before you talk with your doctor, and if you can't find the answers here, contact one of the trained health professionals at AstraZeneca who are waiting to take your call. Contact us.

The information on this web site should not take the place of talking with your doctor or health care professional about how to manage and treat your high cholesterol. If you have any questions about your condition, or if you would like more information about CRESTOR or cholesterol, talk to your doctor or pharmacist. Only your doctor can decide if CRESTOR is right for you.

Important information about CRESTOR

CRESTOR is a prescription medication for use in lowering high cholesterol. In clinical studies, it was generally w most common side effects are muscle pain, constipation, weakness, stomach pain and nausea. These are usuall go away. Your doctor will do blood tests before and during treatment with CRESTOR to monitor your liver functi if you are taking any medications, including cyclosporine, warfarin, gemfibrozil or antacids. CRESTOR is not righ including women who are nursing, pregnant, or who may become pregnant, or anyone with liver problems. Une pain and weakness could be a sign of a rare but serious side effect and should be reported to your doctor right a has not been determined to prevent heart disease, heart attacks, or strokes.

Please see full Prescribing Information for CRESTOR.

If you're a US health care professional, please see our health care professional site.

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Side effects

Common side effects of CRESTOR® (rosuvastatin calcium)

Like all medicines, CRESTOR may cause side effects in some people. These side effects are usually mild and tend to go away. The most common side effects are muscle pain, constipation, weakness, stomach pain, and nausea. For a complete list of side effects, see the full Prescribing Information for CRESTOR.

Rhabdomyolysis — a rare but serious side effect of statins

If you develop any unexplained muscle pain, tenderness, or weakness at any time during treatment with CRESTOR (especially if you also have a fever or feel ill), call your doctor right away. This may be a sign of a very rare, serious side effect called rhabdomyolysis, which is associated with all currently available drugs in the statin class, including CRESTOR.

Rhabdomyolysis is a serious condition that involves muscle damage and that affects the kidneys. This condition is known to be a very rare side effect of all currently marketed statins, the class of cholesterol medications that includes CRESTOR.

Although rhabdomyolysis occurs in fewer than 1 in every 10,000 patients taking statins, the people who are at increased risk include those with:

- Advanced age (65 years or older)
- Low thyroid hormone levels (hypothyroidism)
- Kidney disease

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Benefits of long-term statin treatment

Why is long-term statin therapy important?

You can't do anything to change some of the factors that may affect your cholesterol level, such as your age, gender, and family history.

But there are some things you can do to help lower your cholesterol level, such as changing your diet, losing weight, and increasing your level of physical activity. And if that's not enough — as is the case for many people with high cholesterol — your doctor may add a cholesterol-lowering medication such as a statin to your other cholesterol-lowering activities.

Statins are widely accepted by the medical community to help those who cannot lower their cholesterol enough through diet alone. All statins, including CRESTOR, only gain FDA approval by showing that, when prescribing guidelines are followed, the benefit outweighs the risk for the general population.

You may not be able to "feel" the benefits of the statin you are taking, but that doesn't mean that it is not working, and it is very important to continue taking it as directed. If you stop taking your medication, your cholesterol levels may rise again. **Do not stop taking your medication without talking to your doctor first.**

Daily reminders to help you remember to take your statin

Remembering to take your medicine is important. Daily reminders are helpful when scheduling your medication doses. When taking medication as directed by your doctor, try the following reminders:

- Take your medicine around daily activities such as setting your alarm clock, brushing your teeth, eating a meal, going to work, or going to bed
- Set your watch or cell phone alarm to go off when it's time to take your medicine
- Place a reminder card in a visible place
- Use a medication box that will hold an entire week's supply of medicine. This way you will know if you missed a dose

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Answers to your questions

Answers to commonly asked questions about CRESTOR® (rosuvastatin calcium)

Q: What is the recent news on CRESTOR all about?

A: In March of 2004, the activist group Public Citizen complained to the US Food and Drug Administration (FDA) that a condition called ***rhabdomyolysis*** was occurring more frequently with CRESTOR than with other statins.

Rhabdomyolysis is a serious condition that involves muscle damage and affects the kidneys. This condition is known to be a very rare side effect of all currently marketed statins, the class of cholesterol medication that includes CRESTOR. In medical circles, "very rare" is defined as occurring in fewer than 1 in 10,000 cases.

As with all other currently marketed statins, the rate of rhabdomyolysis with CRESTOR is very rare — less than 1 in 10,000.

Q: Why are news organizations still covering something that happened months ago?

A: In June, Public Citizen's Sidney Wolf repeated his old charges from March against CRESTOR in the British medical journal *The Lancet*, despite the fact that the FDA has continued to say that CRESTOR is safe when prescribed appropriately.

Q: Someone I know was just switched off of CRESTOR — should I stop taking mine?

A: Your doctor knows your complete medical history and considered your individual needs in deciding that you need medical treatment to lower your cholesterol and that CRESTOR is the appropriate medication for you.

High cholesterol is a chronic condition — with potentially serious health consequences. It cannot be cured, but it can be managed succcessfully; ongoing treatment is necessary to keep it under control. CRESTOR, together with a healthy diet and regular exercise, can be a highly effective combination in cholesterol management. Do not discontinue medications without consulting your doctor.

As with all currently marketed statins, if you develop any unexplained muscle pain, tenderness, or weakness, at any time during treatment (especialy if you also have a fever or feel ill), tell your doctor right away, as they may be signs of serious side effects. Be sure to tell your doctor about other medications you are taking. If you have any concerns about taking CRESTOR, please contact your doctor to discuss them.

Q: How do I know if I'm one of the people at risk for rhabdomyolysis?

A: Your doctor took your complete medical history into consideration when he or she prescribed a statin. However, you should talk to your doctor if you have any concerns about this issue. The people who are at increased risk for this very rare but serious side effect when taking a statin include those with:

- Advanced age (65 years or older)
- Low thyroid hormone levels (hypothyroidism)
- Kidney disease

Q: Is there any truth to the report of a death from rhabdomyolysis while using CRESTOR?

A: There have been no deaths due to rhabdomyolysis in patients taking CRESTOR.

Q: Should I be concerned with the safety profile of CRESTOR?

A: In clinical trials, the percentage of patients who stopped therapy with CRESTOR because of side effects was similar to those who took no drug at all (placebo).

The highest priority of AstraZeneca is patient safety. As with all medicines, AstraZeneca carefully monitors adverse events (such as side effects and drug interactions or allergies) reported with CRESTOR. Reports of rhabdomyolysis have been very rare (less than 1 in 10,000 patients). These reports of rhabdomyolysis have occurred with a frequency similar to that occuring with other currently marketed statins.

Q: Is it still safe for me to take CRESTOR?

A: If your doctor has decided that CRESTOR is right for you, he or she has weighed the risks associated with high cholesterol against the potential for side effects associated with all statins.

It is important to remain on your medication and to discuss any concerns you have with your doctor. When taking any statin, if you develop any unexplained muscle pain, tenderness, or weakness at any time during treatment (especially if you also have a fever or feel ill), tell your doctor right away, as they may be signs of a serious side effect.

Q: Is this a similar situation to what happened with Baycol® (cerivastatin), the cholesterol drug that was withdrawn from the market?

A: No. Baycol was associated with a high number of deaths due to rhabdomyolysis (more than 30). For this reason, the drug was withdrawn from the market. In contrast, there are no reported cases of death due to rhabdomyolysis with CRESTOR in the nearly 2 million patients worldwide who have used CRESTOR since launch.

BAYCOL is a registered trademark of Bayer Corporation.

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A letter from AstraZeneca

July 2004

Dear Valued Patient,

In recent days, the safety of AstraZeneca's cholesterol-lowering medication CRESTOR® (rosuvastatin calcium) has been the subject of considerable media interest and, frankly, misleading and sometimes alarmist reporting. When such misleading reports unnecessarily alarm those who have come to trust and depend on us over the years, we feel obliged to set the record straight.

In a letter to a British medical journal last week, the activist group Public Citizen repeated claims it had made in March 2004 when it petitioned the US Food and Drug Administration (FDA) about CRESTOR. The group claimed that a condition called rhabdomyolysis was occurring more frequently with CRESTOR than with other drugs in the class of cholesterol-lowering medicines known as statins. Rhabdomyolysis is a serious condition that involves muscle damage and affects the kidneys.

You should know:

- Rhabdomyolysis is known to be a very rare side effect of all currently available statins, including CRESTOR.
- As with all other currently available statins, the rate of rhabdomyolysis with CRESTOR is very rare (defined in medical circles as occurring in fewer than 1 in 10,000 patients).
- Millions of people in the US with elevated cholesterol levels are either untreated or not being effectively treated for their high cholesterol levels. We believe CRESTOR is an important option for this population.
- Statins are widely accepted by the medical community to help those who cannot lower their cholesterol enough through diet alone.
- All statins, including CRESTOR, only gain FDA approval by showing that, when prescribing guidelines are followed, the benefit outweighs the risk for the general population.
- The safety and efficacy of CRESTOR were evaluated in clinical trials involving more than 12,000 patients before the FDA gave approval in August 2003—more patients studied than were studied with any other statin prior to approval.
- To date, over 42,000 patients have taken CRESTOR in clinical trials and nearly 2 million patients have now been treated with CRESTOR. CRESTOR has been approved in more than 60 countries.

The number-one priority for AstraZeneca is patient safety. AstraZeneca is fully confident in the efficacy and safety profile of CRESTOR. On behalf of the more than 12,000 AstraZeneca employees in the US who come to work every day committed to improving patient health, we pledge to continue to protect your best interests by providing medications of the highest quality and ensuring that they meet rigorous safety standards.

If you have more questions about CRESTOR:

- Call the trained health care professionals at the AstraZeneca Information Center at 1-888-AZ4-FACT (1-888-294-3228); they are available Monday through Friday, from 8:00 AM to 7:00 PM

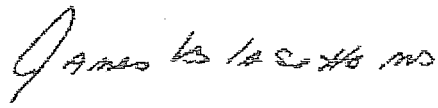
EST.

- Check CRESTOR.com for the latest information about CRESTOR.
- The information that we provide to you cannot take the place of talking with your doctor or health care professional about CRESTOR and how to manage and treat your high cholesterol. Talk to your doctor—only he or she can decide if CRESTOR is right for you.

Please read the important information about CRESTOR below.

AstraZeneca sincerely hopes that this message has helped with any concerns you may have had about CRESTOR.

Sincerely,



James Blasetto, MD, MPH
Executive Director, Strategic
Development

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Comparison of Effectiveness of *Rosuvastatin* Versus *Atorvastatin* on the Achievement of Combined C-Reactive Protein (<2 mg/L) and Low-Density Lipoprotein Cholesterol (<70 mg/dl) Targets in Patients With Type 2 Diabetes Mellitus (from the ANDROMEDA Study)

D. John Betteridge, MD, PhD[a,b,*], J. Martin Gibson, BSc, MD, PhD[c], and Philip T. Sager, MD[d]

Decreasing C-reactive protein (CRP) in addition to decreasing low-density lipoprotein (LDL) cholesterol may further decrease coronary heart disease risk. The effects of rosuvastatin compared with atorvastatin in achieving a combined target of LDL cholesterol <70 mg/dl and CRP <2 mg/L in 509 patients with type 2 diabetes mellitus was evaluated. CRP decreased significantly versus baseline in both treatment groups. Significantly more patients treated with rosuvastatin achieved the combined end point of LDL cholesterol <70 mg/dl and CRP <2 mg/L compared with atorvastatin by the end of the study period (58% vs 37%; p <0.001 vs atorvastatin). In conclusion, CRP was effectively decreased in patients with type 2 diabetes receiving rosuvastatin or atorvastatin, whereas rosuvastatin decreased LDL cholesterol significantly more than atorvastatin. (Am J Cardiol 2007;100:1245–1248)

Guidelines for the prevention of coronary heart disease (CHD) endorse the use of statins to achieve a low-density lipoprotein (LDL) cholesterol goal of <100 mg/dl in patients with type 2 diabetes.[1] Decreasing the threshold to <70 mg/dl may have additional benefits.[2] However, the benefits of statin therapy on CHD prevention may extend beyond LDL cholesterol reduction. Statins showed a variety of additional effects that may contribute to their protective vascular benefit, including anti-inflammatory activities.[3] The inflammatory marker C-reactive protein (CRP) has been closely linked with CHD,[4] and its levels significantly increased in patients with type 2 diabetes.[5] Decreasing CRP to <2 mg/L with statin therapy was associated with decreased risk of CHD events in patients with acute coronary syndromes regardless of LDL cholesterol level achieved.[6] Achievement of LDL cholesterol <70 mg/dl combined with CRP <2 mg/L correlated with improved outcomes after myocardial infarction[6] and may therefore improve CHD risk reduction in high-risk patients. We sought to examine the ability of rosuvastatin and atorvastatin to achieve the goals of LDL cholesterol <70 mg/dl and CRP <2 mg/L in patients with type 2 diabetes.

Methods and Results

We examined the effect of rosuvastatin in comparison to atorvastatin on LDL cholesterol and CRP in 509 men and women (age ≥18 years) with type 2 diabetes and triglycerides ≤532 mg/dl during the A raNdomized, Double-blind, double-dummy, multicenter, phase IIIb parallel-group study to compare the efficacy and safety of Rosuvastatin (10 mg and 20 mg) and atOrvastatin (10 Mg and 20 mg) in patiEnts with type 2 DiAbetes mellitus (ANDROMEDA).[7] Type 2 diabetes was defined as fasting blood glucose ≥125.0 mg/dl on ≥2 occasions (or on 1 occasion with symptoms of hyperglycemia). Patients presenting with uncontrolled diabetes (glycated hemoglobin [hemoglobin A_{1c}] >9%), history of cardiovascular disease, or familial hypercholesterolemia were excluded. Study participants were required to

Table 1
Baseline characteristics (intention-to-treat population)

Characteristic	Rosuvastatin (n = 248)	Atorvastatin (n = 246)
Age (yrs)	61 ± 11	62 ± 11
Men	57%	65%
Caucasian	97%	98%
Body mass index (kg/m^2)	30	31
Antidiabetic medication	79%	82%
Glycated hemoglobin	6.9 ± 0.9%	7.0 ± 0.9%
Insulin resistance ratio	39 ± 41	43 ± 46
Median CRP (mg/L)	2.1 (1.0–4.0)	2.1 (0.9–3.7)
LDL cholesterol (mg/dl)	131 ± 32	131 ± 36
HDL cholesterol (mg/dl)	46 ± 14	46 ± 12
Total cholesterol (mg/dl)	213 ± 38	213 ± 41
Median triglycerides (mg/dl)	169.2 (113.9–236.1)	164.4 (123.2–232.1)
Non-HDL cholesterol (mg/dl)	167 ± 37	168 ± 40
Apolipoprotein A-I (mg/dl)	124 ± 22	122 ± 20
Apolipoprotein A-II (mg/dl)	33 ± 6	32 ± 5
Apolipoprotein B (mg/dl)	109 ± 25	108 ± 27

Values expressed as mean ± SD or median (interquartile range).

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