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Quick Pulse

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THE SAFETY OF ASTRAZENECA'S CRESTOR

On Thursday, March 4, 2004, Public Citizen Health Research Group, a consumer watchdog organization, filed a petition with the FDA asking the agency to remove AstraZeneca's Crestor (rosuvastatin) from the market, charging that there have been post-marketing cases of life-threatening rhabdomyolysis and damage and kidney failure or damage **at even the lowest approved doses**. To try to determine the likely effect of this action on prescribing practices, 12 cardiologists and primary care physicians (PCPs) were interviewed.

- Doctors had not heard about the Public Citizen petition asking the FDA to withdraw Crestor from the market, but all were very concerned about this news. Doctors who read the petition found it credible and said it raised significant questions that the FDA must now address.
- Some cardiologists and family practice doctors may stop putting new patients on Crestor, and some are considering switching existing patients. In addition, doctors who have not yet started using Crestor may decide not to start.
- The FDA has 180 days to respond to this petition, but it sometimes takes longer than that to reply. The immediate impact of the petition is likely to depend on press coverage, and it is too early to gauge that.

Public Citizen (www.citizen.org) opposed FDA approval of Crestor at the FDA Advisory Committee meeting in July 2003. At that time, Dr. Sidney Wolfe, Director of Public Citizen, pointed out Crestor was the only statin to show the following prior to approval:

- Two cases of kidney failure and one case of kidney insufficiency occurred in the Crestor clinical trials.
- These patients had also experienced both protein and blood in the urine.
- There were other patients who had blood and/or protein in their urine but who had not suffered from kidney failure.
- Seven cases of rhabdomyolysis at 80 mg (a dose which was never approved by the FDA).

The Public Citizen petition was based on post-marketing data obtained from Canada, the U.K., and the U.S. (through a Freedom of Information Act request to the FDA). The petition cited:

- Nine cases of kidney failure or kidney damage, including three in the U.S.
  - Four patients had acute kidney failure at 10-40 mg. One of these was a 63-year-old American man who developed acute renal failure after using Crestor 10 mg/day.
  - Five patients had kidney damage at 10-40 mg.

- Seven cases of rhabdomyolysis, including two in the U.S. One patient was taking 10 mg, two 20 mg, one 20-40 mg, two 40 mg, and one 80 mg.
- A 39-year-old American woman on 20 mg/day Crestor who developed both renal insufficiency failure and rhabdomyolysis and then died.
- Another American patient who developed renal insufficiency and renal tubular necrosis after using 10 mg/day Crestor for two weeks.

In the petition, Public Citizen, which opposed the FDA approval in the first place, also noted the decision by WellPoint/Blue Cross, Group Health Cooperative of Puget Sound (GHCPS), and the Swedish government not to reimburse patients for the drug, saying that this underscores the concerns already raised and strengthens the case for banning the drug. The petition noted:

- **WellPoint** decided not to reimburse for Crestor because of the experience with Baycol (Bayer, cerivastatin) and a general "level of nervousness" over the drug.
- **GHCPS** decided not to reimburse for Crestor because of a lack of any advantage (in terms of cost, safety, or efficacy) over other statins on its formulary, lack of safety data beyond the one-year duration of the clinical trials, the recall of Baycol, and "some concern about questions of safety based on evidence from the clinical trials."
- **Swedish officials** recommended against use of Crestor because it "did not meet the criteria of documented safety and cost effectiveness."

In an interview, Dr. Wolfe pointed out that the problem with Crestor is likely to be even worse than post-marketing surveillance indicates due to underreporting. He also thinks that it is unusual to see this many cases of rhabdomyolysis and kidney failure so early after the drug's launch, saying, "The average amount of time for these cases to show up is half a year, so there is no comfort at all in the fact that the number is what it is…This number of cases in such a short time is extremely worrisome…I think this drug is in serious trouble…It is just a matter of time before there are more cases…And the problems are occurring at the lower doses."

The FDA is supposed to respond to citizen petitions within 180 days. Dr. Wolfe said, "Sometimes they do, and sometimes they don't…We do not very often or lightly ask the FDA to ban drugs…We've done this no more than 25 times in 30 years…but we did it with Rezulin (Warner Lambert, troglitazone), Redux (American Home Products, dexfenfluramine), and Ephedra."

One of the key things that doctors want to know to assess the seriousness of Public Citizen's charges is the denominator – what is the incidence, not just the total number of cases. A Washington DC cardiologist said, "It's very tough to know whether this is a significant problem or not if **you don't know the denominator**, and that is key. But it does raise the issue as to post-marketing surveillance and what kind of mechanism do we have in place to make sure these events get reported and not underreported because reporting is voluntary…We need to know the denominator…We'll have to see how this blossoms, and from a scientific standpoint and – the two things we need to know are: (1) what percent of patients this happens to and (2) whether we can identify any risk factors." A New England cardiologist said, "I would be leery of data such as this. It needs to be placed in context – the denominator, how many total patients have received the drug, etc." A Pennsylvania cardiologist said, "Every drug has some side effects. What you really need to know is what the incidence is, and whether it is higher than any other drug. So, it is important to know what the denominator is."

Other comments by cardiologists include:

- *Texas:* "I would like to know more before deciding on its import. **This is interesting and clearly newsworthy**."

- *Massachusetts:* "I don't prescribe Crestor because I feel that the safety isn't as well established as the other statins, and I personally resent the super-aggressive marketing by AstraZeneca. I am not surprised that complications are noted…I don't have major problems with the petition or the press release. Keep in mind, many drugs are given a class effect even if studies don't prove their efficacy...**It is concerning that at this low dose rhabdo is seen**."

- *Texas #2:* "**I've not prescribed this drug yet, and based on this information, I'll be hesitant to do so**."

- *Washington DC:* "This warrants a very high level of vigilance and concomitant effort by the FDA to get their arms around this and release the science…Crestor isn't the only statin with rhabdo, but it was the only one that had a problem before the FDA approved it…The question is whether rhabdo occurs more often with Crestor than with other statins…**The FDA should make some kind of response to this**, probably tomorrow…I'm going to watch my computer and see what the FDA has to say…After this, **I will wait to prescribe Crestor to new patients until I hear some more news, and I have to think about what I'll do with existing Crestor patients**."

- *New York:* "The critical trials of the drug showed some proteinurea – but no renal failure that I'm aware of – so the issue always is that when you have a lot of sick, high-risk people – many of whom have diabetes – some are going to get kidney failure no matter what. Could I believe Crestor is associated with more kidney problems? Yes, I could believe it, but it might or might not be true. **I basically don't use Crestor for new patients if they can use something else**…The 40 mg dose of Crestor does things other statins don't, and it has a role, the other doses don't and I don't use them. **I would still try patients who are refractory to everything else on Crestor**…Tens of thousands of patients have been treated with Crestor, and there's no individual practitioner who will have seen any of the renal failure, so it is

hard to pin it on the drug – even though it may be true…If it turns out to be true, people ought to be aware of it, practice good medicine, and never use a new drug."

➢ *Pennsylvania:* "This class of drugs is very effective in lowering cholesterol, and many of the drugs in the class have been proven to reduce morbidity and mortality. Crestor…probably can reduce the level of cholesterol more than the other drugs – not that the other drugs aren't good – so its advantage is that it's a very powerful statin to lower cholesterol. The problem is it hasn't been studied as extensively as the others…**My reaction to the data is that it's an eye opener, and it raises my interest level. I definitely want to know more about it, but my gut feeling is that the number of patients who have a side effect is very low and is probably similar to the other statins.** Right now, **if someone is on Crestor and doing well, I won't change anything.** To be honest, I haven't put that many people on Crestor because the other statins are very good and very well-known and well-studied. And with the Baycol fiasco, I didn't see that there was a great need to use a brand new drug…Most physicians are very scientific, and it is important not to be emotional about new information, to evaluate it very carefully. Is this the expected number of patients that would have a side effect or more than expected?"

Primary care doctors have been cautious about starting patients on Crestor:

➢ *Wisconsin:* "I don't prescribe Crestor. None of our formularies cover it."

➢ *Virginia:* "This is the first I've heard of such problems with Crestor. I haven't had any problems in my office. I won't change my prescribing practice unless I see data that makes me believe the product is unsafe or doesn't work."

➢ *Illinois:* "I haven't prescribed Crestor yet myself, but many of the physicians in my city have. I'm not surprised to find that there have been adverse reactions, since this happens with every new drug on the market. In the past, Baycol was taken off the market for a similar problem. It should be mentioned, however, that any of the drugs in this HMG Co-A reductase inhibitor category can have the side effect of rhabdomyolysis. I'm not sure what the actual incidence is with Crestor…It is one thing if seven cases are reported out of a thousand and quite another if seven cases are reported out of 10 million…I will say that **this type of notoriety will probably stop physicians from prescribing this medication just because of the liability problems**. If there is a public outcry against a medication and a physician orders it anyway and there is a side effect, the physician has no defense."

➢ *Kansas:* "We have 50 patients on Crestor and have not seen any rhabdo or renal problems. As a matter of fact, **I take Crestor and have not seen any lab abnormalities or experienced any symptoms**. Further evaluation needs to be done to make certain that the actual cases reported were not due to the combination of Crestor with niacin or Lopid (Pfizer, gemfibrozil) which are relative contraindications and increase the risk of rhabdo."

➢ *Another doctor:* "I've been in practice 26 years, and during that time there have been many new medications removed from the market within the first year or two. I never prescribe a new drug until 1-2 million scripts have been written in the U.S. and a safety record in the general population has been established. So, **I have not yet prescribed Crestor, and I have been concerned about the renal issues based on early reports**. We'll have to see what happens."

What if Crestor is withdrawn?

A few sources were asked who would benefit if Crestor is withdrawn from the market. A cardiologist responded, "Lipitor (Pfizer, atorvastatin) would benefit – that's why I asked if Pfizer wrote the petition – but the drug most likely to benefit is Zetia (Schering Plough, ezitimibe) because it's not a statin. The argument has been that you should use this instead of a high dose statin because you won't get as many of the 'statin side effects.'" Another cardiologist said, "Crestor probably took a little of Lipitor's business, and now the new prescriptions may swing back toward Lipitor."

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