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Quick Pulse

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THE FUTURE OF ASTRAZENECA'S CRESTOR

The FDA still has not responded to a consumer watchdog organization's petition in March 2004, asking the FDA to remove AstraZeneca's Crestor (rosuvastatin) from the market. The FDA is supposed to respond to petition like this within six months, in this case by September 3, 2004, but there is no penalty for taking longer. Predicting what the FDA will do in this case is difficult, but the issue gained new visibility recently when an FDA official told a congressional committee that he had safety concerns about Crestor.

Public Citizen Health Research Group warned about safety issues with Crestor even before it was approved, and they have continued to issue warnings. On **November 18, 2004**, Dr. David Graham, Associate Director for Science in the FDA's Office of Drug Safety, also raised questions about the safety of Crestor during his testimony before a Senate Finance Committee hearing on the handling of the withdrawal of Merck's Cox-2 inhibitor, Vioxx (rofecoxib).

The concerns with Crestor are rhabdomyolysis, renal failure, and renal insufficiency – proteinuria and hematuria. Those issues first came up just two days before the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting on Crestor in **July 2003**. Dr. Sidney Wolfe, Director of Public Citizen, argued against approval, telling the panel that Crestor was the only statin to show the following side effects prior to approval:

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

AstraZeneca claimed that the proteinuria is reversible when Crestor is stopped, but the FDA had several unanswered questions about the renal findings, suggesting there was internal debate about the safety of Crestor.

Among the key points made at the panel about proteinuria and hematuria were:

- Proteinuria usually occurs as soon as two weeks, but it can occur later.
- The FDA reported a higher incidence of proteinuria and hematuria than AstraZeneca. The FDA counted any incident of elevated proteinuria/hematuria, but AstraZeneca only counted these problems in patients at 96 weeks, and there was a lower incidence at that time point. Panel members suggested the FDA measuring system was better.

Public Citizen's Analysis of Renal Failure/Renal Insufficiency in Statins

Statin	Renal failure cases	Renal insufficiency cases	# of prescriptions filled	Rate per million prescriptions of renal failure/insufficiency	Rhabdomyolysis	Rate per million prescriptions of rhabdomyolysis
AstraZeneca's Crestor	18 cases	11 cases	4.5 million	6.4	65 cases	14.4
Other statins: Pfizer's Lipitor, Novartis's Lescol, Bristol-Myers Squibb's Pravachol Merck's Mevacor Other lovastatins	27 cases		316 million	0.085	N/A	N/A
Merck's Zocor	N/A	N/A	N/A	0.26	N/A	N/A
Bayer's Baycol	---	---	2.8 million	---	42 cases	15

- AstraZeneca admitted there might be a proteinuria signal at 40 mg, but officials claimed the proteinuria was tubular, similar in frequency to other statins at ≤ 40 mg, did not lead to excessive renal complications except at 80 mg, and was always reversible. An official said, "We are seeing a signal potentially at the 40 mg dose at the end of the day, is the proteinuria causing any detrimental effect in renal function? We just are not seeing that."

An FDA official told the panel, "There is no question the 80 mg dose raises serious safety questions in terms of myopathy, proteinuria, hematuria, rhabdomyolysis, CK elevation, ALT elevation, etc. However, CK elevation and myopathy at 40 mg and lower is similar to other statins." Dr. David Orloff, Director of the FDA's Division of Metabolic and Endocrine Drug Products, said, "There is a small risk of myopathy and a reduced risk of cardiovascular events (with Crestor)... We talk a lot about the risk of myopathy with this class (statins)...but there is absolutely no expectation that we can obviate all myopathy with statins."

However, an FDA reviewer also commented at the panel meeting, "These three cases of renal insufficiency of unknown etiology are of concern...Proteinuria and hematuria could be potentially managed with regular urinalysis screening. However, if they are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects."

The FDA followed the Advisory Committee's recommendation and approved Crestor a month later (**August 2003**). However, the FDA did not require kidney monitoring for patients taking 40 mg, as the Advisory Committee urged.

Then, on **March 4, 2004**, Public Citizen filed a Citizen's Petition, asking the FDA to withdraw Crestor. Over the years, Public Citizen filed about 25 similar Citizen's Petitions challenging drugs, and about six of those drugs were eventually withdrawn from the market. Thus, the Public Citizen petition cannot be easily dismissed.

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) through March 2, 2004. It charged that there have been post-marketing cases of life-threatening rhabdomyolysis and kidney failure or damage **at even the recommended starting dose** (10 mg) of Crestor. 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 **June 2004**, European regulators changed Crestor's label to reflect the increased risk of myopathy associated with high levels of Crestor and to highlight patient populations at higher risk (hypothyroidism, renal insufficiency, Asians, etc.), particularly at the 40 mg dose. The European action came after post-marketing reports of adverse events. U.S. labeling already included the information added to the European label.

September 3rd came and went without any comment from the FDA. Then, on **October 29, 2004**, Public Citizen supplemented its petition to have Crestor banned with new safety information. An updated review by Public Citizen of the FDA's adverse drug reaction database (AERS) through August 26, 2004, suggested the situation with Crestor had

worsened. Dr. Wolfe claimed the rate of acute renal failure or renal insufficiency had risen to 6.4 per million Crestor prescriptions, a rate he described as ~75 times higher than for all other statins combined and 25 times higher than Merck's Zocor (simvastatin).

- 18 cases of acute renal failure.
- 11 cases of renal insufficiency.

On **November 18, 2004**, the FDA's Dr. Graham cited Crestor as one of five drugs currently on the market whose safety concerns him:

- 1. ABBOTT'S Meridia (sibutramine).** This diet drug already has a black box and usage has been declining. Usage will be further negatively impacted by Sanofi-Aventis's Acomplia (rimonabant), when and if that is approved. Thus, it is possible Meridia could be removed after Acomplia arrives, but that is unlikely.
- 2. ROCHE'S Accutane (isotretinoin).** The issue with this acne medicine really is risk management, and the FDA has gotten very aggressive on that point, so the danger may be over for Accutane. However, on November 23, 2004, the FDA announced an expanded risk management monitoring program for Accutane in which the doctors who prescribe it, the pharmacies which prescribe it, and the patients who take it will all have to be recorded and monitored. Dr. Graham was on the February 2004 FDA Advisory Committee that recommended stricter risk management of this and other retinoid medications.
- 3. GLAXOSMITHKLINE'S Serevent (salmeterol xinafoate).** This asthma drug was the most graphically horrible in the news reporting. Dr. Graham said there had been cases of people who died clutching their Serevent inhaler. However, no one is leading a charge to have this drug removed, so it probably would be a long-shot to see anything done other than stronger labeling.
- 4. PFIZER'S Bextra (valdecoxib).** Pfizer has already said it is in discussions with the FDA over a black box warning for this Cox-2 inhibitor, and that may be sufficient to save this drug, allowing Pfizer to convert patients from Bextra to its other Cox-2 inhibitor, Celebrex (celecoxib), with less negative fallout. On the other hand, it is possible that Bextra will become a casualty and get withdrawn altogether.
- 5. ASTRAZENECA'S Crestor.** Since the FDA already is reviewing the safety of Crestor pursuant to a petition for withdrawal by Public Citizen, Crestor and Bextra are the most vulnerable to getting pulled from the market.

The same day, **November 18, 2004**, European regulators (the EMEA) announced that it is now investigating the possibility of recommending a lower – 5 mg – starting dose of Crestor because U.K. officials are worried about the safety of higher doses.

This is what the EMEA memo said:

“The Committee began a Community-wide referral procedure for Crestor (rosuvastatin) 5 mg from AstraZeneca following a referral made by the United Kingdom. The referral was initiated because of public health concerns relating to differing views on whether Crestor 5 mg should be the recommended starting dose for cases with predisposing factors to myopathy only, or for all cases. Crestor is licensed in a number of EU Member States in dosages ranging from 5 to 40 mg. The referral is made under Article 29(2) of the Community Code on medicines for human use.”

On **November 23, 2004**, the Congressional inquiry spread to the House as well as the Senate. The House Commerce Committee announced that it had sent letters to Merck and to the FDA demanding a long list of documents, emails, etc., relating to Vioxx. However, no additional Congressional hearings (either House or Senate) are scheduled yet on Vioxx, Crestor, or any of the other drugs Dr. Graham considers dangerous. A Congressional aide said no decision had been made yet about whether to expand the inquiry to include those five drugs.

The same day (**November 23, 2004**), Dr. Graham and Acting Deputy FDA Commissioner Dr. Janet Woodcock both appeared on ABC's Nightline. Anchor Ted Koppel said the FDA asked to participate after learning Dr. Graham would be on the program, but the two officials did not want to be interviewed together, so they were interviewed one at a time. Dr. Graham maintained his position that the FDA's system “is biased toward approving drugs, almost regardless of the safety risks.” Dr. Woodcock took the position that the Agency's “handling of Vioxx was appropriate.”

ABC's Lisa Stark commented on Nightline, “The FDA painted Graham as a maverick that failed to follow procedure ... (Graham) says the agency needs to pay more attention to drugs already on the market... The FDA has asked for an outside review of how it handles drug safety review... That has not quieted the controversy... Graham names 5 drugs – Bextra, Meridia, Accutane, Serevent, and Crestor. The manufacturers of those drugs insist they are safe.”

On the program, Dr. Woodcock, who is well-respected, circled the FDA wagons and tried to isolate Dr. Graham, but her answers to Ted Koppel's questions may not have advanced the FDA's case. It appeared that she was defending the pharmaceutical industry and not the public.

1. Dr. Woodcock claimed there are no known cases of people hurt by Vioxx.

Koppel: *Even Merck concedes that Vioxx is too dangerous to have on the market right now. How can you continue to argue you responded appropriately?*

Dr. Woodcock: “All drugs have side effects, and some have very rare side effects that are not seen until they are on the market a while. That was the case with Vioxx.”

Koppel: *What about the 100,000 patients with damage (from Vioxx)?*

Dr. Woodcock: “That’s a theoretical model. There isn’t one actual patient in that model to whom we can point.”

Koppel: Have 100,000 people been affected or not?

Dr. Woodcock: “We don’t know the number. The number was generated by a hypothetical model.”

2. Dr. Woodcock said a “drug development expert” wouldn’t agree with Dr. Graham, making it appear that pharmaceutical companies wouldn’t agree with him. This seemed to put her on the side of pharma, and Dr. Graham on the side of the consumer.

3. Dr. Woodcock also defended the FDA’s handling of Vioxx, saying, “We think our handling of Vioxx was appropriate. We dealt with the scientific evidence as we got it. We put it out to the public, and dealt with information as we got it.”

Asked if he is trying to tarnish the reputation of all the doctors and scientists at the FDA, Dr. Graham told Nightline, “I think the FDA reviewers do wonderful jobs. The problem I have is with FDA management and a culture that is averse to consideration of safety, undervalues safety, and overvalues benefits. They do that both pre- and post-approval...I challenge Dr. Woodcock to produce a risk:benefit analysis that showed the benefit exceeded the 500% increased risk (with Vioxx).”

The *Washington Post* reported on **November 24, 2004**, that the Government Accountability Project (GAP), a non-profit whistleblower defense organization, claims FDA officials tried to discredit Dr. Graham with anonymous phone calls to their group. A GAP official told the *Washington Post* that the anonymous callers did not identify themselves, but he was certain they were FDA managers “because of their phone numbers and other identifying information.” According to the *Washington Post*, GAP officials “initially took the callers’ concerns seriously but later came to see the calls as an effort to smear” Dr. Graham. The FDA, in a statement, defended the employees’ right to have called GAP.

State governments also have started to examine the safety of various medications on their own. The effort started as a group effort to shop for better drug prices, but the project also produces safety analyses. Oregon and Washington reportedly used a Vioxx safety analysis to remove Vioxx from their list of preferred Medicaid drugs long before it was withdrawn from the market. According to the Associated Press, Dr. John Santa, medical director of the Drug Effectiveness Review Project, said the project has developed into virtually an

independent office of drug safety, providing information to the states about the drugs it studies. The states then must decide on their own what to do with that information. Reviewing the same data as Dr. Graham, the project found the trial data insufficient for a reliable judgment on the safety of Crestor.

THE OUTLOOK

In this environment, the FDA is between a rock and a hard place in deciding what to do with Crestor. If they pull it in the current environment, it adds fuel to the fire. If they don’t pull it and the situation worsens (e.g., the number of renal failure cases increases), they could have another Vioxx debacle on their hands – and that would be a disaster for the agency and the incoming Commissioner.

Does David Graham have credibility? Yes, even though FDA officials are circling the wagons and trying to marginalize him. He was the lead epidemiologist on Rezulin (Warner Lambert, troglitazone), which was pulled from the market because of liver failure. Dr. Graham warned of Rezulin’s danger from the very beginning. At the Senate Finance hearing, Dr. Graham said that during his tenure at the FDA he had recommended that 12 drugs be withdrawn, and 10 of them have been. The drugs that have been withdrawn since 1997 that Dr. Graham fought to have removed from the market include:

- **JOHNSON & JOHNSON’S Propulsid** (cisapride).
- **WYETH’S Redux** (dexfenfluramine) and **Pondimin** (fenfluramine) -- (then American Home Products)
- **HOECHST MARION ROUSSEL’S Seldane** (terfenadine) – (now Sanofi-Aventis)
- **GLAXOSMITHKLINE’S Raxar** (grepafloxacin).
- **BAYER’S Baycol** (cerivastatin)

Other drugs pulled from the market in which Dr. Graham may have been a warning voice include:

- **GLAXOSMITHKLINE’S Lotronex** (alosetron).
- **WYETH’S Duract** (bromfenac).
- **JOHNSON & JOHNSON/MCNEIL’S Hismanal** (astemizole).
- **ROCHE’S Posicor** (mibefradil).
- **ROXANE LABORATORIES’ Orlaam** (levomethadyl).
- **ORGANON’S Raplon** (rapacuronium).

One of the key concerns at the FDA in the Crestor decision is likely to be whether or not there is a “smoking gun” memo among the FDA internal documents that could come back to haunt the Agency in the future if more problems develop with Crestor. And there may well be internal memos questioning the safety of Crestor. After all, no proteinuria or hematuria had been seen with any other statins, and the drug was taken to an advisory panel even though there were already several marketed statins.

At lower levels of the FDA, there appears to be little worry/discussion/concern over Dr. Graham's claim that five drugs on the market are dangerous. The Agency is tightly managing press inquiries on these topics. However, FDA sources indicate that Dr. Graham does have credibility within the Agency, regardless of any characterization to the contrary by FDA senior officials.

AstraZeneca has continued to advertise Crestor and, if anything, may have stepped up its advertising campaign. On November 23, 2004, the company sent an email to doctors, offering a patient coupon redeemable at the local pharmacy for a 15-day free trial of Crestor 10 mg.

However, personal injury and medical malpractice lawyers have started advertising on television and in other media for Crestor cases as well as Vioxx cases. This appears to indicate the legal situation for Crestor is worsening.

From the Bush administration's standpoint, the Graham/Vioxx flap either hasn't risen to a real level of concern or they believe that by ignoring it, it will go away. Two possible scenarios "handling" the Crestor and Vioxx issues are:

- 1. Bring in a new FDA Commissioner immediately and have him "clean house."** FDA Acting Commissioner Dr. Lester Crawford could be made the scapegoat. This is a reasonable scenario. This also is something Sen. Finance Committee chairman Sen. Chuck Grassley (R-IA) would be likely to accept. However, it does not appear likely. There is no rumor of the White House starting to vet FDA Commissioner candidates, etc. Health and Human Services (HHS) Secretary Tommy Thompson has hinted that he will not stay through Bush's second term, but he has not formally announced he is leaving.
- 2. Let Dr. Crawford continue to take the heat – and twist in the wind – until all the bad news is out that is coming out, and then have a new Commissioner come in and "set a new tone" for the Agency.** This scenario is slightly more likely than the first scenario.

With either scenario, the confirmation hearings for the FDA Commissioner – and for a new HHS Secretary if there is one – will be difficult because Congress will want answers on what happened (whether it is just Vioxx or Vioxx + Crestor). Congress also will want a shake-up of the FDA. It would be easier for a new Secretary and a new FDA Commissioner to "shake things up" and set a new tone if they don't have to do a recall as soon as they take office.

Thus, if there is a recall of Crestor, it is likely to happen before any confirmation hearings – and probably long before the confirmation hearings, which aren't expected until at least February or March 2005. The lame duck Congress is unlikely to get anything done by the end of this year. Congress recessed until December 6, 2004, when it *may* take the intelligence bill back up, but the odds against actually passing

that bill were described as gargantuan. All this means, a Crestor decision (withdrawal ?) is likely to come before the end of 2004 but could occur in January 2005. **Only one thing is certain: The FDA has to make a decision one way or the other.**

