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Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

March 4, 2004

Mark B. McClellan, M.D., Ph.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20854

Dear Commissioner McClellan:

Public Citizen, representing 160,000 consumers nationwide, hereby petitions the U.S. Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market rosuvastatin (Crestor-AstraZeneca) before additional cases of life-threatening rhabdomyolysis and kidney failure/kidney damage occur.

We have obtained new information from the FDA and health agencies in Canada and the U.K. concerning serious post-marketing adverse reactions – including seven cases of life-threatening rhabdomyolysis (muscle destruction) and nine cases of kidney failure or kidney damage – in patients mostly using lower doses of this recently-approved cholesterol-lowering drug, rosuvastatin.¹ We have also become aware of decisions by major U.S. health insurers and by the Swedish government not to reimburse for the drug. This information re-emphasizes the basis for which we strongly urged the FDA not to approve it last year and subsequently advised people not to use the drug once it was approved. The urgency of this petition is heightened by the fact that AstraZeneca is currently launching a major direct-to-consumer advertising campaign to promote the drug.

In opposing the drug's approval at a July 9, 2003 FDA advisory committee meeting, we pointed to two cases of kidney failure and one case of kidney insufficiency in clinical trials prior to approval in which patients had also experienced both protein and blood in the urine. There were also a large number of patients who had blood and/or protein in their urine but had not suffered from kidney failure. In addition to this kidney toxicity, unique among all of the statin drugs, rosuvastatin is the only one of these drugs in which any cases of the life-threatening muscle destruction known as rhabdomyolysis was found to occur prior to approval. Even cerivastatin (Baycol), which was ultimately banned after at least 31 cases of fatal rhabdomyolysis, had not caused a single case of this adverse reaction prior to approval. In contrast, there were seven cases of rhabdomyolysis in patients receiving rosuvastatin before its approval. Although all were receiving a dose (80 milligrams) that was not approved, a small patient getting even the 40 milligram dose might be receiving the same amount of drug per pound of body

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weight and we were concerned that cases would occur at this 40 milligram dose or even lower doses. We stated that it was likely, if not certain, that if it were approved, rosuvastatin would have to be banned because of post-marketing cases of rhabdomyolysis and kidney failure that would inevitably occur.

In the United States, where the drug has only been on the market for a little more than 5 months, a 39-year-old woman, taking only 20 milligrams a day, died of rhabdomyolysis and renal insufficiency. In addition, a 63-year-old man in the U.S. developed acute renal failure using a dose of only 10 milligrams a day and another patient in the U.S. developed renal insufficiency and renal tubular necrosis after using rosuvastatin at a dose of 10 milligrams a day for only 2 weeks. The total number of new cases of adverse reactions after approval in the U.S., Canada and the U.K. combined include:

- 7 patients with rhabdomyolysis (patients using doses of 10, 20, 20, 20-40, 40, 40 and 80 milligrams per day)
- 4 patients with acute kidney failure (patients using 10, 10, 10 and 40 milligrams per day)
- 5 additional patients with kidney damage (patients using 10, 10, 10, 20 and 40 milligrams per day)
- 6 patients with bleeding or abnormal bleeding tests who were also using blood-thinning drugs such as coumadin, known to have an abnormal interaction with rosuvastatin (patients using 10, 10, 10, 10, 20 and unknown milligrams per day)

Two major U.S. insurers, WellPoint/Blue Cross, with 15 million patients insured, and Group Health Cooperative of Puget Sound (GHCPs) with more than 500,000 members have refused to reimburse for Crestor. "We've already been Baycolled," said Dr. Robert Seidman, chief pharmacy officer for the Thousand Oaks, Calif.-based WellPoint. "There is a level of nervousness, and we're being conservative and we're being cautious," Seidman also said.²

Group Health Cooperative of Puget Sound (GHCPs) stated, in its decision not to reimburse for the drug, that "Rosuvastatin offers no advantage over current formulary HMG-CoA reductase inhibitors [other statins] in terms of efficacy, safety, and cost. The effect of rosuvastatin on cardiovascular outcomes has not yet been studied and the safety of rosuvastatin beyond the one-year duration of clinical trials is unknown. Due to the recall of cerivastatin, a statin associated with several cases of rhabdomyolysis, the committee recommends using caution before prescribing statins with limited safety data."³ In addition, a spokesperson from GHCPs expressed some concern about questions of safety based on evidence from the clinical trials.

It is of particular interest that GHCPs has decided to reject from their formulary rosuvastatin because in the past, they similarly rejected other drugs that had come on the market with serious safety questions such as the pain-killer Duract, the high blood

pressure drug Posicor, the diabetes drug Rezulin, and the weight reduction drug Redux, all of which were eventually banned by the FDA.

In Sweden, regional governmental drug advisors recommended against the use of the drug. The committees said in a statement that newer drugs such as Crestor were not recommended because they did not meet the criteria of documented safety and cost effectiveness. The decision was unusual, because the representatives for Sweden's regional governments were unanimous in their decision.⁴

In an editorial in the October 25, 2003 issue of the British medical journal, *The Lancet*, editor Dr. Richard Horton wrote:

"AstraZeneca's tactics in marketing its cholesterol-lowering drug, rosuvastatin, raise disturbing questions about how drugs enter clinical practice and what measures exist to protect patients from inadequately investigated medicines. ...After a damaging delay over safety concerns, rosuvastatin finally won US FDA approval in August and was launched last month, winning a 2% market share after only three weeks. [AstraZeneca CEO] McKillop has pledged to do whatever it takes to persuade doctors to prescribe rosuvastatin, including launching an estimated \$1 billion first-year promotional campaign. "We've got to drive the momentum", he said at a recent investors meeting. "You get one shot at launching a major new product. This is our shot."

Why does the quality of debate about statins matter? First, because safety cannot be assured. Bayer withdrew cerivastatin in August, 2001, after the occurrence of unexpected cases of fatal rhabdomyolysis. The 80 mg dose of rosuvastatin was withdrawn by AstraZeneca because of safety concerns. Some critics are even anxious about the 40 mg dose. The finding of proteinuria [protein in the urine] and microscopic haematuria [blood in the urine] associated with rosuvastatin use are additional worries.... Since there are no reliable data about efficacy [that is, actually decreasing heart attacks and strokes, not merely lowering cholesterol levels] and safety--and AstraZeneca is facing unusually acute commercial pressure to force rosuvastatin into the market--doctors should pause before prescribing this drug. Physicians must tell their patients the truth about rosuvastatin--that, compared with its competitors, rosuvastatin has an inferior evidence base supporting its safe use. AstraZeneca has pushed its marketing machine too hard and too fast. It is time for McKillop to desist from this unprincipled campaign."

At the FDA advisory committee meeting on July 9, 2003 concerning the possible approval of rosuvastatin, I stated:

"In summary, we strongly oppose the approval of rosuvastatin because of its unique renal toxicity. We are also seriously concerned because of the seven cases of rhabdomyolysis that were common enough to have shown up in clinical trials, unlike the

pre-approval studies with all previously approved statins, including cerivastatin. The fact that so few patients on the 20 or 40 mg doses took the drug for a sufficient period of time to have had a chance to develop rhabdomyolysis seems to have imparted a false sense of security about the safety of these doses concerning muscle toxicity... If this drug is approved, it is highly likely it will have to be removed from the market after 'enough' further damage to patients occurs."

The new information from the U.K, Canadian and U.S. governments documenting cases of rhabdomyolysis and kidney damage in people using the using lower (10, 20 and 40 milligram) doses of rosuvastatin confirms these concerns and emphasizes the need for banning this drug.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

ENVIRONMENTAL IMPACT

Nothing requested in this petition will have an impact on the environment.

Sincerely,

Sidney M. Wolfe, MD
Director, Public Citizen's
Health Research Group

¹ FDA data from AERS adverse reaction system, received 3/2/04. Canadian data from Canadian Adverse Drug Reaction Monitoring Program, data through October, 2003. U.K. data from J. Lindfeldt, MD, Medicines and Healthcare Products Regulatory Agency, as of 12/2/03 and Dr. R Suvarna, further details on UK cases, e-mail 2/26/04.

² Delaware News Journal, 10/02/03.

³ Message from Group Health Cooperative Pharmacist Jennifer Hrachovec, 11/18/03.

⁴ Reuters, 10/03/03.



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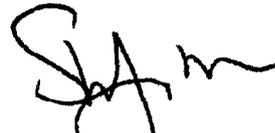
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