

**Memo to the File:**

**NDA #:** 21-366  
**Drug name:** Crestor® (rosuvastatin)  
**Subject:** Review of AERS reports of renal failure in association with Crestor Use in response to Citizen Petition

**Procedures**

Thirty-eight non-duplicated, spontaneous reports involving the use of Crestor which included a diagnosis of renal failure were culled from AERS as of 10-31-04 by ODS. In addition to the review by ODS safety evaluators and the calculation of a reporting rate for renal failure based on the U.S cases, the OND review division undertook an independent review of the cases. The division focused on assessing evidence of potential causation by the drug and considered whether there was compelling evidence of a pathognomonic renal "syndrome" associated with Crestor use. Two experienced medical officers conducted independent reviews of the individual cases. Although the cases were discussed after the fact, no changes in the original reviewer's categorizations were made after each independent review. The cases were grouped as follows:

Group 1: unrelated (Reviewer #1: 2 cases, Reviewer # 2: 3 cases)

Group 2: insufficient information (lack of historical detail, labs, dose, dates, etc.)  
(Reviewer #1: 10 cases, Reviewer #2: 9 cases)

Group 3: confounded by other plausible causes or contributors or potentially related to rhabdomyolysis, thus low probability for primary, direct causation by Crestor (Reviewer #1: 11 cases, Reviewer #2: 19 cases)

Group 4: confounded but history supporting possible direct causation by Crestor  
(Reviewer #1: 15 cases, Reviewer #2: 7 cases)

The difference between the assessments of the two reviewers lies mainly in cases included in Groups 3 and 4. One reviewer (#2) labeled more cases as overly confounded, thus by definition lacking sufficient evidence of direct causation (thus, Group 3). By contrast, the other reviewer (#1), while acknowledging these multiple confounding factors, nevertheless concluded that many of these cases should be classified in Group 4, in most instances because of the temporal sequences of events that supported a judgment that Crestor could have been causative. The numbers in each group are identified by each reviewer for completeness and transparency with regard to process and results. The discussion that follows describes the panoply of confounding factors and of temporal relationships, and examines the cases collectively for evidence of patterns of clinical or pathological presentation. This discussion is not impacted by the specific differences in

the Group 3 and 4 categorizations of individual cases, because confounding factors were identified across the cases included in these groups by both reviewers.

## **Discussion**

### **Group 1**

Among the Group 1 (unrelated) cases were 2 with negative dechallenge and rechallenge. The third case, included by reviewer # 2, was a clear case of contrast-induced acute tubular necrosis (ATN). Reviewer #1 had placed this case in Group 2.

### **Group 2**

We have not included a discussion of cases in Group 2, for the obvious reason that insufficient information was available in the case reports to make any comments regarding diagnosis, presentation, pathology, temporal relatedness to drug use, additional medical history, etc.

### **Group 3**

Among the Group 3 cases, confounding factors that individually or together constituted likely contributing factors or plausible causes included: age, chronic illness (DM, HTN, history of chronic renal failure, ASCVD, CHF, atrial fibrillation, monoclonal gammopathy, hyperuricemia, COPD, biliary tract disease), multiple meds (ACE/ARB, diuretics, allopurinol, NSAID), acute illness (hepatitis, myositis, Stevens Johnson Syndrome, sepsis, hypotension, vomiting, diarrhea, dehydration, post-surgery, pneumonia, s/p renal transplant, warfarin-related renal hemorrhage, small-bowel ileus, and recent open heart surgery). Examples include:

- one case of minimal change nephropathy by biopsy associated with massive proteinuria (12g/day) in a patient with psoriasis which did not respond to dechallenge
- a case of possible rhabdomyolysis in a longstanding diabetic with HTN, CHF, on multiple meds (including diuretics and ARB/ACE) with renal failure preceded by a 3-4 week history of nausea, vomiting, diarrhea, and muscle aches
- an elderly female with a history of hypertension with massive, progressive weight loss, abnormal liver function tests during the course of therapy with Crestor, and a creatinine clearance of 7 mL/minute 5 months after discontinuing Crestor

### **Group 4**

Among the Group 4 cases were several instances where there was an apparent positive dechallenge (i.e., condition improved after discontinuation of Crestor—and often other meds as well), though no rechallenge was documented in any of these cases. Though cases in Group 4 were deemed potentially related by one or both reviewers (cases where Crestor may have had a possible primary causative role), all cases included in Group 4 (regardless of reviewer) were still significantly confounded by pre-existing risk factors for renal failure, including advanced age, DM, HTN, chronic renal failure, history of hyperkalemia prior to Crestor therapy, concomitant meds and acute presentations suggesting other possible causes or contributors (e.g., hepatitis and hyperbilirubinemia in

a patient with history of biliary tract disease; hives, eosinophilia, hypoalbuminemia in an elderly male with DM, HTN; chronic renal failure).

### **Patterns of clinical presentation**

No clear patterns of clinical presentation of renal failure are apparent from these data. Conditions co-occurring with dyslipidemia including advanced age, diabetes, HTN, ASCVD, CHF, and chronic renal insufficiency occur, singly or multiply, in the majority of the cases for which sufficient information is reported. Further, as expected given these co-existing conditions, use of concomitant medications with known renal or pre-renal effects was also reported. Use of diuretics, ACE/ARB, beta blockers, and NSAIDS was reported, singly or multiply, in the majority of cases for which sufficient information was provided.

### **Patterns of pathological presentation**

With regard to patterns of pathological presentation, we note that in 4 cases, a diagnosis of acute tubular necrosis was cited. These cases are summarized briefly in order to illustrate both the confounded nature of the cases and the absence of clinical patterns linking these cases presenting with related pathology (albeit a pathology with a known extensive list of possible causes).

- One case was an elderly female with a history of hypertension on diuretics with unexplained massive, progressive weight loss (>50 lbs), abnormal liver function tests during the course of therapy with Crestor, and a creatinine clearance of 7 mL/minute 5 months after discontinuing Crestor.
- Another was in a 62-year-old male with DM1, CAD, on multiple meds (including lasix) who developed abdominal pain, metabolic acidosis, and ATN 10 days after switching from Lipitor to Crestor. An exploratory lap was negative and renal scan showed enlarged kidneys and increased uptake. Multiple meds were discontinued, including Crestor, and the patient recovered.
- A third case involved a 66 year-old-female with hypothyroidism and hypertension who presented in DKA approximately 7 weeks after starting Crestor 10 mg. She had developed nephrotic syndrome during therapy with Crestor, with workup for other causes negative, which then resolved off Crestor.
- The fourth case included insufficient information beyond the diagnosis of ATN.

We also note that there were three cases of renal failure in association with hepatitis, again without clear clinical similarities.

- A 51 year-old female with no history given on ACE/HCTZ presenting with hepatitis, nausea, vomiting, and creatinine elevation/renal failure 3 months after starting Crestor. Resolved after discontinuation of Crestor.
- 66 year-old-male with history of cholecystectomy in distant past, CAD s/p PTCA, aortic valve replacement, on coumadin, Celebrex, ASA, metoprolol presented with hepatitis, jaundice, and renal failure 3 weeks after starting Crestor. No follow up information given.

- 71 year-old black male with DM, HTN, and CRI on ACE presented with hives, fatigue, weakness, eosinophilia, hepatitis with hyperbilirubinemia. Patient was treated with prednisone, antihistamines and supportive measures and discontinuation of Crestor. Condition resolved.

**Dose clustering**

With regard to dose clustering, the majority of the spontaneous cases of renal failure reported to date in AERS are at the 10 mg dose, which is consistent with the usage pattern for the drug and not necessarily indicative of causation.

**Overall assessment**

There are 38 cases of renal failure in AERS up to a cutoff date of 31 October 2004. The analysis above includes both domestic and foreign reports. There are 2 or 3 (difference by reviewer) in which a role of Crestor in the genesis of the renal failure can, with reasonable confidence, be excluded. Among the 25 or 26 (difference by reviewer) cases where there is sufficient information to conduct a meaningful case review, the vast majority are confounded by concomitant conditions, listed above, and by concomitant medications that suggest at least potential other contributors or causative factors in the presentation of renal failure. However, there are a number of cases in which withdrawal of Crestor, with or without reported withdrawal of other meds, was followed by apparent partial or full resolution of renal failure. In none of these cases was rechallenge reported. Among cases rated as possibly related to Crestor use (Group 4) by one or another of the two reviewers, there were no evident patterns of clinical presentation, save for the preponderance of multiple conditions co-existing with dyslipidemia and themselves constituting risk factors for renal compromise. Likewise, there were no consistent patterns of pathological presentation, with diagnoses including ATN, nephrotic syndrome, and minimal change nephropathy. Across the 4 cases where a diagnosis of ATN was cited, there were no compelling clinical similarities with regard to presentation to permit tentative description of a "Crestor-related renal syndrome."

In sum, the specifics of the cases reported to AERS thus far do not reveal a pattern or patterns of clinical or pathological presentation marking a potential Crestor-associated renal injury syndrome. However, neither do the cases fully dispel concerns of possible renal effect(s) of Crestor that might, in some instances, eventuate in renal insufficiency or failure. At present, given the weight of evidence from pre-clinical data, pre-marketing and post-marketing controlled clinical studies, and spontaneous post-marketing adverse event reports, there is insufficient evidence to conclude a direct renal toxic effect associated with rosuvastatin use. The urine protein laboratory abnormalities noted by the FDA reviewer in the pre-approval database suggest a pharmacologic effect of rosuvastatin, and perhaps the class of statins, on renal tubular protein excretion; however, these laboratory findings are not, alone, evidence of renal toxicity. The currently approved label already describes these renal laboratory abnormalities under the PRECAUTIONS section.