

**ADVISORY COMMITTEE BRIEFING DOCUMENT**

**Pharmacology/Toxicology**

**NDA 21-366**

**Crestor**

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## Nonclinical Findings and Clinical Relevance

Preclinical studies include: toxicology studies in rats, dogs, mice and monkeys with duration of single dose to 12 months, 2-year carcinogenicity studies in mice and rats, genotoxicity studies, reproductive toxicity studies in rats and rabbits, and special toxicology studies. Generally, the toxicology findings are similar to other approved statins. The major target organs were liver, gallbladder (dog, mouse), forestomach (rodents), cornea, lens and retina (dog), kidney, and muscle.

Liver is the major target of rosuvastatin in rats, mice, and dogs. The changes in liver include increases in plasma transaminases, hepatocyte hypertrophy, and single cell necrosis. These findings are consistent with the selective distribution of rosuvastatin in liver. Liver toxicity appeared to be reversible and was also observed in other approved statins. It is considered to be class effect for statins and can be readily monitored during clinical use.

Species	Liver Toxicity: Multiple of human exposure*				
	80 mg	40 mg	20 mg	10 mg	5 mg
Mouse	2	4	11	24	38
Rat	1	2	5	11	17
Dog	7	16	35	78	125

\*: multiples of human exposure at which liver toxicity was observed.

Muscle toxicity was observed in dogs and pregnant rabbits. The toxicity was characterized by blood chemistry change, primarily increase in CPK, and histopathologic change of moderate to severe cardiac or intercostal muscle necrosis in rabbits. Generally, muscle toxicity was observed in animals dead or sacrificed moribund after high level exposure to rosuvastatin.

Species	Muscle Toxicity: Multiple of human exposure*				
	80 mg	40 mg	20 mg	10 mg	5 mg
Rabbit	½	1	3	5	10
Dog	46	99	226	498	1000

\*: multiples of human exposure at which muscle toxicity was observed.

Myopathy/rhabdomyolysis has been demonstrated with rosuvastatin in clinical studies at doses of 80 mg/day. The same effect was also observed sporadically with other approved statins, leading to the withdrawal of cerivastatin. In an *in vitro* study with human skeletal cells, rosuvastatin and other statins were shown to inhibit cholesterol synthesis in a dose-dependent fashion in the absence of cytotoxicity. Rosuvastatin was a significantly less potent inhibitor *in vitro* than cerivastatin, fluvastatin, simvastatin and atorvastatin. Rosuvastatin was also shown to be highly selective to liver. The selectivity for effect in hepatocytes compared to muscle cells was approximately 500-fold for rosuvastatin (IC<sub>50</sub> of 0.1 vs. 91 nM in liver and muscle cells, respectively), much better than atorvastatin, simvastatin and cerivastatin. These data suggest the rosuvastatin is less likely to induce skeletal toxicity in comparison with other statins.

Renal toxicity was seen in rats, dogs, monkeys, and pregnant rabbits. The toxicity was characterized by blood chemistry changes including increases in creatinine and urea nitrogen, and histopathologic change of renal tubular cell degeneration /necrosis. Similar to muscle

toxicity, renal toxicity was only observed in animals dead or sacrificed moribund after high level exposure to rosuvastatin. Similar renal toxicity was also observed in multiple animal species with other approved statins.

Species	Renal Toxicity: Multiple of human exposure*				
	80 mg	40 mg	20 mg	10 mg	5 mg
Rat	39	85	194	427	684
Dog	46	99	226	498	1000
Monkey	2-10	6-21	8-48	18-105	29-167
Rabbit	½	1	3	5	10

\*: multiples of human exposure at which renal toxicity was observed.

A few cases of acute renal failure and marked increased frequency of proteinuria have been seen with rosuvastatin in clinical studies at dose level of 80 mg/day. Similar effect has not been reported in other approved statins. In an *in vitro* study with an opossum kidney (OK) proximal tubular cell line, rosuvastatin and other four statins (simvastatin, fluvastatin, pravastatin, and atorvastatin) were shown to inhibit HMG-CoA reductase and albumin uptake into OK cells in a dose-dependent manner. The IC<sub>50</sub> values for decreases of protein re-absorption were generally 100 times higher than the IC<sub>50</sub> values for the inhibition of HMG-CoA reductase for all four statins tested, indicating significant higher concentration was needed to inhibit protein re-absorption. Compared to other statins, rosuvastatin was a less potent inhibitor of albumin uptake and cholesterol synthesis than fluvastatin, atorvastatin and simvastatin. This inhibiting effect on albumin uptake can be ameliorated by the addition of mevalonate. Based on these results, the Sponsor suggested that the proteinuria observed in the clinic may be due to the inhibition of HMG-CoA reductase in proximal tubular cells.

In general, the results of the *in vitro* studies with OK cells and human skeletal muscle cells support the action consistent with other non-clinical studies. However, the Reviewer thinks that the results from these *in vitro* studies may have been over-interpreted. These studies are valuable to investigate the mechanism of potential toxicity seen in humans, but causal relationship can not be established solely based on these *in vitro* results, because of the general limitations with *in vitro* data, such as the difference between cell lines and living tissue, concentration in cell culture and exposure in humans.

### Additional Nonclinical Findings and Clinical Relevance

Toxicity on gallbladder and biliary duct, including lamina propria mucosa edema, hemorrhage and inflammatory infiltration, were observed in dogs. That was consistent with the excretion route of rosuvastatin. This toxicity was observed in dogs at 6 mg/kg with exposure levels 7, 16, 35, and 78X the human exposure at human doses of 80, 40, 20, and 10 mg/kg, respectively, based on AUC. Gallbladder toxicity was also observed in mice at 250 mg/kg (>10X human exposure at human dose of 80 mg/day), but less severe than in dogs. Gallbladder effects have also been observed with other drugs of this class.

Edema, hemorrhage and partial necrosis in the interstitium of the choroid plexus was observed in one female dog at 90 mg/kg (46X human exposure at human dose of 80 mg/day) that was sacrificed *in extremis* on day 24 of dosing. CNS lesions characterized by

perivascular hemorrhage, edema, mononuclear cell infiltration, fibrinoid degeneration of vessel walls in the choroid plexus of the brain stem, and ciliary body of the eye have been observed with several drugs in this class.

Opacity of cornea and lens were seen in dogs treated for 3 months at 30 mg/kg/day and 1 year at 1 and 6 mg/kg/day. The exposure levels at 1 mg/kg in the 1 year study were comparable to human exposure at 80 mg/day. Cataract was also observed in animals in other approved statins. The clinical association between statin treatment and cataract has not been clearly identified. Current clinical studies have not found direct association between statin treatment and cataracts.

Forestomach toxicity (mucosal hyperkeratosis) was observed in rats at exposure levels 6, 12, 27, and 60X the human exposure at human doses of 80, 40, 20, and 10 mg/kg, respectively, based on AUC. This anatomical feature is unique to rodents and is therefore not considered clinically relevant.

Toxicity on endocrine organs were noted in testis (decrease in spermatogenic epithelium, giant cells and vacuolation in seminiferous tubular epithelium), pancreas (vacuolation of acinar cell), adrenal (necrosis of parenchyma) and thyroid (ectopic thymus) in monkeys at exposure levels 2, 4, 8, and 18X the human exposure at human doses of 80, 40, 20, and 10 mg/day, respectively, based on AUC. Giant cells and/or mild tubular seminiferous degeneration were also observed in a one-month dog study at dose of 90 mg/kg (46X human exposure at human dose of 80 mg/day). The effects on testis in dogs and monkeys have been seen with several drugs in this class.

## Genotoxicity

Rosuvastatin tested negative in Ames test, mouse lymphoma assay, chromosome aberration assay and mouse micronucleus test, suggesting it does not have mutagenic potential.

## Carcinogenicity

In the 2-year oncogenic studies, non-neoplastic alterations included changes in the forestomach (hyperkeratosis and/or hyperplasia and minor erosion and inflammation of the squamous epithelium) and liver (increased foci of alteration) were observed in both species. Neoplastic alterations were limited to hepatocellular adenomas /carcinomas in the mouse at 200 mg/kg/day, and in the rat, there were an increased number of uterine stromal polyps in females at 80 mg/kg/day.

Species	Tumor Findings: Multiple of human exposure*				
	80 mg	40 mg	20 mg	10 mg	5 mg
Rat	11	23	53	116	185
Mouse	10	21	48	107	171

\*: multiples of human exposure at which tumors were observed.

## Reproductive Toxicity

Rosuvastatin induced fetal toxicity in rats at 25 mg/kg and rabbits at 3 mg/kg. In rats, both maternal toxicity (reduced body weight and food consumption, liver and renal toxicity) and fetal toxicity (lower number of pups live born, slight low fetal body weight, low incidence of pups with eyes open, and increase in startle amplitude, increases in visceral malformation and skeletal variations, and slightly retarded ossification) were observed at  $\geq 25$  mg/kg with NOAEL for dams and fetus of 15 mg/kg. In rabbits, severe maternal toxicity (mortality, body weight loss, hypoactivity and debility, and marked histopathologic changes in liver, gallbladder, kidney, heart, and muscle) and fetal toxicity (increase in dead fetuses, decrease in fetal viability index) were observed at 3 mg/kg with NOAEL for dams and fetus of 1 mg/kg.

Species	Fetal Toxicity: Multiple of human exposure*				
	80 mg	40 mg	20 mg	10 mg	5 mg
Rat	3	6	13	28	50
Rabbit	1/2	1	3	5	10

\*: multiples of human exposure at which fetal toxicity was observed.

There was a low distribution of rosuvastatin to fetus in rats (3% or 20% of maternal plasma concentration in fetal tissue or amniotic fluid, respectively) following a single oral dose of 25 mg/kg. Relatively higher distribution in fetal tissue (25% maternal plasma concentration) was observed in 1/4 fetuses in rabbits following a single oral dose of 1 mg/kg. However, in the lactating rat, rosuvastatin was found in milk at concentrations up to 3 times those in plasma. These data suggested that there is a risk to pregnant women and nursing mothers treated with rosuvastatin.

## Conclusion:

The results from the *in vitro* studies with OK cells and human skeletal muscle cells support a mechanism of action consistent with the non-clinical data. However, a causal relationship between *in vitro* data and clinical adverse events is tenuous at best. Concern exists for the apparent increased clinical incidence of muscle and renal toxicity with rosuvastatin compared to data available from other statins.