7. Integrated Review of Safety

7.1. Brief Statement of Conclusions

As a group, statins have been associated with liver transaminase elevation and rarely hepatitis and liver failure. The data presented by the sponsor show a frequency of transaminase elevations, which is similar to that seen in the currently approved statins. No cases of hepatitis or liver failure were seen in these clinical trials.

Statins also have been associated with myopathy and rare cases of rhabdomyolysis, which can lead to acute renal failure and death. The data presented here show that the highest proposed dose of rosuvastatin, 80 mg, was associated with six cases of rhabdomyolysis and 14 cases of myopathy, considerably higher than had previously been observed in any of the clinical trials of the currently approved statins.

In contrast to currently approved statins, rosuvastatin was also associated with novel renal findings not previously seen with other statins. Patients exposed to doses of 40 and 80 mg of rosuvastatin had an increased frequency of persistent proteinuria and hematuria, which in a substantial number of patients was also associated with an increase in serum creatinine. The reversibility of these findings has still not been determined. In addition, two cases of renal failure and one case of renal insufficiency of unknown etiology were observed at the 80 mg dose.

7.2. Materials Utilized in the Review

The materials submitted by the sponsor for this review was summarized previously in section 5.2.

The review involved analysis of the acrobat files submitted electronically as part of the sponsor's original submission, 4-month Safety Update and PreApproval Safety Update.

SAS formatted data sets submitted electronically were analyzed using JMP 4 software, by this reviewer and utilizing CrossGraphs and data mining analysis by Ana Szarfman and Joy Mele.

7.3. Description of Patient Exposure

According to ICH guidelines the total number of patients exposed to an investigational drug for long-term treatment of non-life-threatening conditions should be at least 1500, with 300 to 600 exposed at 6 months and at least 100 patients exposed at one year. Our division has routinely required a minimum of 200 patients exposed for at least one year for the approval of medications intended for chronic use.

Table 18 Maximum continuous duration of treatment for each dose of rosuvastatin in the All Controlled / Uncontrolled Pool from Pre-Approval Safety Update 1/30/02

	Rosuvastatin dose [a,b]					
Cumulative duration of treatment [c]	5 mg N=1293	10 mg N=2174	20 mg N=1220	40 mg N=1249	80 mg N=1365	Total rosuvastatin [d,e] N=3903
≥6 weeks	1200	2009	1033	1084	1247	3722
≥12 weeks	974	1642	308	302	1003	3416
≥24 weeks	621	1122	183	184	927	2988
≥48 weeks	345	730	67	82	810	2471
≥72 weeks	145	311	11	8	446	1449
≥96 weeks	85	59	0	0	0	396
Mean days of treatment	240	251	92	93	338	394
Subject years ISS	673	930	197	179	645	2595
Subject years 4MSU	735	1112	220	212	792	3073
Subject years PASU	846	1482	303	317	1260	4209

Table 3 PreApproval SUR.
Data derived from PASU Tables S2.4.3 and 2.4.4, 4MSU Tables S2.4.3 and S2.4.4, and ISS Tables S2.4.3 and S2.4.4.
[a] Subjects are counted in each dose group to which they were exposed; therefore, subjects may be counted in more than 1 dose group.
[b] Subjects received rosuvastatin either alone or with another non-statin lipid regulating agent as combination treatment at any point during a feeder trial and/or Trial 34.
[c] For subjects with more than 1 exposure to a given rosuvastatin dose, only the longest duration of exposure to that dose is counted.
[d] Each subject is counted only once in the Total rosuvastatin column.
[e] Maximum continuous exposure in the Total rosuvastatin column includes all rosuvastatin continuous exposure, regardless of titration of dose. For this reason, counts of subjects in the individual duration categories cannot be added across doses to obtain the count in the Total rosuvastatin column.
SD = Standard deviation.

The total patient exposure in this NDA, including the latest safety updates, is adequate for the 5, 10 and 80 mg daily oral dosages. Doses of 20 and 40 mg do not have adequate safety exposure. This would not necessarily be an issue if no significant safety concerns were identified in patients receiving the 80 mg daily dose. However, as muscle and renal toxicity's were identified in this NDA for the

40 mg dose (renal), and 80 mg dose (muscle and renal) the current exposures of 67 and 82 patients beyond 48 weeks for the 20 and 40 mg dose, respectively, are inadequate to conclude that safety concerns observed at the 80 mg dose will not also be associated with use at the intermediate doses.

7.4. Specific Findings of Safety Review

7.4.1. DEATHS-

There was a combined total of 15 deaths in subjects taking rosuvastatin in the ISS, 4 month SUR and PreApproval SUR. Most cases can be attributed to events associated with ongoing cardiovascular disease. There was one case of lung carcinoma, one case of hepatitis B, one case of sudden death of unknown etiology, one case of accidental injury (passenger in MVA), and one suicide (self inflicted gunshot wound). All case narratives were reviewed and none of these events appeared to be directly related to the study drug.

7.4.2. ADVERSE EVENTS LEADING TO WITHDRAWAL FROM TREATMENT-

ALL CONTROLLED POOL:

Myalgia was the most common adverse event leading to withdrawal in subjects given rosuvastatin in the All Controlled Pool. It occurred at a rate of 0.6% in the rosuvastatin group which was more frequent than seen with any of the other statin comparators (0-0.4%).

CK elevations were the third most common adverse event leading to withdrawal in subjects given rosuvastatin in the All Controlled Pool. It occurred at a rate of 0.3% in the rosuvastatin group, 0.4% in the simvastatin group, but was not seen with atorvastatin or pravastatin (0%).

Withdrawals due to paresthesias, hypertonia, generalized edema, coronary artery disorder, and weight gain were only seen in the rosuvastatin group and not with any of the other statin comparators or the placebo group. However, the incidence was low $\leq 0.2\%$. It is not known if such cases would have been seen in the Total Statin Comparator and placebo groups if they had contained a similar number of patients.

All other adverse events leading to withdrawals in the All Controlled Pool occurred at a rate of 0.3% or lower and were seen more frequently with other statin comparators than in the rosuvastatin group.

When looking at fixed doses of rosuvastatin it appears that the incidence of withdrawals due to myalgia, CK elevation, and transaminase elevations occurred more frequently at the dose of 80 mg than at the lower doses of 5 to 40 mg. However, the small number of

patients in the Fixed-dose Controlled Pool, makes it difficult to draw clear conclusions from these data.

ALL CONTROLLED/UNCONTROLLED POOL:
When looking at the combined feeder trials and open label extensions the most common cause for withdrawals again was myalgia (0.6%), followed by CK (0.3%), AST (0.3%) and ALT (0.3%) elevations and abdominal pain (0.3%). In most of these cases these adverse events were considered drug-related by the clinical investigator. In the PreApproval Safety Update the frequency of these adverse events continued to increase as patients were followed longer during the open label extensions. The five most frequent adverse events leading to withdrawal were still the same: myalgia (0.9%), abdominal pain (0.5%), elevations in CK (0.4%), ALT (0.4%) and AST (0.4%).

7.4.3. NON FATAL SERIOUS ADVERSE EVENTS-

ALL CONTROLLED POOL:
The incidence of nonfatal serious adverse events was 3.4% in the All Controlled Pool, which is similar to the rate seen with the other statins in these trials, 2.0%-4.8%. Most of these serious adverse events were related to ongoing cardiovascular disease in these patients and are unlikely to be drug-related. There were a few cases of CK (0.1%), AST (0.1%) and ALT (0.1%) elevations which were considered serious and are likely to be drug related.

There was no clear association with the dose of rosuvastatin and the development of any nonfatal serious adverse events. However, there was one case of myopathy in the fixed-dose-controlled pool that was considered serious and was attributed to therapy with rosuvastatin by the clinical investigator.

ALL CONTROLLED/UNCONTROLLED POOL:
The incidence of nonfatal serious adverse events in the combined feeder trials and open label extensions was slightly higher 5.3% than in the All Controlled Pool. However, most of these serious adverse events continued to be related to ongoing cardiovascular disease in these patients and were unlikely to be drug-related. The incidence of CK, AST and ALT elevations considered serious and probably drug related continued to stay low (0.1%). Elevations in CK and transaminases will be described in more detail in the subsequent sections, MUSCULOSKELETAL-RELATED ADVERSE EVENTS and LIVER-RELATED ADVERSE EVENTS.

There were six cases of rhabdomyolysis in patients receiving 80 mg of rosuvastatin during the open label extensions. Data for only two of these patients were included in the initial laboratory data (Lab.xpt) submitted by the sponsor, because the other four cases occurred after the cut off date for the ISS. The incidence of rhabdomyolysis and myopathy will be discussed in more detail in the subsequent section, MUSCULOSKELETAL-RELATED ADVERSE EVENTS.

There were five cases of renal failure reported in the pre-approval safety update. Two of these cases occurred secondary to rhabdomyolysis and the other three cases were associated with multi-organ failure. After the date of cut off for the ISS, an additional two cases of renal failure and one of renal insufficiency without a clear etiology were reported as Med Watch 15 day alerts to the IND. These cases may be drug related and will be described in more detail in the subsequent section RENAL-RELATED ADVERSE EVENTS.

7.4.4. LIVER-RELATED ADVERSE EVENTS

LIVER TRANSAMINASE ELEVATIONS -
Liver transaminase elevations have been widely used to screen statins for potential hepatotoxicity. Since patients can have random isolated elevations which turn out to be nonspecific and unrelated to the study drug, sponsors typically present data for persistent elevations to try to identify patients who are more likely to have clinically significant elevations. In this submission the sponsor presented data for "clinically significant Alt elevations" defined as consecutive elevations >3xULN measured 4 to 10 days apart. Such an analysis unfortunately is likely to miss relevant cases for several reasons:

1) abnormal >3xULN repeat measurements which are performed either less than 4 days or more than 10 days after the initial abnormality would not be considered significant
2) abnormal repeat measurements > 1xULN but <3xULN could represent persistent disease but would not be considered significant
3) patients who do not have repeat values because of scheduling difficulty within the week long period from 4 to 10 days after the initially unexpected event would never be clinically significant even if the measurements would have been abnormal if they were performed at the correct time
4) if the drug is stopped or the dose lowered before the repeat dose it is not possible to tell if the change was significant. In such cases a repeat challenge with the drug would confirm a drug-related effect yet the elevation on the rechallenge could be considered another isolated elevation and the drug would likely be discontinued with out ever causing two consecutive elevations > 3xULN.

Therefore, an analysis of multiple elevations > 3xULN is likely to be more informative than persistent elevations 4 to 10 days apart.

Total single elevations are also useful for analysis and comparison between control groups as long as it is taken into account that they may over represent the incidence of significant disease. Data for single elevations are easier to collect and therefore less likely to be affected by ad hoc data manipulation. When analyzing single elevations it is useful to compare the drug to active controls or placebo and to compare relative frequency of elevations at several higher levels, such as >6xULN or >9xULN. Such higher single elevations are more likely to represent relevant toxicity.

Identification of patients with simultaneous elevations of different tests of liver function is also another potential approach for identifying patients with more significant disease. The most useful application of this approach is illustrated in Hy's law which states that patients with elevations in both bilirubin and transaminases have a 10% chance of severe liver injury. Therefore, patients in these trials will also be screened for evidence of bilirubin >1.5xULN associated with transaminase elevations >3xULN.

LIVER TRANSAMINASE ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN
An analysis of single, and multiple Alt elevations was performed. Multiple elevations do not depend on the time of the measurement and therefore do not necessarily represent persistent elevations as reported by the sponsor.

Table 19
Alt elevations in patients taking Rosuvastatin All controlled/Uncontrolled Pool

	5mg		10mg		20mg		40mg		80mg	
Single elevations	N (1221)	%	N (1967)	%	N (1125)	%	N (1123)	%	N (1314)	%
>3xULN	11[a]	0.9	11[a]	0.6	6	0.5	6	0.5	41[a]	3.1
>6xULN	0	0	2	0.1	0	0	2	0.2	9[b]	0.7
>9xULN	0	0	1	0.05	0	0	1	0.1	4[b]	0.3
Multiple elevations										
>3xULN	5	0.4	0	0	0	0	2	0.2	15	1.1
>6xULN	0	0	0	0	0	0	1	0.1	4	0.3
>9xULN	0	0	0	0	0	0	1	0.1	2	0.15

[a]While rhabdomyolysis can also be associated with elevations in transaminases most of the mild elevations in Alt > 3xULN reported here were not associated with CK elevations > 10xULN. Only 9 pts with Alt > 3xULN also had CK elevations >10xULN. One on 5mg, one on 10mg and 7 on 80mg.

[b]At the higher transaminase elevations about half of the cases were also associated with CK elevations > 10xULN and this was only seen at the 80 mg dose.
5 out of 9 pts with Alt > 6xULN and
2 out of 4 pts with Alt > 9xULN

Data were derived from Labs.xpt data file submitted 6/26/01

There is an increase in the incidence of single transaminase elevations > 6xULN and >9xULN at doses of 40 and 80 mg of rosuvastatin. There is also an increase in the incidence of multiple transaminase elevations > 3xULN, > 6xULN and > 9xULN at doses of 40 and 80 mg of rosuvastatin.

While there appears to be a slight increase in the frequency of single transaminase elevations > 3x, >6x, and > 9xULN at 40 mg, it is low ranging from 0.1% to 0.5%. This is less than the frequency of transaminase elevations >3xULN reported in healthy patients in Phase 1 trials receiving placebo i.e. < 2% (Rosenzweig et al. 1999). Even though direct comparisons of data from independent trials are difficult because of different patient populations, study protocols and lengths of drug exposure, this can, at times, be useful.

In comparison to 40 mg and lower doses, the frequency of single elevations >3xULN at 80 mg is 3.1%, which is higher than seen in healthy patients in Phase 1 trials. This relative increase in transaminase elevations at the 80 mg dose is also higher for single elevations >6x and >9xULN and for multiple elevations >3x, >6x and >9xULN. This might suggest the potential for a clinically significant signal. In comparison to other currently approved statins however, similar elevations in transaminases have also been

seen at the highest approved doses and careful monitoring has shown statins to be relatively safe and rarely associated with potential cases of liver failure. The incidence of persistent elevations in transaminases, as it is currently reported in the labels of these drugs, is shown in the Table 20 below. These data are in the same range as the frequency of multiple elevations >3xULN reported above for rosuvastatin (1.1%).

Table 20-
Dose related incidence of persistent transaminase elevations in statins in clinical trials

Statin	Placebo	10mg	20mg	40mg	80mg
Pravachol	0.3%			0.3%	
Mevacor	0.1%		0.1%	0.9%	1.5%
Lipitor		0.2%	0.2%	0.6%	2.3%
Zocor				0.9%	2.1%
Lescol			0.2%	1.5%	2.7%

Data taken from currently approved labels or NDA19898/Se8-042.

Liver function monitoring appears to identify a small group of subjects with evidence of hepatotoxicity for which the study drug should be discontinued. Out of 22 subjects with multiple elevations, at least 12 had the drug withdrawn, two had the dose lowered and one had the drug withheld temporarily. For all subjects, for whom follow up data are available, transaminase levels improved. A small number of subjects, at least five, continued to have mild low grade elevations <3xULN when continued on the study drug. No cases of liver failure or unexplained hepatitis were observed in these trials. In these clinical trials liver function tests appear to permit safe and adequate monitoring for hepatotoxicity in patients on rosuvastatin.

BILIRUBIN AND ALT ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN
Patients with concurrent elevations in bilirubin and liver transaminases are much more likely to have significant liver disease. Screening for such patients is a useful way to try to identify patients who might represent significant drug toxicity.

Seven patients were identified in the Labs.xpt database with bilirubin>1.5xULN and Alt >3xULN. One patient on 10 mg of rosuvastatin turned out to have adenocarcinoma of the bile ducts as the likely cause for these findings. There was also one patient on 40 mg of rosuvastatin, and five other patients on 80 mg of rosuvastatin. Even after excluding one patient on 80 mg with diagnosed Hepatitis B, the overwhelming signal for liver toxicity is at the 80 mg dose.

Screening the SUR narratives identified one additional patient (0034/0440/005) with concurrent bilirubin and Alt elevations in the open label extension. This patient was on 40 mg of rosuvastatin and 1 g of Niaspan. He was noted to have a normal baseline Alt of 14 but had minor elevations from 1.1xULN to 2.8xULN during the 445 days the patient was enrolled in the trial. This patient had two consecutive 2.8xULN elevations on days 36 and

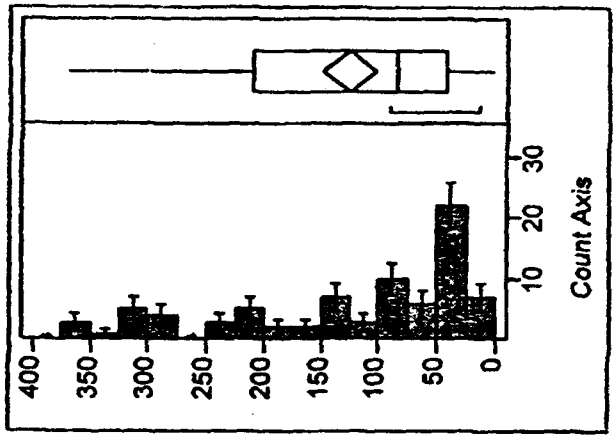
43 of the trial, which did not satisfy the sponsor's definition of clinically significant, and so was continued in the trial. On day 438 his Alt was 3.2xULN and bilirubin was 2xULN. Repeat values on day 440 were Alt 2.2xULN and bilirubin 2.1xULN. By day 445 Alt was normal at 15 and bilirubin had dropped to 1.3xULN. The patient was continued on medication and the episode was considered "resolving".

In conclusion there were two subjects on 40 mg and four subjects on 80 mg of rosuvastatin with concurrent hyperbilirubinemia and Alt elevations suggestive of more significant liver disease without a known etiology. Careful monitoring of liver function tests especially at the highest doses of 40 and 80 mg of rosuvastatin is recommended.

TIME TO ONSET OF TRANSAMINASE ELEVATION IN PATIENTS ON ROSUVASTATIN

Most subjects present with transaminase elevations within the first 85 days (12.1 weeks) after the start of therapy. The range is from 3 to 370 days with a mean of 126 days and a standard deviation of 105 days. The median is 85 days.

Figure 6 **Duration at Time of Onset of Transaminase Elevations**



Quantiles		
100.0%	maximum	370.00
99.5%		370.00
97.5%		357.98
90.0%		302.70
75.0%	quartile	209.25
50.0%	*median*	*85.00*
25.0%	quartile	42.00
10.0%		29.10
2.5%		3.12
0.5%		3.00
0.0%	minimum	3.00

Moments	
Mean	125.725
Std Dev	104.49093
Std Err Mean	11.682441
upper 95% Mean	148.97832
lower 95% Mean	102.47168
N	80

The sponsor recommends liver function tests be preformed before and at 12 weeks following initiation of therapy and any elevation of dose, and periodically (e.g. semiannually) thereafter. While most patients who had elevations >3xULN in these

clinical trials had elevations by 12 weeks, the most frequent period during which elevations were identified was from 3.5 to 7 weeks (25 to 50 days) after the start of therapy. Therefore it may be a more appropriate to recommend testing between 1 and 2 months after the start of therapy instead of at 12 weeks.

ALT ELEVATIONS IN COMBINATION TRIALS WITH ROSUVASTATIN
No patients were identified in the Labs.xpt database with transaminase elevations >3xULN in combination trials with niacin or cholestyramine.

Seven subjects were identified with Alt elevations > 3xULN in the combination trial with fenofibrate, Trial 36:

1/47 (2%) on fenofibrate alone
3/52 (5.8%) on 5mg of rosuvastatin and fenofibrate
3/51 (5.9%) on 10mg of rosuvastatin and fenofibrate

This suggests a higher incidence of Alt elevations on this combination than with either component alone. But the small numbers of patients in this trial make these data less reliable. In a pooled analysis of 10 clinical trials in the fenofibrate label, transaminase elevations > 3xULN has been reported to occur in 5.3% of the patients taking fenofibrate compared to 1.1% of patients on placebo. This is similar to the rate seen here in combination therapy and suggests the incidence of ALT elevations in the fenofibrate alone group may have been underestimated. Therefore, rosuvastatin probably does not increase the frequency of Alt elevations in patients on fenofibrate beyond that due to fenofibrate alone.

DEMOGRAPHIC ANALYIS OF PATIENTS WITH TRANSAMINASE ELEVATIONS
In order to look for potential patient populations who might be at higher risk of transaminase elevations, which might require different labeling, data was analyzed to see if there was an association with transaminase elevations and the patient's age, sex, weight, baseline creatinine or baseline transaminase levels.

Table 21 Demographic Information On Patients With Transaminase Elevations

		Lab Abnorm[a]	Age[b](yrs) Mean±SD	Sex[b] (% male)	Weight[b](kg) Mean±SD	BaselineCr Clearance[b] Mean±SD	% with Baseline >1xULN[b]
Control (all randomized subjects)	4335		56 ± 12	53%	81 ± 16	81 ± 24	11%
Dose	N						
5-40 mg	33	>3xULN	47 ± 13	67%	85 ± 14	92 ± 29	52%
80 mg	41	>3xULN	51 ± 16	71%	81 ± 14	85 ± 28	22%
80 mg	10	>6xULN	60 ± 17	50%	75 ± 11	72 ± 29	30%

[a]Data were derived from Labs.xpt data file submitted 6/26/01
[b] Data were derived from DDEMOG.xpt data file submitted 6/26/01

While patients with the highest elevations >6xULN on 80 mg of rosuvastatin were older, weighed less and had a lower baseline creatinine than subjects with lower 3xULN

elevations, they were not outside one standard deviation of all the patients in the randomized pool.

Males appeared to account for more of the patients with lower 3xULN transaminase elevations.

Baseline elevations in transaminases were more common in subjects who went on to have significant elevations >3xULN during the trials. These data suggest that patients with baseline transaminase elevations will probably need more careful monitoring on the study drug.

Data were also analyzed to see if there was an association with transaminase elevations and the medical history of patients on rosuvastatin in these clinical trials.

Table 22 Medical History Of Patients With Transaminase Elevations On Rosuvastatin

		Lab Abnorm[a]	CHD[b]	Smoker[b]	Htn[b]	Diabetes[b]
Control (all randomized subjects PreApproval SUR)	N=4335		29%	15%	40%	10%
Dose of Rosuvastatin						
5-40 mg	N=33	>3xULN	15%	12%	39%	9%
80 mg	N=41	>3xULN	54%	24%	32%	7%
80 mg	N=10	>6xULN	60%	30%	40%	20%

[a] Data were derived from Labs.xpt data file submitted 6/26/01

[b] Data were derived from DDEMOG.xpt data file submitted 6/26/01

Smokers and patients with atherosclerotic disease were more likely to have transaminase elevations on the 80 mg dose. Data for diabetics was mixed.

SUMMARY/RECOMMENDATIONS FOR LIVER-RELATED ADVERSE EVENTS

As a group statins have been associated with liver transaminases elevations but rarely hepatitis and liver failure. Currently all approved statins have recommendations for liver function monitoring.

Rosuvastatin like other statins shows a dose-related increase in liver transaminases. The incidence of multiple transaminase elevations is similar at 80 mg of rosuvastatin to that seen at the highest approved doses of other statins.

Patients with baseline liver transaminase elevations were more likely to have significant elevations >3xULN during the trials.

Most patients showed elevations between 1 to 2 months after the start of therapy but subjects continued to show elevations through out the length of the trial.

I would recommend liver function monitoring tests be performed before and at 1 to 2 months following the initiation of therapy or dose escalation, and semiannually thereafter.

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7.4.5. MUSCULOSKELETAL-RELATED ADVERSE EVENTS

CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN

An analysis of single CK elevations > 5x and > 10xULN was performed using data derived from the all controlled and uncontrolled database in the 6/26/01 submission. There was an increase in the frequency of CK elevations in patients taking the 80 mg dose. About half of the subjects with CK>10xULN also had elevations in Alt and symptoms of myopathy. The incidence of myopathy at the 80 mg dose is clearly higher than estimated for statin users by Gaist et al. (0.023%), or Omar et al. (0.1-0.5%). In the pravastatin database the incidence of CK>10xULN was 0.07% for placebo and 0.12% for the 40 mg dose over an average of five years of follow up. The frequency of 1.1% reported here for 80 mg of rosuvastatin is in the range seen between 0.2 mg (0.2%) and 0.4 mg (1.5%) of Baycol in clinical trials. All cases of myopathy at doses below 80 mg were associated with exercise or physical injury.

Table 23

CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN IN THE ALL CONTROLLED/UNCONTROLLED POOL

	5mg		10mg		20mg		40mg		80mg	
	N (1221)	%	N (1967)	%	N (1125)	%	N (1123)	%	N (1314)	%
Single CKelevations[a]										
CK >5xULN	8	0.7	12	0.6	4	0.3	6	0.5	32	2.4
CK>10xULN	4	0.3	4	0.2	2	0.2	1	0.1	17	1.3
Single CK elevations associated with Alt >3xULN[a]										
CK >5xULN	1	0.1	1	0.1	0	0	0	0	12	0.9
CK>10xULN	1	0.1	1	0.1	0	0	0	0	10	0.8
Single CK Elevations associated with myopathy[b]										
CK >5xULN	2	0.2	2	0.1	1	0.1	0	0	14	1.1
CK>10xULN	2	0.2	2	0.1	1	0.1	0	0	14	1.1
Rhabdo-myolysis[c]	0	0	0	0	0	0	0	0	6	0.5

[a]Data were derived from Labs.xpt data file submitted 6/26/01. The Labs.xpt data base did not include data on 4 patients with rhabdomyolysis at the time this data base was submitted. Therefore the frequency of CK elevations and CK elevations associated with Alt elevations is probably underestimated.

[b]Data was derived from Table 22 in the Pre-Approval SUR therefore it includes all patients with rhabdomyolysis during these trials

[c]These include 4 cases of rhabdomyolysis diagnosed by the treating physician, 1 case originally diagnosed as myositis and one diagnosed as myopathy and renal failure. These last two cases had peak CK's of 34,548 and 16,280 U/L with increased plasma myoglobulin. All six patients had to be hospitalized for IV hydration.

While a similar number of patients (1100-1300) were exposed to doses of 5, 20, 40 and 80 mg of rosuvastatin, most patients at 20 and 40 mg doses were exposed for < 12 weeks whereas over half the patients on 80 mg were exposed for > 24 weeks. The total exposure in subject years at the 20 and 40 mg doses was less than 1/3 of the exposure at 80 mg.

Therefore, it is not possible to rule out that there is some increased frequency in CK elevations and possibly a small but increased frequency of rhabdomyolysis at these lower doses.

CK ELEVATIONS IN PATIENTS TAKING OTHER STATINS OR LIPID ALTERING AGENTS IN THESE CLINICAL TRIALS

No subjects taking atorvastatin in the All controlled/Uncontrolled Pool had CK>5xULN at any of the doses from 10 to 80 mg (10mg N=451, 20mg N=271, 40mg N=366, 80mg N=350).

No subjects taking pravastatin in the All controlled/Uncontrolled Pool had CK>5xULN at any of the doses from 20 to 40 mg (20mg N=252, 40mg N=68).

Only one subject taking simvastatin in the All controlled/Uncontrolled Pool had CK>5xULN at any of the doses from 20 to 80 mg (20mg N=250, 40mg N=46, 80mg N=23). The CK value was 2220 (18.5xULN) in a subject on 20 mg of Zocor. It was not associated with an elevation in Alt.

Two subjects taking niacin in the All controlled/Uncontrolled Pool (N=224) had CK>5xULN at any of the doses. The peak CK values were 999 (8.3xULN) on 0.5g and 3594 (30xULN) on 1.0g. CK values in these subjects were not associated with an elevation in Alt.

Only one subject taking fenofibrate alone in the All controlled/Uncontrolled Pool had CK>5xULN at any of the doses. The CK value was 701 (5.8xULN) in a subject on 67 mg of fenofibrate. It was not associated with an elevation in Alt. There was also one subject on 10 mg of rosuvastatin and 134 mg of fenofibrate with a peak CK value of 651 (5.4xULN) also not associated with an increase in Alt.

No subjects on Placebo in the All controlled/Uncontrolled Pool had CK>5xULN.

In summary, although the total exposure to other statins or other lipid altering agents is lower in these clinical trials, there were only 5 such cases of CK> 5xULN and 2 cases of CK>10xULN. None of these cases of CK elevations were associated with myopathy or concurrent Alt elevations.

COULD FORCE TITRATION BE CONTRIBUTING TO THE HIGHER FREQUENCY OF CK ELEVATIONS SEEN AT 80 MG?

Since most cases of myopathy occurred at the 80 mg dose in trials where patients were force titrated, the sponsor suggests that subjects were given higher doses than they might have needed to achieve target NCEP goals. At least 2 patients with myopathy in the All

controlled/Uncontrolled pool achieved LDL-cholesterol levels below 50 mg/dL. The sponsor argues that this would not have happened in routine clinical practice.

However, there is no clear association with final LDL level or percent decrease in LDL and the risk of myopathy or rhabdomyolysis (Berg et al. 1996). Clearly patients who did not attain final LDL-cholesterol levels of <100 on rosuvastatin still had myopathy.

Table 24
Change In LDL-Cholesterol associated with CK >10xULN and Myopathy in the All Controlled/Uncontrolled Pool submitted in the PreApproval Safety Update

Dose (mg)	Peak CK U/L	Baseline LDL (max)	Treated LDL	% decrease in LDL	Rhabdomyolysis[a]
5	3954	158	114	28	
5	2496	188	106	44	
10	1626	207	119	43	
10	1888	117	67	43	
20	4550	206	94	54	
80	5380	267	193	28	
80	1393	197	122	38	
80	11123	65	96	(42) Increase[b]	Rhabdo
80	2570	257	131	49	
80	3610	260	122	53	
80	3486	412	177	57	Rhabdo
80	1780	232	96	59	
80	2417	217	80	63	Rhabdo
80	2154	110	39	65	
80	34548	238	75	68	rhabdo
80	2184	226	66	71	
80	5480	163	48	71	
80	>20000	279	74	73	Rhabdo
80	16280	242	62	74	rhabdo

Data derived from Table 22 Pre Approval SU 1/30/02
[a] Rhabdomyolysis diagnosed by patients treating physician is labeled with a capital "R" ie. Rhabdo, The two additional cases considered rhabdomyolysis by this reviewer are labeled with a lower case "r" ie. Rhabdo.
[b]This was a patient with Type IV dyslipidemia in Trial 35, who probably should not have been started on Rosuvastatin with the low baseline LDL-C of 65.

Data from trials with Atorvastatin (Bakker-Akema et al. 2000) showed that lowering LDL-cholesterol to < 50 mg/dl did not alter the safety profile of that statin.

Out of 149 subjects identified in the rosuvastatin All Controlled Pool who achieved LDL-cholesterol < 50mg/dl, only one (0.7%) had increased CK and two (1.3%) had myalgia. The frequency of these events was less than observed in the total rosuvastatin group. In addition nine patients in this All Controlled Pool achieved LDL-cholesterol below 30 mg/dl and only two adverse events, both unlikely to be related to the study drug i.e. pharyngitis and lacrimation disorder, were observed. Therefore, eliminating force titration

in clinical trials or in routine clinical practice may not impact on the frequency of CK elevations seen with rosuvastatin.

RHABDOMYOLYSIS IN ROSUVASTATIN OPEN LABEL TRIALS

All 6 cases of rhabdomyolysis in patients taking rosuvastatin occurred on the 80 mg dose during the open label extension trials. The average length of time on the drug prior to the development of rhabdomyolysis was 160 days (5.3months) with a standard deviation of 126 days. The median was 150 days with a range of 20 to 384 days. Periodic CK monitoring is unlikely to be of benefit in identifying these cases.

All hospitalizations were preceded by a 3 to 28 day prodrome with one or more of the following symptoms: loss in appetite, fatigue, malaise, muscle soreness, muscle weakness, nausea, vomiting, and abdominal distension. CK measurements should be taken in any patients taking rosuvastatin, who develop muscle soreness or weakness that lasts for more than a few days. The other symptoms of loss in appetite, fatigue, malaise, nausea, vomiting and abdominal distension are more nonspecific. Physicians should be aware that such nonspecific symptoms may also be associated with the development of rhabdomyolysis and they should be recommended to use their discretion in measuring CK levels in these patients.

None of the other currently marketed statins showed evidence of rhabdomyolysis in the clinical trials submitted for NDA approval. The incidence seen here with 80 mg of 0.5% is clearly higher than estimated by Omar et al. 2001 at 0.04-0.2% or by Farmer JA and Torre-Amione G. et al. 2000 at 0.1%.

DEMOGRAPHIC ANALYIS OF PATIENTS WITH TRANSAMINASE ELEVATIONS

In order to look for potential patient populations who might be at higher risk of CK elevations, which might require different labeling, data were analyzed to see if there was an association with CK elevations and the patient's age, sex, weight, baseline creatinine level or past medical history of smoking, cardiovascular heart disease, diabetes, or hypertension. Data were taken from the DDEMOG.xpt in the 4-month SUR ISS.

Table 25-

Demographic Information On Patients With CK Elevations >10xULN

Dose	Age (yrs) Mean±SD	Sex (male)	Weight (kg) Mean±SD	**Baseline Cr Clearance** Mean±SD (ml/min)	CHD	Smoker	Htn	DM
Control (all randomized subjects) N=4505	56 ± 12	52%	81 ± 16	80 ± 24	28%	15%	40%	10%
CK>10xULN [a] (N=35)	57 ± 15	66%	77 ± 14	72 ± 23	46%	11%	46%	9%
CK>10xULN + myopathy [b] (N=18)	59 ± 15	67%	77 ± 13	70 ± 21	56%	6%	50%	17%
Rhabdomyolysis (N=6)	67 ± 8	33%	75 ± 10	59 ± 13	83%	0%	67%	0%

[a] Data from Table 21 PreApproval SUR 1/30/02

[b] Data from Table 22 PreApproval SUR 1/30/02

Data did not include one patient with myopathy on 20 mg (65/83/03).

Patients, who developed rhabdomyolysis, were more likely to be older women with a lower baseline creatinine clearance. They also were more likely to have cardiovascular heart disease and hypertension. It is possible that these co-morbid conditions may impact on their baseline renal function or alternatively this may reflect a potential interaction with cardiac or antihypertensive medications and rosuvastatin.

Looking at creatinine clearance in the six individuals who developed rhabdomyolysis, it can be seen that these patients were at increased risk because they started out with poor renal function and then progressed to worse renal function while on rosuvastatin. The mean baseline creatinine clearance for all these patients was 59 (between 10% and 25% iles). On rosuvastatin the mean creatinine clearance values dropped to 52 (<10% ile)!

Table 26-
Creatinine Clearance in Patients Who Developed Rhabdomyolysis

Baseline Cr Clearance					Min Cr Clearance		Last Cr Clearance		
All pts on Rosuvastatin[a] with baseline data		Rhabdomyolysis[c]			All pts on Rosuvastatin[b] with data after week 0		Rhabdomyolysis[c]		
ml/min	N=3726	N	%	Fold Inc	ml/min	N=2791	N[c]	%	Fold Inc
≥80	1742	1	0.06	1	≥80	1536	0	0	0
<80	1984	5	0.3	5x	<80	1596	6	0.4	1x
<70	1327	5	0.4	7x	<70	1101	6	0.5	1.3x
<60	709	3	0.4	7x	<60	590	5	0.8	2x
<50	262	2	0.8	13x	<50	247	1	0.4	1x

[a]Data is derived from Labs.xpt data file submitted 6/26/01, refers to all who received rosuvastatin alone or in combination therapy patients for whom data points are available.
[b]Data refers to all patients with recorded values starting from week 0. Pts maybe counted twice if they had more than one recorded value with one value above 80 and the other below 80.
[c]Data refers to last value recorded before episode of rhabdomyolysis

The data in Table 26 suggest that patients with lower creatinine clearance values are at increased risk of developing rhabdomyolysis. This may partially be explained by the fact that patients with severe renal impairment had a 3 fold increase in the Cmax and AUC for rosuvastatin (see PK study 0017). While none of the renal impaired patients in study 0017 developed myopathy or rhabdomyolysis, the study was too short in duration (i.e. 14 days) to see an effect. Rhabdomyolysis occurred after a mean duration of 5.3 months during the open label extensions.

Looking at the concomitant medications in the COMMED.xpt files there was no clear association. Four out of the six patients had been on aspirin, half (3/6) the patients had been on a diuretic (hydorchlorothiazide or furosemide), an ACE inhibitor (lisinopril or ramipril) or a quinilone (cipro, ofloxacin or levofloxacin). None of these drugs had previously been reported as a potentially interacting drug in statin-associated rhabdomyolysis (Omar and Wilson, 2002). A recent review (Jan 2002) of rhabdomyolysis associated with Baycol performed by OPDRA did find spontaneous reports of drug interactions with norfloxacin, trovafloxacin and levofloxacin.

SUMMARY/RECOMMENDATIONS FOR MUSCULOSKELETAL-RELATED ADVERSE EVENTS

There is a higher incidence of myopathy (1.1%) and rhabdomyolysis (0.5%) observed in the clinical trials with rosuvastatin than reported in the original NDA for any of the currently approved statins.

Most cases of myopathy (14/19=74%) and all six cases of rhabdomyolysis occurred at the 80 mg dose. The few cases of myopathy at doses of 5 to 20 mg were confounded with a

history of vigorous exercise or physical injury. However since there was less than 1/3 the subject-years of exposure at doses of 20 and 40 mg compared to 80 mg, safety at these lower doses is unknown.

The risk of rhabdomyolysis in patients taking 80 mg of rosuvastatin is too high to recommend approval of this dose for patients with familial or nonfamilial hypercholesterolemia or mixed dyslipidemia.

One of the cases of rhabdomyolysis occurred in study 35, which enrolled patients with Fredrickson Type IIB and IV dyslipidemia to study the effect of rosuvastatin on the change in triglyceride levels. This patient started in the study with an average baseline LDL-cholesterol of 65 mg/dl. Since the greatest reduction in triglycerides was seen at doses up to 10 mg of rosuvastatin (-37%), with only small increases of ≤ 3% at higher doses (20mg, -37%; 40mg, -40%; and 80mg, -40%), it seems prudent to recommend a maximal dose of 10 mg for triglyceride lowering.

7.4.6. RENAL-RELATED ADVERSE EVENTS

PROTEINURIA IS SEEN in PATIENTS TAKING 40 and 80 MG DAILY DOSES of ROSUVASTATIN

In the All Controlled Pool it was observed that there was an increase from baseline in the frequency of proteinuria in the rosuvastatin group. The number of patients with all grades of proteinuria, from trace to ++++, went from 20.5% at baseline to 29.5% at the end of the controlled phase of the trials on rosuvastatin. This is in contrast to a decrease from 21.0% to 17.3% for patients on total other statins and a decrease of 27.6% to 23.3% for patients on placebo (see Table 56 ISS). The increase seemed greatest in patients with + and ++ proteinuria. However, this analysis did not look directly at individual patients to confirm that more patients were developing higher grades of proteinuria compared to their individual baseline values.

In response to these unexpected findings in the All Controlled Pool, the sponsor amended the protocols in the open label extension to add urinalysis testing and serum creatinine measurements for all subjects at follow-up visits. Data in Table 27 was separated by drug dose at the onset of proteinuria. These data show an increase of proteinuria at 40 and 80 mg of rosuvastatin for patients with 1, 2 or 3 grade increases in proteinuria and an increase of 4 grades in proteinuria in patients on 80 mg of rosuvastatin as well.

Table 27
Proteinuria from Open Label Extension Trials Submitted in PreApproval SUR

Increase from baseline	Rosuvastatin Dose									
	5 mg		10 mg		20 mg		40 mg		80 mg	
	N= 270	%	N= 577	%	N= 123	%	N= 155	%	N= 631	%
>1 grade	34	12.6	56	9.7	17	13.8	39	25.2	201	31.9
>2 grades	12	4.4	12	2.1	7	5.7	17	11.0	106	16.8
>3 grades	0	0	2	0.3	1	0.8	3	1.9	34	5.4
>4 grades	0	0	1	0.2	0	0	0	0	5	0.8

Data from Table 14 PreApproval SUR 1/30/02

The urinalysis data submitted with the original database URIN.xpt were analyzed to look for patients who had at least a ++ grade of proteinuria and an increase of at least one grade between the baseline and final protein measurements. These data correspond to more patients than were included in the open label extension, Table 27 above, and attempted to focus on patients likely to have more significant levels of proteinuria, i.e. ≥++. In addition, these patients were screened to see if they had increased levels of hematuria or if these two findings were unrelated. Data from patients in similar trials taking Lipitor were used as controls.

PROTEINURIA IS ASSOCIATED WITH HEMATURIA IN PATEINTS TAKING 40 AND 80 MG OF ROSUVASTATIN

Table 28
PROTEINURIA AND HEMATURIA IN PATIENTS TAKING ROSUVASTATIN WITH AT LEAST A ++ MEASUREMENT ON THEIR FINAL URINE DIPSTICK*

Rosuvastatin (mg)	N (patients)	Proteinuria ≥ ++			Hematuria (associated with proteinuria)		
		N	%	Fold Inc	N	%	Fold Inc
5	863	7	0.8	1	2	0.2	1
10	1025	13	1.3	1.4	2	0.2	1
20	705	8	1.1	1.4	1	0.1	0.5
40	830	24	2.9	3.6	14	1.7	8.5
80	859	94	10.9	13.6	66	7.6	38

*This data includes only patients with an increase of at least one protein category above baseline in their final reading. In the few cases where no baseline values were present it was assumed the baseline value was no protein.
Patients with abnormality during dietary run in or randomization periods were excluded.
Data taken from URIN.xpt data file 6/26/01

The data showed an increase in proteinuria, and proteinuria associated with hematuria, in doses of 40 and 80 mg. The effect was most pronounced at 80 mg with a 13.6-fold increase in proteinuria and a 38-fold increase in patients with proteinuria and hematuria compared to the 5 mg dose. This analysis is helpful because it shows the trend with higher doses only, so lower doses such as 10 and 20 mg may be safe.

Table 29-
PROTEINURIA AND HEMATURIA IN PATIENTS TAKING LIPITOR WITH AT LEAST A ++ MEASUREMENT ON THEIR FINAL URINE DIPSTICK*

Lipitor (mg)	(pts)	Proteinuria		Hematuria (and proteinuria)	
		N	%	N	%
10	451	9	2.0	2	0.4
20	261	4	1.5	0	0
40	251	1	0.4	1	0.4
80	350	3	0.9	1	0.3

Data taken from URIN.xpt data file 6/26/01

The baseline levels of for proteinuria (< 2%) and for hematuria with proteinuria (<0.5%) are comparable for all doses of Lipitor and 5 to 20 mg doses of rosuvastatin.

PERSISTENCE OF PROTEINURIA FROM THE CONTROLLED TRIALS DURING THE OPEN LABEL EXTENSION

To get an estimate for the persistence of the proteinuria identified during the controlled feeder trials, the sponsor looked at a subgroup of 297 patients who demonstrated an increase in urine protein in their last feeder trial visit. These patients were screened to see how many had no change or a further increase in their level of proteinuria at the last recorded visit of the open label extension. Out of these patients 71.4% improved, 20.9% showed no change, and 7.7% showed worsening of proteinuria on therapy with rosuvastatin. While the data for no change are mixed across all doses, it is clear that patients on 80 mg are more likely to have progressive proteinuria.

Table 30-
Urine Protein Change in Patients with an Increase in Urine Protein Noted During the Feeder Trial

	5 mg N=18		10 mg N=60		20 mg N=21		40 mg N=37		80 mg N=161		All doses N=297	
	N	%	N	%	N	%	N	%	N	%	N	%
No change in proteinuria	5	28	12	20	1	5	3	8	41	25	62	20.8
Increase in proteinuria	0	0	1	2	1	5	2	5	19	12	23	7.7

Data taken from Table 15 PreApproval SUR 1/30/02

The sponsor emphasized that most patients (71.4%) with proteinuria improve on continued therapy (including data from all doses). While the number of patients who progress on therapy may be small, this may still be clinically significant if it can be associated with increases in creatinine and renal insufficiency.

It is not known what percentage of the 20.8% with no change and the 7.7% with worsening proteinuria would have improved if rosuvastatin had been discontinued.

QUANTITATION OF URINE PROTEIN IN PATIENTS WITH PROTEINURIA ON ROSUVASTATIN

The sponsor did not do 24 hour urine collections to quantify urine protein in these patients. Instead the sponsor used (total urine protein-to-urine creatinine) ratios from spot collections to estimate total urinary protein. 28.8% of the subjects who had at least a two category shift in urine protein dipstick measurements had a (total urine protein-to-creatinine) ratio of >0.5 representing a urine protein excretion > 3XULN according to the sponsor.

POSSIBLE RENAL TUBULAR DAMAGE ASSOCIATED WITH ROSUVASTATIN
Analysis of the urine protein in patients taking rosuvastatin revealed elevated levels of beta-2-microglobulin and N-acetyl-beta-D-glucosaminidase suggesting a renal tubular etiology according to the sponsor. Drug insolubility or crystallization in the renal tubules would be a potential mechanism for renal tubular damage.

CHANGES IN SERUM CREATININE IN PATIENTS TAKING ROSUVASTATIN
According to the sponsor, no changes in the mean or median serum creatinine were seen during the open label extension. However, since the standard deviation around the mean percent change was large such an analysis could miss small but important changes in a subgroup.

More older patients had elevated serum creatinine.

men <65 (1.1%), men > 65 (5.5%) women <65 (2.1%), women > 65 (7.8%)

While this probably reflects the general decrease in renal function with age and is not necessarily due to rosuvastatin, the increase does appear to be slightly higher in women. It would have been useful to have data from a placebo group or active comparator for comparison.

The sponsor looked at 35 patients that had a >30% increase in serum creatinine in the open label extension Trial 34. More patients on the 80 mg dose had a >30% increase in serum creatinine compared to the patients on lower doses.

5 mg (1.6%), 10 mg (0.6%), 20 mg (0%), 40 mg (1.4%), 80 mg (2.6%).

Analysis of the data submitted by the sponsor shows that subjects with greater levels of proteinuria such as ++ or higher did have an increase in the mean serum creatinine at doses of 40 and 80 mg.

Table 31
Mean Serum Creatinine (µMOL/L) increase in patients with ≥++ Proteinuria [a]

Dose (mg)	Baseline Cr Mean ± SD	Final Cr Mean ± SD	Baseline N	Final [b] N	Mean % change in Cr
5-20	100.6 ± 19.9	101.8 ± 20.2	28	25	1
40	106.8 ± 21.8	123.6 ± 35.6	24	22	16
80	98.4 ± 16.9	114.9 ± 27.9	94	90	17
Mean Serum Creatinine increase in patients with ≥++ Proteinuria and Hematuria [a]					
5-20	95.6 ± 15.6	99.3 ± 4.5	5	4	4
40	104.2 ± 21.7	121.4 ± 31.2	14	12	17
80	96.5 ± 17.1	118.1 ± 31.7	66	63	22

[a] Data derived from Urine.xpt 6/26/01 [b] Final data was not available for all patients.

As a result of these findings, the sponsor was asked to do a more complete analysis of changes in serum creatinine in patients with proteinuria and hematuria. The database was reanalyzed using the Pre-Approval Safety Update cut off date. Only patients on 40 and 80 mg of rosuvastatin showed increases in serum creatinine (see appendix). On the 40 mg dose, 7/14=50% of the subjects had an increase of serum creatinine of > 20%, and out of these 2/14=14% had increases > 30%. On the 80 mg dose, 47/96=49% of the subjects had an increase of serum creatinine of >20%, and 29/96=30% had increases >30%. These data suggest that some patients with greater levels of proteinuria may progress to clinically relevant renal disease. It is not known if these increases in proteinuria, hematuria and serum creatinine would have resolved if rosuvastatin had been withdrawn or if they are unrelated to the use of this drug.

KIDNEY FAILURE/ INSUFFICIENCY IN PATIENTS ON 80 MG OF ROSUVASTATIN

Three cases of renal failure were associated with rhabdomyolysis during the open label extension trials. All patients were on 80 mg of rosuvastatin.

In addition two cases of renal failure and one case of renal insufficiency, all with unknown etiology were seen in the open label extensions and ongoing trials in patients receiving 80 mg of rosuvastatin.

A 70 y/o female taking 80 mg of rosuvastatin developed acute tubular necrosis on Day 15 of ongoing Trial 65. She was also taking rofecoxib, valsartan and amlodipine at the time of the adverse event. She presented with generalized body aches, right-sided abdominal pain radiating to the right flank, nausea and vomiting. A CT urogram showed no evidence of hydronephrosis or urinary calculi. At least 3 gallstones were seen in the gallbladder but the f/u HIDA scan was negative. Her serum creatinine was 3.4mg/dl and her urinalysis showed ≥300 protein, moderate occult blood, 0-1 granular casts and 1+ calcium oxalate crystals. She was treated with hydration and the study drug was discontinued. Her serum creatinine continued to rise to 9 mg/dl and she needed to be dialyzed. CPK went from 69 to 137 U/L (10-130 U/L) and myoglobin was 195 ηg/dl (19-51 ηg/dl), both only mildly elevated (not c/w rhabdomyolysis). Renal biopsy showed tubular degenerative changes with prominent vacuolization consistent with of acute tubular necrosis. Dialysis was stopped after about 2 months, and her last reported serum creatinine was 1.8 mg/dl.

A 69-y/o male developed chronic tubulo-interstitial nephritis with proteinuria, active urine sediment and a rise in serum creatinine after he had been on 80 mg of rosuvastatin for 1 year and 6 months. He had a h/o hospitalization at 8 years of age for inflammation of the kidneys, which resolved without known sequelae. (Probably, "minimal change disease" and unrelated to the present episode). During the 6-week dietary lead in he had one urine with no protein but active sediment? (Not described), and one urine with 1+ protein and some bacteria but no active sediment. He also had a normal baseline serum creatinine 1.1 mg/dl. At the one-year visit his creatinine was up to 1.6 mg/dl but a

urinalysis was not done. His urinalysis at the time of the renal biopsy was 1+ protein, 3+ blood and numerous granular casts with moderate numbers of renal tubular cells. Daily protein excretion was 1.6 g/day, serum creatinine was still 1.6 mg/dl. The biopsy showed moderate increase in fibrous tissue and occasional inflammatory cells in the interstitium, suggestive of a chronic process present for many months and resulting in gradual collagen deposition within the interstitium rather than an acute process. Rosuvastatin was officially stopped at 2 years (Dec. 14, 2001) to see if renal function improved. No f/u data has yet been submitted, but a possible causal relationship was confirmed for this event.

A 46 year old female with normal baseline lab values presented with nausea, anorexia, and fatigue and an abnormal urinalysis (proteinuria (30mg/dl), hematuria (small), coarse granular and hyaline casts in the urine sediment) after 31 days on rosuvastatin. Her creatinine went from 1.1 to 13.7 mg/dl. CPK was normal at 41 U/L. A renal scan showed multiple cystic masses in both kidneys. The drug was stopped. She responded to IV hydration and was discharged from the hospital with a serum creatinine of 3.8 mg/dl. Azithromycin and candesartan were possible contributing medications.

These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis. All cases occurred at the 80 mg dose which was also associated with the greatest renal effects in these clinical trials. 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.

SUMMARY/ RECOMMENDATIONS FOR RENAL-RELATED ADVERSE EVENTS

In addition to the known association of statins with rhabdomyolysis and elevation in liver transaminases, rosuvastatin appears to be responsible for the development of proteinuria associated with hematuria at doses greater than 40 mg.

The fact that proteinuria is associated with increases in beta-2-microglobulin and N-acetyl-beta-D-glucosaminidase suggesting tubular damage and that it appears to persist or get worse with time in about 30% of the patients suggests that it may be drug-related.

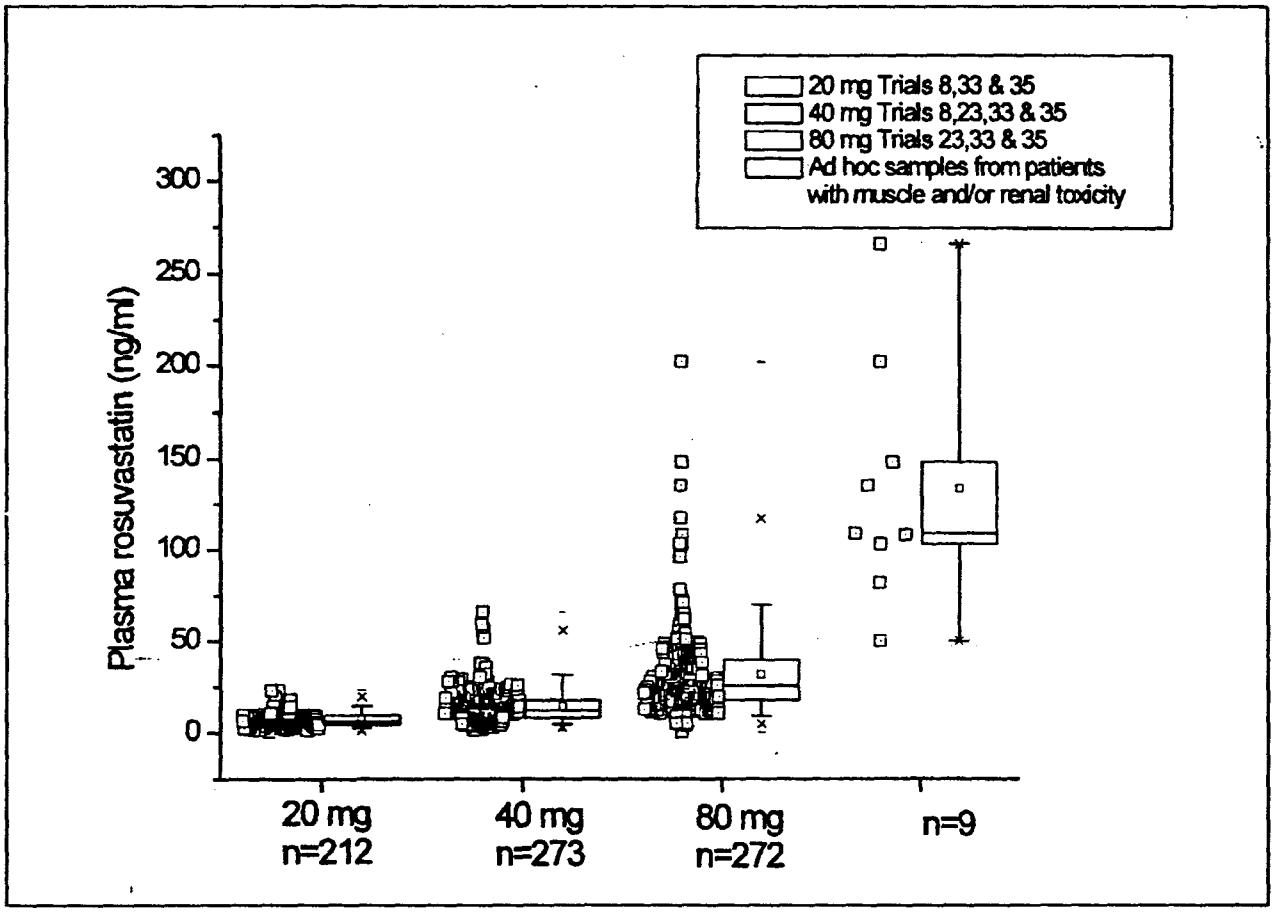
I would recommend regular urinalysis testing for patients taking more than 40 mg of rosuvastatin. For patients with persistent or progressive proteinuria, I would recommend withdrawing the drug or lowering the dose to see if the proteinuria resolves.

If additional studies show that there is a clear association with the use of 80 mg of rosuvastatin and the development of renal failure I would recommend against the marketing of this dose.

7.4.7. CORRELATION with SERIOUS ADVERSE EVENTS and SERUM ROSUVASATIN LEVELS

At the request of the agency, the sponsor submitted the limited data they had for rosuvastatin serum levels in patients with serious adverse events. Plasma concentrations for patients receiving 20, 40 or 80 mg of rosuvastatin in clinical trials 8, 23, 33, and 35 are show in Figure 7 below. These values are compared to nine plasma samples obtained from six patients with serious adverse events involving muscle and or renal toxicity.

Figure 7 **Steady State Plasma Rosuvastatin Levels**



Two of these patients had myopathy with peak CK values of 5,380 and 2,154, two patients had rhabdomyolysis with peak CK values of 16,280 and >20,000 and two patients had renal failure of unknown etiology with normal CK values.

There is no overlap in exposure among patients receiving 20 mg and those showing evidence of toxicity. 5/273 patients (<2%) at 40 mg and 33/272 (33%) at 80 mg had steady-state plasma concentrations above 50ng/ml, the lowest observed plasma concentration associated with toxicity in these six patients.

In conclusion, elevated serum rosuvastatin levels, > 50ng/ml, seen with daily doses of 40 mg or higher, were associated with severe adverse events such as rhabdomyolysis and renal failure. Although not seen in this small subset of patients, the potential also exists for higher unsafe serum levels of rosuvastatin at lower daily doses (such as 10 to 20 mg) as a consequence of drug-drug interactions (e.g. with cyclosporine or gemfibrozil) or use in patients with severe renal disease.

7.5. Miscellaneous Studies

None

7.6. Literature Review for Safety

Relevant literature references were described in the efficacy and safety summaries above. A list of these references is included in the appendix.

7.7. Post Marketing Surveillance-If Applicable

Not applicable

7.8. Safety Update

Information from the 4 month Safety Update 10/10/01 and Pre Approval Safety Update 1/20/02 were reviewed and included in the Safety Analysis, section 7.4., above.

7.9. Drug Withdrawal, Abuse and Overdose Experience

There is no prior history of drug abuse potential or withdrawal with other members of the statin drug group. No specific trials to test for drug abuse potential were performed.

There were no reported cases of overdoses during the rosuvastatin clinical trial program. The sponsor recommends that subject be treated for symptoms with supportive measures as required. There is no evidence that hemodialysis would significantly enhance the clearance of rosuvastatin.

7.10. Adequacy of Safety Testing

Rosuvastatin was effective at producing a significant reduction in the % change from baseline in total cholesterol, LDL-cholesterol, nonHDL-cholesterol and

ApoB at daily doses of 1 to 80 mg compared to placebo in patients with mixed dyslipidemia (Fredrickson Type IIA and IIB). The percent change from baseline in LDL-cholesterol ranged from 1 mg (-33%) to 80 mg (-65%). While the percent change from baseline in LDL-cholesterol appeared dose dependent, it was not linear. Most of the effect at LDL-cholesterol lowering was seen with just 1 mg of rosuvastatin (-33%). At the highest doses the curve flattens out and there is no clear difference between the effect seen at 40 and 80 mg (i.e. 2%).

Similarly in the heterozygous and homozygous familial hypercholesterolemia populations most of the effect at LDL-cholesterol lowering was seen at 20 mg (-47% and –19% respectively). There were only small additional decreases in LDL-cholesterol between 40 and 80 mg (i.e. –4% in heterozygous FH and +1% in homozygous FH).

In contrast to the efficacy data, which show most of the drug effect leveling off at the higher doses, most of the safety concerns including liver transaminase elevations (80 mg), myopathy and rhabdomyolysis (80 mg) and renal effects (40 to 80 mg) occur primarily at these higher doses. However, the exposure at doses of 20 and 40 mg was less than 1/3 the subject-years of exposure at 80 mg, so the safety of these doses cannot be adequately assessed. After drug approval the number of patients exposed to drug will greatly exceed that seen in these clinical trials and so even a low incidence of rhabdomyolysis or renal failure/insufficiency observed in this NDA may translate into a substantial number of cases post-marketing. In addition, it is not know at this time if the proteinuria, hematuria and increase in serum creatinine seen in a subset of patients taking rosuvastatin are reversible after the drug is discontinued. Therefore, it is not possible to assume routine urinalysis testing for patients taking 40 mg or more of rosuvastatin would result in adequate safety monitoring.

In conclusion, additional safety data at doses of 20 and 40 mg are necessary before these doses could be safely approved. The limited benefit in efficacy at the 80 mg dose does not out weigh the additional safety risk and approval of this dose is not recommended.

7.11. Labeling Safety Issues and Postmarketing Commitments

CONTRAINDICATIONS-The same as for all other statins:

- Hypersensitivity to any component of this medication
- Active liver disease or unexplained persistent elevations in liver transaminases
- Pregnancy and lactation

WARNINGS-

- Liver dysfunction-The incidence of persistent liver transaminase elevations should be listed for all approved doses. Liver enzyme monitoring should be recommended before and at 1 to 2 months following the initiation of therapy or dose escalation, and semiannually thereafter.
- Skeletal Muscle-The incidence and time to onset of rhabdomyolysis in the clinical trials should be listed. The correlation with lower creatinine clearance and frequency of rhabdomyolysis in the clinical trials should be mentioned. Conditions that can lead to elevated levels of the drug such as concomitant use of cyclosporine or gemfibrozil, severe renal or liver disease should be mentioned.
- Renal-The incidence of proteinuria, hematuria and increases in serum creatinine observed in the clinical trials should be listed. Monitoring of urinalysis and serum creatinine should be recommended for doses of 40 mg and higher if they are approved.

PRECAUTIONS-

- General-The increase in plasma concentrations of rosuvastatin in patients with severe renal impairment should be listed in the Warnings sections and not in the Precautions as proposed by the sponsor.
- Drug Interactions-This section should include information on drug interactions with cyclosporine, gemfibrozil, warfarin, and co-magaldrox.

8. Dosing, Regimen, and Administration Issues

Rosuvastatin was studied at single daily oral doses of 1, 2.5, 5, 10, 20, 40 and 80 mg. The sponsor proposed a starting dose of 10 mg daily with a dose range of 10 to 80 mg once daily for patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIA and IIB). The sponsor proposed the option of a start dose of 20 mg for patients with severe hypercholesterolemia (heterozygous or homozygous familial hypercholesterolemia), with a dose range up to 80 mg.

However, safety concerns at the higher doses of rosuvastatin preclude a recommendation for approval of doses greater than 5 mg at this time. A higher frequency of myopathy (1.1%) and rhabdomyolysis (0.5%) was observed in clinical trials with rosuvastatin than had previously been reported for any of the currently approved statins. Most cases of myopathy (14/19=74%) and all six cases of rhabdomyolysis occurred at the highest dose, 80 mg. A few cases of myopathy were seen at doses of 5 to 20 mg but they were confounded by a history of vigorous exercise or physical injury. The level of exposure at

doses of 5 and 10 mg was similar to that at 80 mg but no cases of rhabdomyolysis were seen at these lower doses. However the exposure at doses of 20 and 40 mg was less than 1/3 the subject-years of exposure at 80 mg, so the safety of these doses is uncertain. After drug approval the number of patients exposed to drug will greatly exceed that seen in these clinical trials and so even a low incidence of rhabdomyolysis observed in this NDA may translate into a substantial number of cases post marketing. Therefore, since it is known that this drug is associated with a serious and potentially life threatening adverse event, this medical reviewer believes that it is prudent to limit initial exposure to this drug to multiples of the no adverse event level to provide a safety margin. Since the highest dose with an adequate safety exposure was 10 mg, I would recommend initial approval of doses up to 5 mg only. As the sponsor collects adequate long-term safety data at doses of 20 and 40 mg, approvability of doses of 10 and 20 mg could be reconsidered.

Approvability of the daily dose of 40 mg would also depend on further clinical trials to show that the renal effects are reversible and not associated with progression in renal insufficiency and elevation in serum creatinine levels.

Approval of 80 mg is not recommended as the risks of renal disease, myopathy and rhabdomyolysis do not out weigh the benefits of a marginal decrease of 3-5% in LDL-cholesterol compared to 40 mg of rosuvastatin.

The maximum recommended daily dose for rosuvastatin in patients taking cylcosporine or with severe renal or severe hepatic disease is [redacted] Approvability of higher doses will depend on the safety profile of the 20 and 40 mg doses in ongoing clinical trials.

The maximum recommended daily dose of rosuvastatin in combination with gemfibrozil is [redacted] Approvability of higher doses will depend on the safety profile of the 20 and 40 mg doses in ongoing clinical trials.

9. Use in Special Populations

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Analyses

9.1.1. EFFICACY

AGE/GENDER-

Rosuvastatin was effective at lowering LDL-cholesterol in both men and women and in older and younger populations. The 10 mg dose appeared to be slightly more effective in women and in older patients (>65 y/o) than the 5 mg dose. Postmenopausal women showed the greatest response to the 10 mg dose.

RACE/ETHNIC ORGIN-

Rosuvastatin appears to be effective in Caucasians, Blacks, Hispanics, and Asians. However, the number of patients in the non-Caucasian subgroups is too small to

draw any meaningful comparisons. A PK study in healthy Japanese volunteers showed an approximately two-fold increase in AUC and Cmax for rosuvastatin relative to Western counterparts (see section 2.6.).

SPECIAL POPULATIONS-
Rosuvastatin showed a trend towards greater LDL-cholesterol reduction with worsening renal function. In contrast, rosuvastatin showed a trend towards lower LDL-cholesterol reduction with worsening liver function.

9.1.2. SAFETY

GENDER-
Adverse events occurred slightly more frequently in women in the All Controlled Pool 66.7% than in men 60.9%. The overall incidence and profile of adverse events was similar in the total rosuvastatin population, except that pain (7.8% vs. 5.6%), headache (8.2% vs. 5.2%), myalgia (6.0% vs. 4.3%), abdominal pain (5.1% vs. 3.3%), nausea (5.3% vs. 2.6%), and dizziness (3.8% vs. 1.8%) were slightly more frequent in women. The overall incidence and profile of adverse events was similar in pre and postmenopausal women.

AGE
The overall incidence and profile of adverse events was similar in patients ≥ 65 years of age and those < 65 years of age. The overall incidence and profile of adverse events was similar in the small group of patients > 75 years of age (N=104) given rosuvastatin, except that myalgia (9.6% vs. 4.9%), diarrhea (6.7% vs. 4.2%), dizziness (5.8% vs. 2.6%), constipation (5.8% vs. 2.5%), dyspepsia (5.8% vs. 2.5%), ALT elevations (5.8%-2.1%), rhinitis (4.8%-2.1%), and CK elevations (5.8%-1.9%) were slightly more frequent in these elderly patients. These data suggest that elderly patients, > 75 years of age, should be followed more closely for possible gastrointestinal, hepatic and musculoskeletal related adverse events.

RACE/ETHINIC ORGIN
The total number of patients in each of the ethnic subgroups given rosuvastatin (Hispanic N=48, Black N=86, Asian N=31, Indian/Eskimo N=24) was too small to adequately compare the overall incidence and profile of adverse events in these groups relative to Caucasians (N=2390). But there is a suggestion that CK elevations were higher in these subgroups (Hispanic 4.2%, Black 7.0%, Asian 6.5% vs. Caucasian 1.8%) and that Alt elevations were higher in Hispanics 8.3% compared to the other groups (Caucasians 2.1%, Blacks, 2.3%, Asians 3.2%).

COMORBIDITIES

The overall incidence and profile of adverse events was similar in patients with diabetes compared to nondiabetics, in patients with hypertension compared to nonhypertensive patients, and in patients with overt coronary heart disease compared to those with out coronary heart disease in subjects given rosuvastatin in the All Controlled Pool.

Patients with baseline elevations in transaminases were more likely to have ALT >3xULN (6.8% vs. 1.7%), abdominal pain (6.2% vs. 3.9%) and asthenia (6.5% vs. 3.9%) on rosuvastatin in the All Controlled Pool. These data suggest that patients with baseline transaminase abnormalities should have liver transaminases monitored more closely while taking rosuvastatin.

Patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) had an overall incidence and profile of adverse events which was similar to patients with normal renal function (>80ml/min) on rosuvastatin. Patients with moderate renal impairment (creatinine clearance <30ml/min) were more likely to complain of myalgia, diarrhea, asthenia, nausea, dizziness, and constipation compared to patients with normal renal function on rosuvastatin, but it is possible that this maybe due to consequences of their renal disease. These patients also were more likely to have CK elevations compared to patients with normal renal function, or mild renal impairment (5.1% vs. 2.2% or 1.4%), which may be drug related.

9.2. [redacted]

9.3. **Comments on Data Available or Needed in Other Populations (Renal or Hepatic Compromised Patients or Use in Pregnancy)**

Two clinical studies in renal or hepatic compromised patients were submitted in this NDA. One was a 14 day open label PK study performed in patients with renal impairment (6 severe, 4 moderate, 8 mild and 4 on dialysis), and one was a 14 day open label PK study performed in patients with alcohol-induced cirrhosis (18 subjects). Data from these trials on short-term efficacy and safety in patients with impaired hepatic or renal function was previously summarized in sections 2.6. and 9.1. There is no long-term data for use of rosuvastatin in these populations, so the long-term safety and efficacy of rosuvastatin in these populations is unknown.

However, there is reason to suspect from the clinical trials in this NDA that patients with renal disease may have an increased safety risk during long term use. The Cmax and AUC (0-24) for rosuvastatin was 3 fold higher in patients with severe renal impairment, and serum rosuvastatin levels were significantly higher in patients with serious adverse events such as myopathy, rhabdomyolysis and renal failure (section 7.4.7.). In addition, in the open label long-term extension trials, rhabdomyolysis was seen in patients with a much lower mean baseline creatinine clearance (59 ±13ml/min) compared to all randomized patients (80±24ml/min). Taken together these data suggest that patients with impaired renal function may be at increased risk of higher serum rosuvastatin levels and rhabdomyolysis.

The long-term safety profile in patients with impaired renal and liver function needs to be determined with future clinical trials.

No pregnant patients were studied during these clinical trials. Statins are currently contraindicated for use in pregnancy and lactation.

10. Conclusions, Recommendations and Labeling

10.1. Conclusions Regarding Safety and Efficacy

Rosuvastatin is effective at lowering LDL-cholesterol, total cholesterol, non HDL-cholesterol and ApoB at daily doses of 1 to 80 mg.

However, several safety concerns have been identified in this review which will limit the approvability of this entire dose range. Specifically six cases of rhabdomyolysis were seen at 80 mg and insufficient safety data at 20 and 40 mg limit the ability to adequately assess safety at these doses. Even at the 10 mg dose, which appears safe with an exposure of 1482 patient years, it is possible that cases of rhabdomyolysis may occur as many more patients are exposed to the drug after it is approved. In particular, cases may occur at this dose in the presence of drugs or conditions, which would increase rosuvastatin drug levels.

Cases of proteinuria and hematuria associated with an increase in serum creatinine have been seen at 40 and 80 mg doses. The sponsor has not adequately clarified these renal findings and it is unknown at this time if these symptoms are reversible or, if left untreated, can progress to renal failure.

Drug-drug interactions with cyclosporine or gemfibrozil or use in patients with severe renal disease could result in higher potentially unsafe rosuvastatin levels in some patients even. These conditions will require lower starting and lower maximal daily doses of rosuvastatin.

10.2. Recommendations on Approvability

It is recommended that daily doses of 1, 2.5 and 5 mg of rosuvastatin be approved for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB), once any outstanding chemistry issues with respect to these doses are resolved.

Approvability of higher doses would depend on the results of additional safety data and evidence that the renal effects are reversible and do not progress to renal failure.

10.3. Labeling

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11. Appendix

11.1. Other Relevant Materials

URINE BLOOD INCREASES IN SUBJECTS WITH AN INCREASE IN URINE PROTEIN TO ++ OR GREATER FROM BASELINE [1] TO AVAILABLE URINALYSIS VISIT BY DOSE: ALL PHASE II/III CONTROLLED AND UNCONTROLLED CLINICAL TRIALS

DOSE AT URINALYSIS VISIT	NUMBER OF SUBJECTS WITH URINALYSIS RESULTS	INCREASE IN URINE PROTEIN TO ++ OR GREATER		INCREASE IN URINE BLOOD ASSOCIATED WITH INCREASE IN URINE PROTEIN TO ++ OR GREATER									
				INCREASE IN URINE BLOOD ASSOCIATED WITH INCREASE IN URINE PROTEIN TO ++ OR GREATER		CREATININE INCREASED > 30%		CREATININE INCREASED >20-30%		CREATININE INCREASED >10-20%		CREATININE INCREASED >0-10%	
	N	N	%	N	%	N	%	N	%	N	%	N	%
ZD4522 5 MG	852	15	1.8	5	0.6	1	0.1	0	0.0	1	0.1	2	0.2
ZD4522 10 MG	1258	20	1.6	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
ZD4522 20 MG	796	10	1.3	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
ZD4522 40 MG	997	34	3.4	14	1.4	2	0.2	5	0.5	2	0.2	1	0.1
ZD4522 80 MG	1129	149	13.2	96	8.5	29	2.6	18	1.6	14	1.2	13	1.2

[1] baseline is defined as the baseline from the controlled trial.

note*: denominators for percentages within a row are the number of subjects with urinalysis results within the dose.

note**: if baseline urine blood and/or urine protein values are unknown, these values are assumed to be 'none'.

NOTE*: 6 OUT OF 14 PATIENTS WITH PROTEINURIA AND HEMATURIA ON THE ROSUVASTATIN 40 MG DOSE HAD MISSING CREATININE DATA. DATA FROM THE NEXT AVAILABLE VISIT WAS USED FOR 5 OF THESE PATIENTS (NO FURTHER CREATININE DATA WAS AVAILABLE FOR ONE PATIENT). HOWEVER, AT THE NEXT AVAILABLE VISIT, ALL FIVE PATIENTS WERE ON THE 80 MG DOSE. THE CREATININE DATA FROM THESE 5 PATIENTS WAS AS FOLLOWS: CR > 30% - ONE PATIENT, CR >20-30% - ONE PATIENT, CR >0-10% - ONE PATIENT, CR < 0% 2 PATIENTS.

note*: 7 out of 96 patients with proteinuria and hematuria on the rosuvastatin 80 mg dose had missing creatinine data.

11.2. Detailed Labeling Changes or Revised Drug Label

The label needs to be revised by the sponsor to include the labeling recommendations listed in section 10.3. A detailed analysis of the labeling changes will be preformed when the label is resubmitted.

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