Epidemiological studies have established that high LDL-C and TG, and low HDL-C are risk factors for cardiovascular disease.

The involvement of LDL-C in atherogenesis has been well documented. LDL-C is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver. Rosuvastatin produces its lipid-modifying effects in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

The phase 3 CRESTOR phase 3 dose ranging study of 2,239 patients with Type IIa and IIb hypercholesterolaemia, intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to the lowering of non-HDL-C (ie all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/Apo-A-I ratio.

**PHARMACOKINETICS**

**Absorption**

Peak plasma levels occur 5 hours after dosing. Absorption increases linearly over the dose range. Absolute bioavailability is 20%. The half-life is 19 hours and does not increase with increasing dose. There is minimal accumulation on repeated once daily dosing.

**Distribution**

Volume of distribution of rosuvastatin at steady state is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

**Clinical Efficacy**

A therapeutic response (reduction in LDL-C) to rosuvastatin is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

**Special Populations**

*Race:* A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**CLINICAL TRIALS**

**Hypercholesterolaemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidaemia**

The clinical trial program showed that CRESTOR is effective in a wide variety of patient populations regardless of race, age or sex, and in special populations such as diabetics or patients with familial hypercholesterolaemia. The Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, or pravastatin (Figure 1 and Table 1). The primary endpoint for this study was the percent change from baseline in LDL-C at week 6.
Figure 1. Percent LDL-C Change by Dose of CRESTOR, Atorvastatin, Simvastatin and Pravastatin at Week 6 in Patients with Type I/IIb Dyslipidaemia.

Box plots are a representation of the 25th, 50th, and 75th percentile values, with whiskers representing the 10th and 90th percentile values. Mean baseline LDL-C: 189 mg/dL.

Table 1. LS Mean% change in LDL-C from Baseline to Week 6 for each statin treatment group. N=number of patients at each dose of each statin.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Daily Dose</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>158</td>
<td>-31 (38, 35)</td>
<td>154</td>
<td>-43 (45, 41)</td>
<td>156</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>160</td>
<td>-26 (22, 26)</td>
<td>164</td>
<td>-24 (26, 22)</td>
<td>161</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>165</td>
<td>-39 (30, 36)</td>
<td>162</td>
<td>-35 (37, 33)</td>
<td>158</td>
</tr>
</tbody>
</table>

*Rosuvastatin 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10 mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg (p<0.002).

†Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg (p<0.002).

‡Rosuvastatin 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg (p<0.002).

§Corresponding standard errors are approximately 1.00.

The percent change from baseline in LDL-C at week 6 is shown in Figure 2 below.

Figure 2. Mean (LS mean) Percent Change from Baseline in HDL-C to Week 6

The mean percent change in HDL-C from baseline to Week 6 for each statin treatment group represented in Figure 2 is summarised with 95% CI in Table 2.

Table 2. LS Mean% change in HDL-C from Baseline to Week 6 for each statin treatment group. N=number of patients at each dose of each statin.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Daily Dose</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>156</td>
<td>8 (6, 9)</td>
<td>160</td>
<td>9 (8, 11)</td>
<td>157</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>158</td>
<td>6 (4, 7)</td>
<td>154</td>
<td>5 (3, 7)</td>
<td>156</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>160</td>
<td>3 (2, 5)</td>
<td>164</td>
<td>4 (3, 6)</td>
<td>161</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>165</td>
<td>5 (4, 7)</td>
<td>162</td>
<td>6 (4, 8)</td>
<td>158</td>
</tr>
</tbody>
</table>

Table 3 below summarises the pooled lipid variable data for rosuvastatin 5 mg and 10 mg from 5 Phase III efficacy trials (Trials 24-28).

Table 3. Pooled lipid variable data for rosuvastatin at 12 weeks from Trials 24-28. The data is presented as both the mean% and mean absolute change (mg/dL) from baseline with 95% CI for each lipid variable. N=number of patients at each dose of CRESTOR.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Treatment Daily Dose</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean (95%CI)</td>
<td>N</td>
<td>Mean (95%CI)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-29 (30, 39)</td>
<td>-41 (32, 40)</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>-29 (30, 29)</td>
<td>-81 (33, 79)</td>
<td></td>
</tr>
<tr>
<td>HLD-C</td>
<td>4 (-3, 5)</td>
<td>9 (4, 9)</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>-33 (37, 29)</td>
<td>-37 (23, 37)</td>
<td></td>
</tr>
<tr>
<td>NonHDL-C</td>
<td>-38 (39, -37)</td>
<td>-50 (38, -42)</td>
<td></td>
</tr>
<tr>
<td>ApoB</td>
<td>-33 (33, 33)</td>
<td>-16 (15, -16)</td>
<td></td>
</tr>
<tr>
<td>ApoA-I</td>
<td>6 (5, 7)</td>
<td>8 (4, 8)</td>
<td></td>
</tr>
</tbody>
</table>

Heterozygous Familial Hypercholesterolaemia

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given CRESTOR 20 mg to 80 mg in a force-titration design. All doses of CRESTOR showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to 40 mg (12 weeks of treatment), LDL-C was reduced by 53%.

Hypertriglyceridaemia (Fredrickson Type IIb & IV)

In a double blind, placebo controlled dose response study in patients with baseline TG levels from 273 to 817 mg/dL, CRESTOR given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 4).
Homozous Familial Hypercholesterolaemia

In a force-titration open label study, 42 patients with homozous familial hypercholesterolaemia were evaluated for their response to CRESTOR 20-40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction by week 12 (considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose and 30% at the 40 mg dose. Of the 13 patients with an LDL-C reduction of less than 15%, 3 had no response or an increase in LDL-C.

High Risk Hypercholesterolaemic Patients

In a 26 week double-blind forced titration study, 871 high risk hypercholesterolaemic patients with established CHD or multiple risk factors for CHD, were randomised to receive either rosuvastatin or atorvastatin. Patients in the rosuvastatin arm were titrated to 40 mg, while in the atorvastatin arm patients were titrated to 80 mg. The primary objective of the study was to compare rosuvastatin 40 mg with atorvastatin 80 mg in high risk patients, by measuring the percentage change in LDL-C from baseline to Week 8. Table 5 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

Table 5: Summary of the mean percentage changes in lipid and lipoprotein variables in high risk hypercholesterolaemic patients after 8 weeks treatment with either rosuvastatin 40 mg or atorvastatin 80 mg.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean % change</th>
<th>Mean % change</th>
<th>Difference in % mean % changes</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-55.89</td>
<td>-52.18</td>
<td>-3.71</td>
<td>-5.61 to -1.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>9.58</td>
<td>4.35</td>
<td>5.23</td>
<td>3.04 to 7.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC</td>
<td>-40.40</td>
<td>-39.27</td>
<td>-1.13</td>
<td>-2.63 to 0.36</td>
<td>0.138</td>
</tr>
<tr>
<td>NonHDL-C</td>
<td>-50.75</td>
<td>-48.27</td>
<td>-2.48</td>
<td>-4.25 to -0.72</td>
<td>0.006</td>
</tr>
<tr>
<td>ApoB</td>
<td>-44.64</td>
<td>-42.29</td>
<td>-2.35</td>
<td>-4.17 to -0.52</td>
<td>0.012</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>4.20</td>
<td>-0.47</td>
<td>4.67</td>
<td>2.71 to 6.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>-22.21</td>
<td>-27.02</td>
<td>4.81</td>
<td>1.10 to 8.53</td>
<td>0.011</td>
</tr>
</tbody>
</table>

* Mean % change from baseline

** 95% confidence interval for the difference between the least squares means

† p<0.05 was statistically significant

‡ statistically significant in favour of atorvastatin

§ ns = not significant

RSV = rosuvastatin; ATV = atorvastatin; ls = least squares
Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (>65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy increased at doses of rosuvastatin above the recommended dosage range.

Consequently: 1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism. 2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. 3. The 40 mg dose of rosuvastatin is reserved only for those patients who are not adequately controlled at the 20 mg dose, considering their level of LDL-C and overall CV risk profile. 4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporin (see INTERACTIONS). The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided (see DOSAGE AND ADMINISTRATION and INTERACTIONS). 5. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances that increase rosuvastatin drug levels (see PHARMACOLOGY: Special populations, and PRECAUTIONS: Renal insufficiency). 6. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, or uncontrolled seizures).

In rosuvastatin trials there was no evidence of increased skeletal muscle effects when rosuvastatin was dosed with any concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with niacin, niacinopropion, nicoxacin, niacin, azole antifungals, macrolide antibiotics and fibric acid derivatives including gemfibrozil (see ADVERSE REACTIONS, INTERACTIONS and DOSAGE AND ADMINISTRATION).

Special Patient Populations

Renal insufficiency
Pharmacokinetic evaluation in subjects with varying degrees of renal impairment, determined that mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl <30 mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers (see DOSAGE AND ADMINISTRATION).

Hepatic dysfunction
Pharmacokinetic evaluation in subjects with varying degrees of hepatic impairment determined that there was no evidence of increased exposure to rosuvastatin other than in 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores (see DOSAGE AND ADMINISTRATION).

Race
The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

Age and Sex
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Use in pregnancy
Category D is defined as drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Cholesterol and other products of cholesterol biosynthesis are essential components for foetal development, including synthesis of steroids and cell membranes. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis, rosuvastatin is contraindicated during pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Use in Lactation
The safety of rosuvastatin while breast-feeding has not been established. It is not known if rosuvastatin is excreted into human milk, but a study in rats showed that unchanged drug and metabolites are excreted in milk at concentrations up to 3 times greater than those in maternal plasma. Therefore rosuvastatin is contraindicated in breastfeeding women.

The results of animal and in vitro studies of rosuvastatin are summarised below.

Carcinogenicity
Oral administration of rosuvastatin for 2 years to rats and mice increased the development of benign uterine stromal polyps in both species and malignant uterine sarcomas and adenosarcomas in rats. Systemic concentrations of rosuvastatin (AUC) at the no-effect dose for benign and malignant uterine tumours in either species were lower than or similar to those expected in humans taking 40 mg/day rosuvastatin.

Genotoxicity
Rosuvastatin showed no evidence for mutagenic activity (in vitro assays of reverse mutation in bacterial cells and forward mutation in mammalian cells) or clastogenic activity (in vitro assay in mammalian cells and in vivo in the mouse micronucleus test).

There have been no adequate studies investigating the potential carcinogenic or genotoxic activity of the main human metabolite of rosuvastatin, N-desmethyl rosuvastatin.

Effects on fertility
In 1 of 3 monkeys treated with rosuvastatin PO at 30 mg/kg/day for 6 months degenerative changes in the testicular epithelium were seen. The no-effect dose of 10 mg/kg/day was associated with rosuvastatin plasma concentrations (AUC) similar to those expected in humans taking 40 mg rosuvastatin daily. Rosuvastatin had no effect on male or female fertility when administered to rats at PO doses of 50 mg/kg/day (systemic rosuvastatin concentrations (AUC) 4.8-6.6 times those expected in humans). The main human metabolite of rosuvastatin, N-desmethyl rosuvastatin, has not been assessed for activity in rat fertility studies.

Animal Studies
Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/ day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons).

Effects on ability to drive and operate machinery
Pharmacological testing revealed no evidence of a sedative effect of rosuvastatin. From the safety profile, rosuvastatin is not expected to adversely affect the ability to drive or operate machinery.
Interactions with other medicines

Warfarin and Other Coumarin Anticoagulants
Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant increases in INR (≥4, baseline 2–3). In patients taking coumarin anticoagulants and rosuvastatin concurrently, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Cyclosporin
Co-administration of rosuvastatin with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state AUCmax increased up to 7-fold over that seen in healthy volunteers administered the same dose. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin (See DOSAGE AND ADMINISTRATION).

Digoxin
Co-administration of digoxin with rosuvastatin resulted in no change to digoxin plasma concentrations.

Fenofibrate
Co-administration of fenofibrate with rosuvastatin resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate.

Gemfibrozil
Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC0-∞. This increase is considered to be clinically significant (see DOSAGE AND ADMINISTRATION).

Protease Inhibitors
Increased systemic exposure to rosuvastatin has been observed in subjects receiving CRESTOR with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the use of CRESTOR in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating CRESTOR doses in patients treated with protease inhibitors.

Antacids
Simultaneous administration of rosuvastatin and an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Cytochrome P450 enzymes
In vitro and in vivo data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketocazole, erythromycin, itraconazole).

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin. Erythromycin: Co-administration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and Cmax of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole: Itraconazole (200 mg twice daily for 5 days) resulted in a 39% and 28% increase in AUC and Cmax of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole: Co-administration of fluconazole (200 mg twice daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Oral contraceptives
Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively. This increase is not considered clinically significant.

Other medications
In clinical studies, rosuvastatin was co-administered with anti-hypertensive agents and anti-diabetic agents. These studies did not produce any evidence of clinically significant adverse interactions.

ADVERSE EFFECTS
Rosuvastatin is generally well tolerated. The adverse events seen with rosuvastatin are generally mild and transient. In controlled clinical trials less than 4% of rosuvastatin treated patients were withdrawn due to adverse events. This withdrawal rate was comparable to that reported in patients receiving placebo.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare: ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Central Nervous System
Common: dizziness

Gastrointestinal
Common: constipation, nausea, abdominal pain
Rare: pancreatitis

Musculoskeletal
Common: myalgia, asthenia
Rare: myopathy (including myositis) and rhabdomyolysis

Skin
Uncommon: pruritus, rash, urticaria
Rare: hypersensitivity reactions including angioedema

Miscellaneous
Common: headache

Laboratory effects
As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to increase with increasing dose.

Skeletal muscle effects
Rare cases of rhabdomyolysis, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin.

Post marketing Experience
In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin:

Musculoskeletal disorders
Very rare: arthralgia

Hepatobiliary disorders
Rare: increased hepatic transaminases

Nervous system disorder
Very rare: memory loss
DOSAGE AND ADMINISTRATION

Prior to initiating CRESTOR, the patient should be placed on a standard cholesterol-lowering diet. The recommended starting dose is 5 mg or 10 mg once per day both in statin naïve patients and in those switched from another HMG-CoA reductase inhibitor. The choice of starting dose should take into account the individual patient’s cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below).

A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of rosuvastatin is 20 mg once per day. A dose of 40 mg once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg must not be exceeded in any patient taking rosuvastatin. Specialist supervision should be considered when the dose is titrated to 40 mg.

CRESTOR may be given at any time of the day, with or without food.

Dosage in Asian patients

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20 mg once daily (see PHARMACOKINETICS and PRECAUTIONS).

Dosage in patients taking other drugs

Cyclosporin
In patients taking ciclosporin, CRESTOR dosage should be limited to 5 mg once daily (see INTERACTIONS).

Gemfibrozil
Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant CRESTOR and gemfibrozil (see INTERACTIONS). If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily.

Use in children

The safety and efficacy of rosuvastatin in children has not been established. Use of this agent for the treatment of homozygous familial hypercholesterolaemia in this age group is not recommended.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca
AstraZeneca Pty Ltd
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NSW 2113

POISON SCHEDULE OF THE MEDICINE S4

Prescription only medicine (Schedule 4)

DATE OF APPROVAL

Date of TGA Approval: 2 September 2008
Date of Most Recent Amendment: 3 April 2009
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