CRESTOR®
rosuvastatin

PBS Dispensed Price: 5 mg $45.75; 10 mg $62.50; 20 mg $86.21; 40 mg $120.19

PBS Information: Restricted Benefit.
For use in patients that meet the criteria set out in the General Statement for Lipid-lowering Drugs.

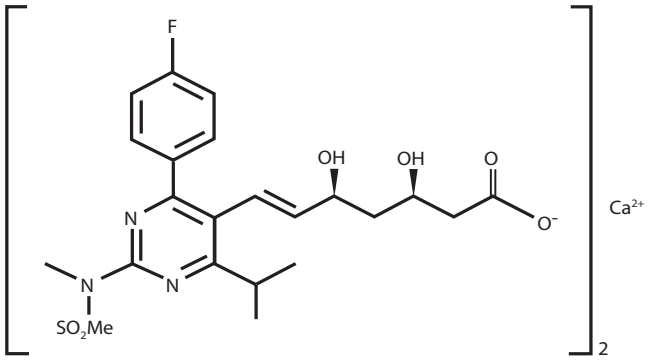
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in CRESTOR® is rosuvastatin, as rosuvastatin calcium. The chemical name is bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl] (3R, 5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

CRESTOR, rosuvastatin calcium, is a HMG-CoA reductase inhibitor for the treatment of dyslipidaemia.

The chemical structure of rosuvastatin calcium is:



CAS Number: 147098-20-2 Molecular formula: $(C_{22}H_{27}FN_3O_6S)_2Ca$
Molecular weight: 1001.14

DESCRIPTION

Rosuvastatin calcium is an amorphous solid, which is slightly soluble in water (7.8 mg/mL at 37°C) and has a pKa of 4.6. Rosuvastatin calcium is the (3R,5S,6E) enantiomer.

CRESTOR film-coated tablets contain 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin (as calcium). The tablets also contain the following inactive ingredients: crospovidone, lactose, microcrystalline cellulose, calcium phosphate, magnesium stearate, glycerol triacetate, hypromellose and titanium dioxide. The 5 mg tablets also contain iron oxide yellow CI77492 whereas the 10 mg, 20 mg and 40 mg tablets contain iron oxide red CI77491.

PHARMACOLOGY

Rosuvastatin is a fully synthetic competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) 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.

High density lipoprotein (HDL), which contains ApoA-I, is involved, amongst other functions, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C and TG, and low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease.

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 nonHDL-C (ie all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-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.

Metabolism

Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion

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

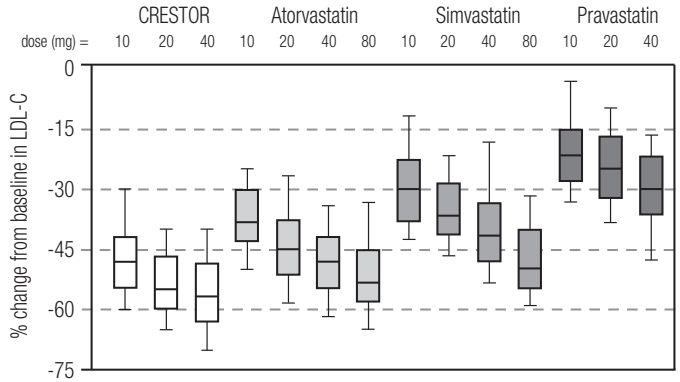
Hypercholesterolaemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidaemia (Fredrickson Type IIa and IIb)

CRESTOR reduces total-C, LDL-C, ApoB, nonHDL-C, and TG, and increases HDL-C, in patients with hypercholesterolaemia 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.

Active-Controlled Study: CRESTOR was compared with the HMG-CoA reductase inhibitors atorvastatin, simvastatin, and pravastatin in a multicenter, open-label, dose ranging study of 2,239 patients with Type IIa and IIb hypercholesterolaemia. After randomization, patients were treated for 6 weeks with a single daily dose of either CRESTOR, 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 IIa/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.

	Treatment Daily Dose							
Treatment	10 mg		20 mg		40 mg		80 mg	
	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)
Rosuvastatin	156	-46* (-48, -44)	160	-52† (-54, -50)	157	-55‡ (-57, -53)	-	-
Atorvastatin	158	-37 (-39, -35)	154	-43 (-45, -41)	156	-48 (-50, -46)	165	-51 (-53, -49)
Pravastatin	160	-20 (-22, -18)	164	-24 (-26, -22)	161	-30 (-32, -28)	-	-
Simvastatin	165	-28 (-30, -26)	162	-35 (-37, -33)	158	-39 (-41, -37)	163	-46 (-48, -44)

* 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)

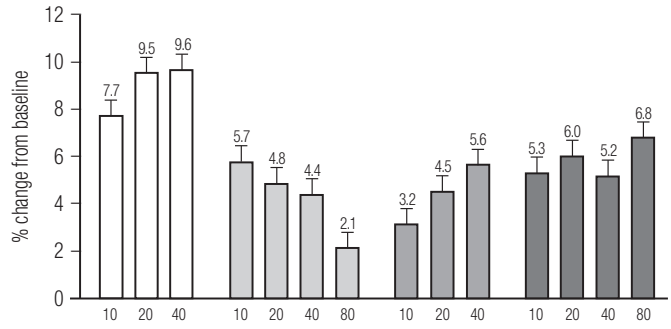
† Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)

‡ 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 HDL-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



p<0.002 Rosuvastatin 10 mg vs Pravastatin 10 mg.

p<0.002 Rosuvastatin 20 mg vs Atorvastatin 20 mg, 40 mg, 80 mg; Pravastatin 20 mg, 40 mg; Simvastatin 40 mg.

p<0.002 Rosuvastatin 40 mg vs Atorvastatin 40 mg, 80 mg; Pravastatin 40 mg; Simvastatin 40 mg.

Data presented as LS means±SE

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.

	Treatment Daily Dose							
Treatment	10 mg		20 mg		40 mg		80 mg	
	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)	N	Mean (95%CI)
Rosuvastatin	156	8 (6, 9)	160	9 (8, 11)	157	10 (8, 11)	-	-
Atorvastatin	158	6 (4, 7)	154	5 (3, 7)	156	4 (3, 6)	165	2 (0, 4)
Pravastatin	160	3 (2, 5)	164	4 (3, 6)	161	6 (4, 7)	-	-
Simvastatin	165	5 (4, 7)	162	6 (4, 8)	158	5 (4, 6)	163	7 (5, 8)

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.

Dose	Rosuvastatin 5 mg N = 630		Rosuvastatin 10 mg N = 615	
	% change (95% CI)	Absolute change mg/dL (95% CI)	% change (95% CI)	Absolute change mg/dL (95% CI)
LDL-C	-41 (-42, -40)	-78 (-80, -76)	-47 (-48, -46)	-88 (-90, -86)
TC	-29 (-30, -29)	-81 (-83, -79)	-33 (-34, -32)	-91 (-93, -88)
HDL-C	8 (7, 9)	4 (3, 4)	9 (8, 10)	4 (4, 5)
TG	-16 (-18, -14)	-33 (-37, -29)	-20 (-21, -18)	-37 (-41, -34)
NonHDL-C	-38 (-39, -37)	-85 (-87, -82)	-43 (-44, -42)	-95 (-98, -93)
ApoB	-33 (-33, -32)	-59 (-61, -57)	-37 (-38, -36)	-66 (-68, -64)
ApoA-I	6 (5, 7)	8 (6, 9)	7 (6, 8)	9 (7, 10)

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).

Table 4. Dose-Response in Patients With Primary Hypertriglyceridaemia Over 6 Weeks Dosing Median (Min, Max) Percent Change From Baseline

Dose	Placebo N=26	Rosuvastatin 5 mg N=25	Rosuvastatin 10 mg N=23	Rosuvastatin 20 mg N=27	Rosuvastatin 40 mg N=25
TG	1 (-40,72)	-21 (-58,38)	-37 (-65,5)	-37 (-72,11)	-43 (-80,-7)
NonHDL-C	2 (-13,19)	-29 (-43,-8)	-49 (-59,-20)	-43 (-74,-12)	-51 (-62,-6)
VLDL-C	2 (-36,53)	-25 (-62,49)	-48 (-72,14)	-49 (-83,20)	-56 (-83,10)
Total-C	1 (-13,17)	-24 (-40,-4)	-40 (-51,-14)	-34 (-61,-11)	-40 (-51,-4)
LDL-C	5 (-30,52)	-28 (-71,2)	-45 (-59,7)	-31 (-66,34)	-43 (-61,-3)
HDL-C	-3 (-25,18)	3 (-38,33)	8 (-8,24)	22 (-5,50)	17 (-14,63)

Homozygous Familial Hypercholesterolaemia

In a force-titration open label study, 42 patients with homozygous 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.

Variable	Mean % change* RSV 40 mg N=432	Mean % change* ATV 80 mg N=439	Difference in ls mean % changes	95%CI§	p value‡
LDL-C	-55.89	-52.18	-3.71	-5.61 to –1.82	<0.001
HDL-C	9.58	4.35	5.23	3.04 to 7.43	<0.001
TC	-40.40	-39.27	-1.13	-2.63 to 0.36	0.138[b]
NonHDL-C	-50.75	-48.27	-2.48	-4.25 to –0.72	0.006
ApoB	-44.64	-42.29	-2.35	-4.17 to –0.52	0.012
ApoA-I	4.20	-0.47	4.67	2.71 to 6.63	<0.001
TG	-22.21	-27.02	4.81	1.10 to 8.53	0.011[a]

* Mean % change from baseline

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

‡ $p<0.05$ was statistically significant

[a] statistically significant in favour of atorvastatin

[b] ns = not significant

RSV = rosuvastatin; ATV = atorvastatin; ls = least squares

Ultrasonographic study in carotid atherosclerosis

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/l (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness, which is measured using B-mode ultrasonography) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years, using a 5:2 randomisation split (rosuvastatin:placebo).

Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; $p<0.0001$]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year ($p<0.0001$)) for placebo.

There was an absence of disease progression in 52.1% of patients in the rosuvastatin group compared to 37.7% of patients in the placebo group ($p=0.0002$). A multi-level fixed effects regression model was used for the statistical analysis and the cited results were calculated using the ITT population.

No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of CRESTOR 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see DOSAGE AND ADMINISTRATION).

INDICATIONS

CRESTOR is indicated as an adjunct to diet when the response to diet and exercise is inadequate for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia).

Prior to initiating therapy with CRESTOR, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients.

Patients with active liver disease, or unexplained persistent elevations in serum transminases.

During pregnancy, in nursing mothers and in women of childbearing potential, unless they are taking adequate contraceptive precautions.

CRESTOR 40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in rosuvastatin plasma levels may occur
- severe renal impairment (CrCl <30 mL/min)
- Asian patients
- concomitant use of fibrates.

PRECAUTIONS

Liver effects

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see Special Patient Populations, DOSAGE and ADMINISTRATION). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS).

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 may 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 cyclosporin, nicotinic acid, 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 rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, 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 $AUC_{(0-t)}$ 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 C_{max} and $AUC_{(0-t)}$. 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 (ketoconazole, 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 C_{max} 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 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

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.

Laboratory effects
As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases and CK has been observed in a small number of patients taking rosuvastatin. Proteinuria has been detected by dipstick testing in the clinical trial program in a small number of patients taking rosuvastatin and other HMG-CoA reductase inhibitors at their recommended doses. The proteinuria was mostly tubular in origin and was more frequent in patients on rosuvastatin 40 mg. It was generally transient and not associated with worsening renal function. Although the clinical significance is unknown, dose reduction should be considered in patients on rosuvastatin 40 mg with unexplained persistent proteinuria.

Other effects
In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens.

In rosuvastatin-treated patients, there was no impairment of adrenocortical function.

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

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Hepatobiliary disorders
Rare: increased hepatic transaminases
Very rare: jaundice, hepatitis

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 cyclosporin, 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.

Geriatrics

The usual dose range applies.

Hepatic insufficiency

The usual dose range applies for patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with CRESTOR 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above CRESTOR 10 mg should be carefully considered (see PRECAUTIONS).

Renal insufficiency

The usual dose range applies in patients with mild to moderate renal impairment.

For patients with severe renal impairment (CL_{cr}<30 mL/min/1.73m^2) not on dialysis the dose of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily (see PRECAUTIONS).

OVERDOSAGE

There is no specific treatment for overdose. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised. Haemodialysis is unlikely to be of benefit. Contact the Poisons Information Centre for advice on management.

PRESENTATION AND STORAGE CONDITIONS

CRESTOR 5 mg are yellow, round, film-coated, biconvex tablets impressed with "ZD4522 5" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 10 mg are pink, round, film-coated, biconvex tablets impressed with "ZD4522 10" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 20 mg are pink, round, film-coated, biconvex tablets impressed with "ZD4522 20" on one side. Packed in blister packs of 7 and 30 tablets.

CRESTOR 40 mg are pink, oval, film-coated, biconvex tablets, impressed with "ZD4522" on one side and "40" on the other side. Packed in blister packs of 30 tablets.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road NORTH RYDE
NSW 2113

POISON SCHEDULE OF THE MEDICINE S4

Prescription only medicine (Schedule 4)

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