AUSTRALIAN PRODUCT INFORMATION

CRESTOR® (rosuvastatin calcium) film-coated tablets

1 NAME OF THE MEDICINE

Rosuvastatin calcium.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of CRESTOR contains 5 mg, 10 mg, 20 mg and 40 mg of rosuvastatin (as calcium).

Excipient with known effect: Sugars (as lactose).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

CRESTOR 5 mg are yellow, round, film-coated, biconvex tablets impressed with “ZD4522 5” on one side.

CRESTOR 10 mg are pink, round, film-coated, biconvex tablets impressed with “ZD4522 10” on one side.

CRESTOR 20 mg are pink, round , film-coated, biconvex tablets impressed with “ZD4522 20” on one side.

CRESTOR 40 mg are pink, oval, film-coated, biconvex tablets, impressed with “ZD4522” on one side and “40” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CRESTOR should be used as an adjunct to diet when the response to diet and exercise is inadequate.

Prevention of cardiovascular events

CRESTOR is indicated for prevention of major cardiovascular events in men ≥50 years old and women ≥60 years old with no clinically evident cardiovascular disease but with at least two conventional risk factors for cardiovascular disease (hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease). CRESTOR is indicated to:

- Reduce the risk of nonfatal myocardial infarction
- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularisation procedures.

In patients with hypercholesterolaemia

CRESTOR is indicated 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Prior to initiating CRESTOR, the patient should be placed on a standard cholesterol-lowering diet. The dose should be individualised according to the goal of therapy and patient response and should take into account the potential risk for adverse reactions (see Section 4.8 Adverse effects (Undesirable effects)).

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

Hypercholesterolaemia

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.

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.

Specialist supervision should also be considered when initiating co-administration of CRESTOR with other medicinal products known to increase exposure to rosuvastatin (see Sections 4.2 Dose and method of administration - Dosage in patients taking other drugs, 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.5 Interactions with other medicines and other forms of interactions).

Prevention of cardiovascular events

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events (see Section 5.1 Pharmacodynamic properties - Prevention of cardiovascular events).

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 Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Dosage in patients taking other drugs

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when CRESTOR is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin, ticagrelor and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir). It is recommended that prescribers consult the relevant product information when considering administration of such

products together with CRESTOR. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing CRESTOR therapy. In situations where co-administration of these medicinal products with CRESTOR is unavoidable, the benefit and the risk of concurrent treatment and CRESTOR dosing adjustments should be carefully considered (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.5 Interactions with other medicines and other forms of interactions).

Ciclosporin

In patients taking ciclosporin, CRESTOR dosage should be limited to 5 mg once daily (see Section 4.5 Interactions with other medicines and other forms of interactions).

Gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant CRESTOR and gemfibrozil (see Section 4.5 Interactions with other medicines and other forms of interactions). If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily.

Paediatric use

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.

Use in the elderly

The usual dose range applies.

Hepatic impairment

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 Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Renal impairment

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

For patients with severe renal impairment (CL_{cr}<30 mL/min/1.73 m^2) not on dialysis the dose of CRESTOR should be started at 5 mg once daily and not exceed 10 mg once daily (see Section 4.4 Special warnings and precautions for use).

Genetic polymorphisms

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients who are known to have such specific types of polymorphisms, a lower daily dose of CRESTOR is recommended (see Section 5.2 Pharmacokinetic properties).

4.3 CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients.

Patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).

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

Concomitant use of fusidic acid (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

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 (see Sections 4.4 Special warnings and precautions for use, 4.5 Interactions with other medicines and other forms of interactions, and 5.2 Pharmacokinetic properties)
- severe renal impairment (CrCl <30 mL/min)
- Asian patients
- concomitant use of fibrates.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.2 Dose and method of administration). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see Section 4.3 Contraindications).

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo.

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 Section 4.8 Adverse effects (Undesirable effects)). 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 post-marketing 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, protease inhibitors, or ciclosporin (see Section 4.5 Interactions with other medicines and other forms of 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 Sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions).**

5. **The risk of myopathy during treatment with rosuvastatin may be increased in circumstances that increase rosuvastatin drug levels (see Sections 4.4 Special warnings and precautions for use - Use in renal impairment and 5.2 Pharmacokinetic properties - Special populations).**

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).**

There have been very rare reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

HMG-CoA reductase inhibitors may in rare instances induce or aggravate myasthenia gravis or ocular myasthenia (see Section 4.8 Adverse effects (Undesirable effects)) including reports of recurrence when the same or a different HMG-CoA reductase inhibitor was administered. Rosuvastatin should be used with caution in patients with these conditions, and should be discontinued if these conditions are induced or aggravated.

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 ciclosporin, nicotinic acid, azole antifungals, macrolide antibiotics and fibric acid derivatives including gemfibrozil (see Sections 4.2 Dose and method of administration, 4.5 Interactions with other medicines and other forms of interactions, and 4.8 Adverse effects (Undesirable effects)).

Fusidic acid must not be co-administered with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination (see Sections 4.3 Contraindications, 4.5 Interactions with other medicines and other forms of interactions, and 4.8 Adverse effects (Undesirable effects)). In patients where the use of systemic fusidic acid is considered essential, rosuvastatin treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Rosuvastatin therapy may be re-introduced seven days after the last dose of fusidic acid.

Endocrine effects

Increases in HbA1c and fasting serum glucose levels have been reported with rosuvastatin. Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Caution in prevention of cardiovascular events

The long-term safety and efficacy of rosuvastatin treatment in patients commencing treatment with LDL-C <3.4 mmol/L who have been assessed to be at risk of cardiovascular events have not been established. There is also uncertainty associated with the safety of long-term intensive reduction of LDL-C to very low levels. Data are currently available for up to 2 years for the 20 mg dose only (see Section 5.1 Pharmacodynamic properties - Prevention of cardiovascular events). The risk benefit balance for longer term use of rosuvastatin in this population has therefore not been established. The benefits of longer term treatment should be weighed against safety and tolerability risks (see Section 4.8 Adverse effects (Undesirable effects)). Clinically significant benefit in using CRESTOR in patients without clinically evident cardiovascular disease and who are assessed as having a low risk of cardiovascular events (men ≥50 and women ≥60 years of age with hsCRP >2 mg/L, but no other cardiovascular disease risk factor) has not been established.

Use of CRP testing in prevention of cardiovascular effects

Recent studies indicate that elevated levels of C Reactive Protein (≥2 mg/L) may be a marker for increased risk of cardiovascular disease. However, elevated CRP is not a widely established marker of cardiovascular disease and concerns remain over its validity to predict cardiovascular disease risk. The JUPITER trial was conducted in a population with elevated CRP levels however there is no comparative data of rosuvastatin in patients with normal CRP levels or in patients with elevated CRP levels compared to other traditional cardiovascular risk factors. In conjunction with cardiovascular risk assessment, testing for CRP levels may be useful to assist in determining those individuals at higher risk of cardiovascular events. In the JUPITER trial, the hsCRP test was used but this specific test is not widely available. The usCRP test is also suitable for identifying patients with elevated CRP levels and is widely available.

Diabetes mellitus

Increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin, including increases that exceeded the threshold for the diagnosis of diabetes mellitus in some cases (see Sections 4.8 Adverse effects (Undesirable effects) and 5.1 Pharmacodynamic properties - Clinical trials).

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, rosuvastatin therapy should be discontinued.

Special patient populations

Age and sex

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

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 Sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

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 Section 4.2 Dose and method of administration).

Hepatic insufficiency

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 Section 4.2 Dose and method of administration).

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases, CK, glucose, glutamyl transpeptidase, alkaline phosphatase and bilirubin and thyroid function abnormalities have been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin. Proteinuria and microscopic haematuria 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 and/or haematuria.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

4.5.1 Effect of co-administered medicinal products on rosuvastatin

In vitro and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent (see Table 11 for interaction studies with ketoconazole, erythromycin, fluconazole and itraconazole).

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of CRESTOR with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma

concentrations and an increased risk of myopathy (see Table 11; Sections 4.2 Dose and method of administration, 4.3 Contraindications, and 4.4 Special warnings and precautions for use).

Ticagrelor

Ticagrelor has been shown to increase rosuvastatin AUC by 2.3-fold, which may result in increased risk of myopathy. In some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CK level and rhabdomyolysis. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

Interactions requiring rosuvastatin dose adjustments (see also Table 1 and Section 4.2 Dose and method of administration)

When it is necessary to co-administer CRESTOR with other medicinal products known to increase exposure to rosuvastatin, doses of CRESTOR should be adjusted. It is recommended that prescribers also consult the relevant product information when considering administration of such products together with CRESTOR.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of CRESTOR should not exceed 5 mg once daily. The maximum daily dose of CRESTOR should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of the daily recommended dose of CRESTOR taken without interacting medicinal products (see Section 4.2 Dose and method of administration). Note, the 40 mg dose is not approved for use in prevention of cardiovascular events. Please also see Section 4.3 Contraindications for the use of the 40 mg dose.

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the CRESTOR dose above 20 mg.

Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure (AUC) up to 7-fold (see Table 11). Dose adjustment are needed depending on the level of effect on rosuvastatin exposure (see Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Table 11 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*	Change in rosuvastatin C_{max}
2-fold or greater than 2-fold increase in AUC of rosuvastatin			
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) OD for 15 days	10 mg, single dose	7.39-fold ↑	18.88-fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑	10.6-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2-fold ↑	~5-fold ↑
Belumosudil 200 mg OD, 8 days	10mg, single dose on 2 separate days	4.6-fold ↑	3.6-fold ↑
Regorafenib 160 mg OD, 14 days	5 mg, single dose	3.8-fold ↑	4.6-fold ↑
Enasidenib 100 mg OD, 28 days	10 mg, single dose	3.4-fold ↑	3.7-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑	7.0-fold ↑

Roxadustat 200 mg QOD	10 mg, single dose	2.9-fold ↑	4.5-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2.8-fold ↑	3.2-fold ↑
Momelotinib 200 mg OD, 5 days	10 mg, single dose	2.7-fold ↑	3.2-fold ↑
Velpatasvir 100 mg OD	10 mg single dose	2.69-fold ↑	2.61-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID	5mg single dose	2.59-fold ↑	7.13-fold ↑
Teriflunomide	Not available	2.51-fold ↑	2.65-fold ↑
Vadadustat 600 mg OD, 8 days	20 mg, single dose on 2 separate days	2.47-fold ↑	2.75-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10mg single dose	2.26-fold ↑	5.49-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5mg once daily	2.2-fold ↑	5.62-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑	4.7-fold ↑
Capmatinib 400 mg BID	10 mg, single dose	2.08-fold ↑	3.04-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑	2.2-fold ↑
Less than 2-fold increase in AUC of rosuvastatin			
Tafamidis 61 mg BID on Days 1 & 2, followed by OD on Days 3 to 9	10 mg, single dose	1.97-fold ↑	1.86-fold ↑
Fostamatinib 100 mg BID	20 mg, single dose	1.96-fold ↑	1.88-fold ↑
Febuxostat 120 mg OD	10 mg, single dose	1.9-fold ↑	2.1-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑	2.2-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑	2.0-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑	2.4-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑	2.2-fold ↑
Dronedarone 400 mg BID	10 mg	1.4-fold ↑	
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑	1.2-fold ↑
Fluconazole 200 mg OD, 11 days	80 mg, single dose	14% ↑	9% ↑
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	8% ↑	45% ↑
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	7% ↑	21% ↑
No change in AUC of rosuvastatin			
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔	10% ↑
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔	5% ↓
Decrease in AUC of rosuvastatin			
Rifampicin 450 mg OD, 7 days	20 mg, single dose	4% ↓	12% ↑
Silymarin 140 mg TID, 5 days	10 mg, single dose	6% ↓	7% ↓
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓	31% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓	

* Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", no change as "↔", decrease as "↓".

** Several interaction studies have been performed at different Crestor dosages, the table shows the most significant ratio

AUC = area under curve; QOD = every other day; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Other interacting medicinal products

Antacids

The simultaneous dosing of CRESTOR with 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 CRESTOR. The clinical relevance of this interaction has not been studied.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with rosuvastatin is necessary, rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Adverse effects (Undesirable effects)).

4.5.2 Effect of rosuvastatin on co-administered medicinal products

Warfarin and other Vitamin K antagonists

Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking vitamin K antagonists 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 vitamin K antagonists. 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.

Gemfibrozil / fenofibrates / fibric acid derivatives

Co-administration of rosuvastatin with gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (see Table 11 and Section 4.2 Dose and method of administration). Co-administration of fenofibrate with rosuvastatin resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate (see Table 11). However, a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate and other fibric acids, including nicotinic acid, may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors (see Section 4.4 Special warnings and precautions for use).

Ciclosporin

Co-administration of rosuvastatin with ciclosporin resulted in no significant changes in ciclosporin plasma concentration and a 7-fold increase in rosuvastatin exposure (see Table 11 and Section 4.2 Dose and method of administration).

Digoxin

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

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 (see Table 11 and Section 4.2 Dose and method of administration).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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.

Use in pregnancy – Category D

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 as there is a potential risk for adverse events in the foetus. 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. It is recommended that rosuvastatin is discontinued as soon as pregnancy is recognised.

Use in lactation

The safety of rosuvastatin while breastfeeding has not been established. 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. Limited data from published reports indicate that rosuvastatin is present in human milk. Due to rosuvastatin's mechanism of action, there is a potential risk for adverse reactions in the infant. Therefore rosuvastatin is contraindicated in breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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

Endocrine System Disorders

Common diabetes mellitus (observed in the JUPITER study, see below)

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. Rhabdomyolysis may be fatal. Examples of signs and symptoms of rhabdomyolysis are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.5 Interactions with other medicines and other forms of interactions).

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.

JUPITER study

In the JUPITER study the safety profile for subjects taking rosuvastatin 20 mg was generally similar to that of subjects taking placebo. There were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued study medication due to an adverse event, irrespective of treatment causality. The most common adverse reactions that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.03% rosuvastatin, 0.03% placebo).

A significantly higher frequency of diabetes mellitus was reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients (see Section 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties - Clinical trials).

Increased hepatic transaminases were observed in 1.9% of rosuvastatin and 1.5% of placebo subjects and renal events were reported in 6.0% of rosuvastatin and 5.4% of placebo subjects. Confusion was reported in 0.2% of rosuvastatin and 0.1% of placebo subjects.

Adverse reactions in JUPITER reported in ≥2% of patients and at a rate greater than or equal to placebo were myalgia (7.6% rosuvastatin, 6.6% placebo), arthralgia (3.8% rosuvastatin, 3.2% placebo), constipation (3.3% rosuvastatin, 3.0% placebo), nausea (2.4% rosuvastatin, 2.3% placebo) and haematuria (2.4% rosuvastatin, 2.0% placebo).

METEOR study

In the METEOR study, involving 981 participants treated with rosuvastatin 40 mg (n=700) or placebo (n=281) with a mean treatment duration of 1.7 years, 5.6% of subjects treated with rosuvastatin versus 2.8% of placebo-treated subjects discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: myalgia, hepatic enzyme increased, headache, and nausea.

Adverse reactions in METEOR reported in ≥ 2% of patients and at a rate greater than placebo were myalgia (12.7% rosuvastatin, 12.1% placebo), arthralgia (10.1% rosuvastatin, 7.1% placebo), headache (6.4% rosuvastatin, 5.3% placebo), dizziness (4.0% rosuvastatin, 2.8% placebo), increased CPK (2.6% rosuvastatin, 0.7% placebo), abdominal pain (2.4% rosuvastatin, 1.8% placebo) and ALT>3x ULN (2.2% rosuvastatin, 0.7% placebo).

Post-marketing experience

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

Eye disorders

Frequency unknown	ocular myasthenia

Haematological disorders

Frequency unknown	thrombocytopenia

Hepatobiliary disorders

Rare	increased hepatic transaminases
Very rare	jaundice, hepatitis

Frequency unknown	hepatic failure

Musculoskeletal disorders

Very rare	arthralgia
Frequency unknown	immune-mediated necrotising myopathy

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Rhabdomyolysis may be fatal. Examples of signs and symptoms of rhabdomyolysis are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia (see Sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.5 Interactions with other medicines and other forms of interactions).

Nervous system disorder

Very rare	memory loss
Frequency unknown	peripheral neuropathy (including paraesthesia), myasthenia gravis

Psychiatric disorders

Frequency unknown	depression, sleep disorders (including insomnia and nightmares)

Reproductive system and breast disorders

Frequency unknown	gynaecomastia

Skin and subcutaneous tissue disorders

Frequency unknown	drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

CRESTOR, rosuvastatin calcium, is a HMG-CoA reductase inhibitor for the treatment of dyslipidaemia. 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 (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

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 randomisation, patients were treated for 6 weeks with a single daily dose of either CRESTOR, atorvastatin, simvastatin, or pravastatin (Figure 11 and Table 22). The primary endpoint for this study was the percent change from baseline in LDL-C at week 6.

Figure 11 Percent LDL-C change by dose of CRESTOR, atorvastatin, simvastatin and pravastatin at Week 6 in patients with type IIa/IIb dyslipidaemia

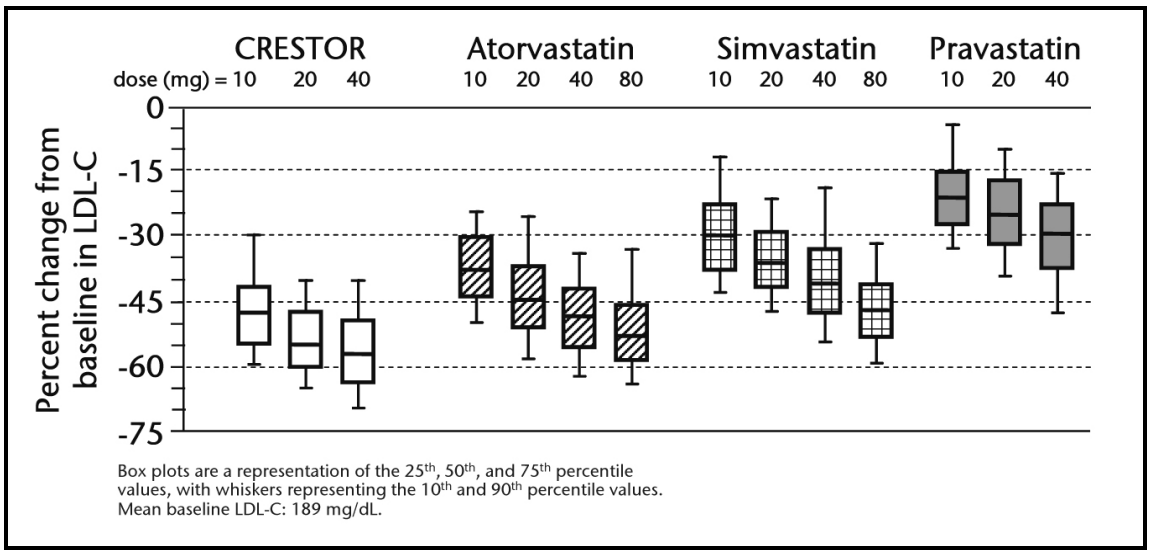


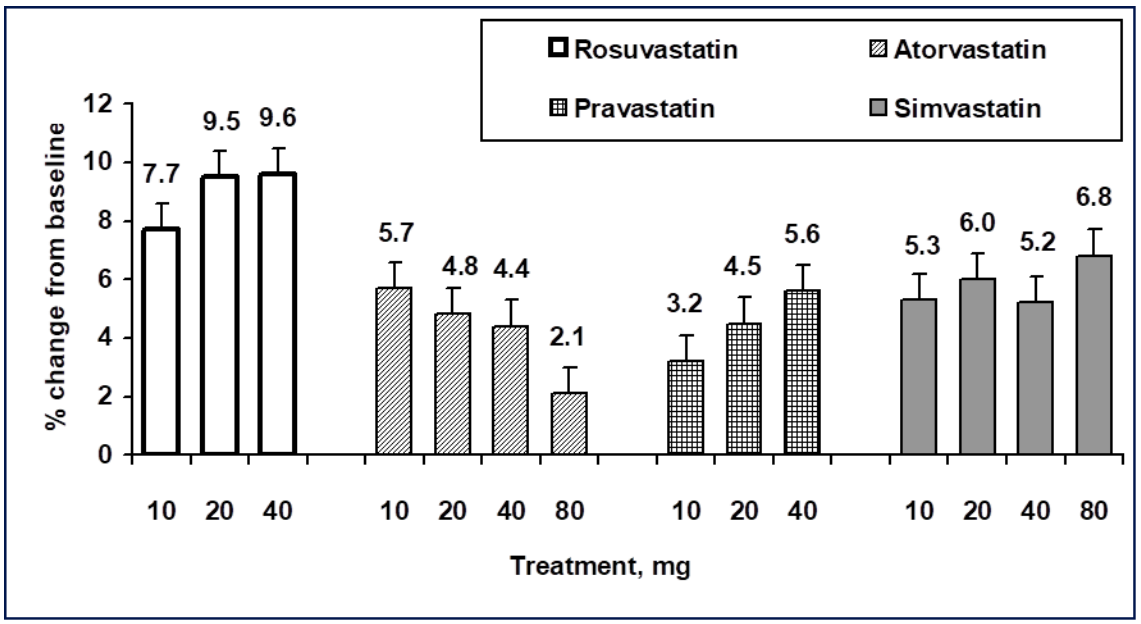
Table 22 **LS Mean§ % change in LDL-C from baseline to Week 6 for each statin treatment group.**

Treatment	Treatment Daily Dose							
	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	-46ψ (-48, -44)	160	-52β (-54, -50)	157	-55ω (-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)

N = number of patients at each dose of each statin.
ψ 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)
β 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)
ω 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 22 below:

Figure 22 **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 22 is summarised with 95% CI in Table 33.

Table 33 **LS Mean % change in HDL-C from baseline to Week 6 for each statin treatment group.**

Treatment	Treatment Daily Dose							
	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)

N = number of patients at each dose of each statin.

Table 44 below summarises the pooled lipid variable data for rosuvastatin 5 and 10 mg from 5 Phase III efficacy trials (Trials 24-28).

Table 44 **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.**

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)

N = number of patients at each dose of CRESTOR.

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 55).

Table 55 Dose-response in patients with primary hypertriglyceridaemia over 6 weeks dosing median (min, max) percent change from baseline

Dose	Placebo	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Rosuvastatin 20 mg	Rosuvastatin 40 mg
	N=26	N=25	N=23	N=27	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 66 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

Table 66 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[Ψ] RSV 40 mg N=432	Mean % change[Ψ] ATV 80 mg N=439	Difference in LS mean % changes	95%CI[§]	p value[ω]
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]

Ψ Mean % change from baseline
§ 95% confidence interval for the difference between the least squares means
ω 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 section 4.2 Dose and method of administration).

Prevention of Cardiovascular Events

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <3.3 mmol/L (130 mg/dL) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 2.8 mmol/L (108 mg/dL) and hsCRP of 4.3 mg/L. The average age of study participants was 66 years. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary endpoint was a composite endpoint consisting of the time-to-first occurrence of any of the following CV events: CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or an arterial revascularisation procedure.

Rosuvastatin significantly reduced the risk of CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44%; absolute risk reduction of 1.2% (see Figure 33 and Table 77). The benefit was apparent within the first 6 months of treatment (HR 0.62; 95% CI 0.40-0.96; p=0.029). The risk reduction was consistent across multiple predefined population subsets based on assessments of age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C or hsCRP levels at the time of entry into the study.

In JUPITER, there was a statistically significant increase in the frequency of diabetes mellitus reported by investigators; 2.8% of patients in the rosuvastatin group and 2.3% of patients in the placebo group (HR: 1.27, 95% CI: 1.05-1.53, p=0.015). The difference between treatment groups (rosuvastatin versus placebo) in mean HbA1c change from baseline was approximately 0.1%. The

number of patients with HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients.

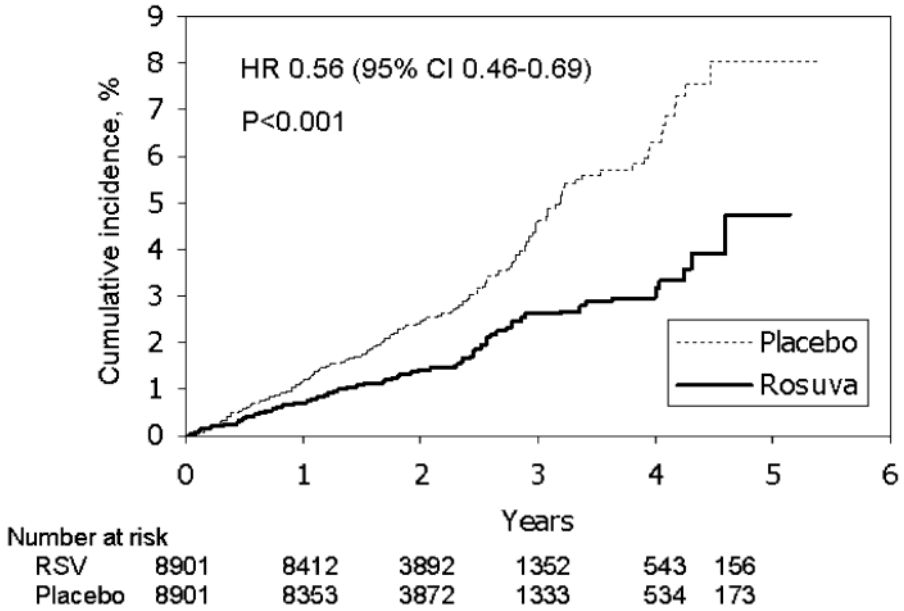
Table 77 Summary of Risk Reductions from JUPITER trial

Endpoint	Placebo N (%)	RSV 20 mg N (%)	HR (95% CI)	RRR*(%)	ARR*(%)
Primary (major cardiovascular event)	252 (2.8)	142 (1.6)	0.56 (0.46-0.69) p<0.001	44	1.2
Secondary					
CV death, stroke and MI	158 (1.8)	83 (0.9)	0.52 (0.40-0.68)	48	0.9
Fatal or non-fatal MI	68 (0.8)	31 (0.3)	0.46 (0.30-0.70)	54	0.3
Fatal or non-fatal stroke	64 (0.7)	33 (0.4)	0.52 (0.34-0.79)	48	0.3
Total mortality	247(2.8)	198 (2.2)	0.80 (0.67-0.97)	20	0.6
Venous thromboembolism	46 (0.5)	26 (0.3)	0.57 (0.35-0.91)	43	0.2

HR = Hazard Ratio; RRR = Relative Risk Reduction; ARR = Absolute Risk Reduction
* Calculated values were at 1.9 years median follow-up

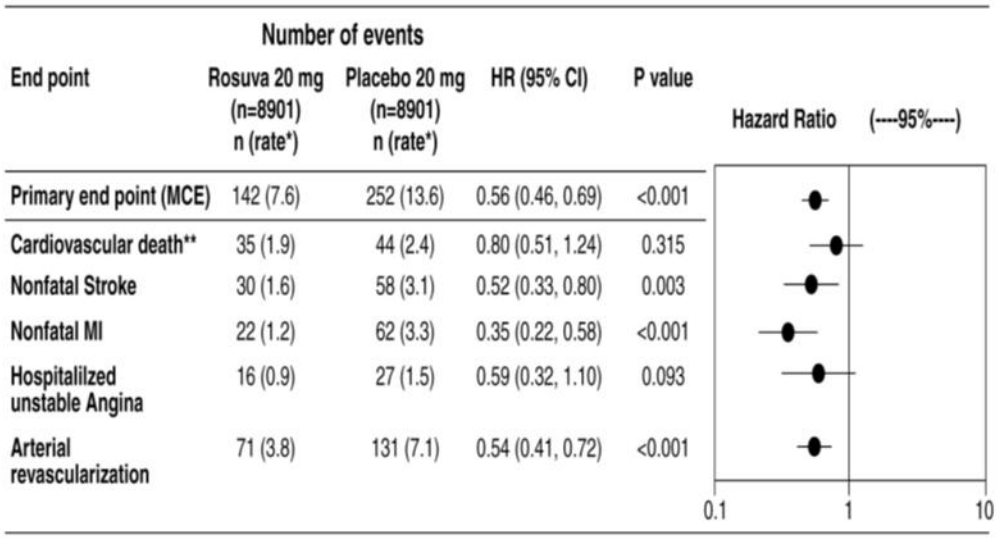
There were no statistically significant reductions in the rate of noncardiovascular death or the incidence of bone fractures in the rosuvastatin treated group compared to placebo.

Figure 33 Time to occurrence of major cardiovascular events in JUPITER



The individual components of the primary end point are presented in Figure 44. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularisation procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalisations for unstable angina.

Figure 44 Major CV events by treatment group in JUPITER



* event rate/1000-patient years

** Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

In a post-hoc subgroup analysis of JUPITER subjects (n =1405; rosuvastatin = 725, placebo = 680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

At one year, rosuvastatin increased HDL-C (1.41 vs 1.34 mmol/L) and reduced LDL-C (1.59 mmol/L vs. 2.82 mmol/L), hsCRP (2.20 vs. 3.50 mg/L), total cholesterol and serum triglyceride levels ($p<0.001$ for all versus placebo).

In separate studies of patients with established heart failure (CORONA study) and those with end-stage renal disease (AURORA study), rosuvastatin did not reduce cardiovascular events.

5.2 PHARMACOKINETIC PROPERTIES

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 Cmax) in Asian subjects when compared with a Caucasian control group (see Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Genetic polymorphisms

Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. The individual polymorphism of SLCO1B1, c.521CC, and the individual polymorphism of ABCG2, c.421AA, are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT and ABCG2 c.421CC genotypes, respectively. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of CRESTOR is recommended (see section 4.2 Dose and method of administration).

5.3 PRECLINICAL SAFETY DATA

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

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).

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Crospovidone, lactose monohydrate, microcrystalline cellulose, calcium phosphate, magnesium stearate, triacetin, hypromellose and titanium dioxide. The 5 mg tablets also contain iron oxide yellow, whereas the 10 mg, 20 mg and 40 mg tablets contain iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine

See Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The 5 mg, 10 mg and 20 mg film coated tablets are packed in calendar blister packs of 7 and 30 tablets*.

The 40 mg film coated tablets are packed in calendar or standard blister packs of 7 and 30 tablets*.

*Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

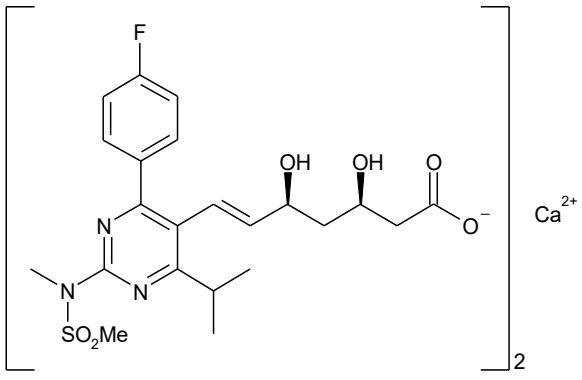
6.7 PHYSICOCHEMICAL PROPERTIES

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 (3*R,5S,6E*) enantiomer.

Chemical structure

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.

Figure 55 Chemical structure/general structure of rosuvastatin calcium



CAS Number: 147098-20-2

Molecular formula: $(C_{22}H_{27}FN_3O_6S)_2Ca$

Molecular weight: 1001.14

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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Telephone: 1800 644 542

9 DATE OF FIRST APPROVAL

26 April 2006

10 DATE OF REVISION

23 March 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5	Addition of AUC value for drug-drug interaction with ticagrelor and rosuvastatin. Addition of drug-drug interactions with belumosudil and momelotinib with rosuvastatin. Corrected AUC value for drug-drug interaction between enasidenib with rosuvastatin. Addition of drug-drug interaction between vadadustat and rosuvastatin