**NEW ZEALAND DATA SHEET**
**ROSUVASTATIN SANDOZ® (ROSUVASTATIN CALCIUM)**

# 1. PRODUCT NAME

Rosuvastatin Sandoz 5 mg film-coated tablets
Rosuvastatin Sandoz 10 mg film-coated tablets
Rosuvastatin Sandoz 20 mg film-coated tablets
Rosuvastatin Sandoz 40 mg film-coated tablets

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin as rosuvastatin calcium.

Excipients with known effect: Sugars (as lactose).

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

# 3. PHARMACEUTICAL FORM

Film Coated Tablet

Rosuvastatin Sandoz **5 mg**: brown, round, film-coated tablets.

Rosuvastatin Sandoz **10 mg**: brown, round, film-coated tablets, debossed with "RSV 10" on one side.

Rosuvastatin Sandoz **20 mg**: brown, round, film-coated tablets, debossed with "RSV 20" on one side.

Rosuvastatin Sandoz **40 mg**: brown, round, film-coated tablets, debossed with "RSV 40" on one side.

# 4. CLINICAL PARTICULARS

## 4.1. THERAPEUTIC INDICATIONS

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

**Prevention of Major Cardiovascular events**

In adult patients without documented history of cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease, (see section 5.1 Clinical Efficacy and Safety) Rosuvastatin Sandoz is indicated to:

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

**Hypercholesterolaemia**

Rosuvastatin Sandoz is indicated to:

- Reduce elevated LDL-C, total cholesterol, triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolaemia (heterozygous familial and

non familial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb). Rosuvastatin Sandoz also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG, the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I ratios and increases ApoA-I in these populations.

- Treat isolated hypertriglyceridaemia (Fredrickson Type IV hyperlipidaemia).
- Reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or alone if such treatments are unavailable.

Prior to initiating therapy with rosuvastatin, 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

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

**Prevention of Major Cardiovascular events**

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events.

**Hypercholesterolaemia**

The usual dose range is 10 - 40 mg orally once a day.

The dosage of Rosuvastatin Sandoz should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the start dose. However, if necessary, dose adjustment can be made at 2 to 4 week intervals. (See section 5.1 Pharmacodynamic properties).

A dose of 40 mg once a day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once a day is assessed. 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.

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia and isolated hypertriglyceridaemia

The usual start dose is 10 mg once a day.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia

For patients with homozygous familial hypercholesterolaemia a start dose of 20 mg once a day is recommended.

**Use in children**

In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

**Use in the elderly**

The usual dose range applies.

**Dosage in patients with renal insufficiency**

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

For patients with severe renal impairment the dose of Rosuvastatin Sandoz should not exceed 10 mg once daily. (See sections 5.2 Pharmacokinetic properties and 4.3 Contraindications).

**Dosage in patients with hepatic insufficiency**

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

Patients with severe hepatic impairment should start therapy with Rosuvastatin Sandoz 10 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above Rosuvastatin Sandoz 10 mg should be carefully considered. (See section 5.2 Pharmacokinetic properties).

**Race**

A 5 mg starting dose of Rosuvastatin Sandoz should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicines and other forms of interactions4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolaemia is not adequately controlled at doses up to 20 mg daily.

**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 known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of Rosuvastatin Sandoz is recommended (see sections 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicines and other forms of interactions and 5.2 Pharmacokinetic properties).

**Concomitant therapy**

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosuvastatin Sandoz 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 and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicines and other forms of interactions). It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatin Sandoz. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing Rosuvastatin Sandoz therapy. In situations where co-administration of these medicinal products with Rosuvastatin Sandoz is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin Sandoz dosing adjustments should be carefully considered (see 4.5 Interaction with other medicines and other forms of interactions).

## 4.3. CONTRAINDICATIONS

Rosuvastatin Sandoz is contraindicated in patients with hypersensitivity to any component of this product.

Rosuvastatin Sandoz is contraindicated in patients with active liver disease or persistent, unexplained elevations in transaminases.

Rosuvastatin Sandoz is contraindicated during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.

Rosuvastatin Sandoz 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.

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Liver

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.

As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

### Skeletal muscle

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with rosuvastatin. As with other HMG-CoA reductase inhibitors, the reported rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. rosuvastatin therapy should be discontinued if CK levels are markedly elevated (>10xULN) or if myopathy is diagnosed or suspected. There have been very rare reports of an immune-mediated necrotizing myopathy clinically characterized 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 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, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

Rosuvastatin should be prescribed with caution in patients with pre-disposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur (see sections 4.5 Interaction with other medicines and other forms of interactions and 5.2 Pharmacokinetic properties).

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Rosuvastatin should 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).

**Diabetes Mellitus**

There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at increased risk of developing type 2 diabetes. Risk factors for the development of type 2 diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass index. Patients at risk should be monitored both clinically and biochemically according to national guidelines.

There is insufficient evidence to confirm or exclude an increased risk for any individual statin or a dose-response relationship and the cardiovascular benefits of statin therapy continue to outweigh the risk of developing type 2 diabetes.

As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin and in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus, primarily in patients already at high risk for developing diabetes (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties).

**Race**

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

**Interstitial Lung Disease**

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8 Undesirable effects). 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, statin therapy should be discontinued.

**Children and Adolescents 6 to 17 Years of Age:**

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a two year period (See section 5.1 Pharmacodynamic properties – Clinical Safety and Efficacy).

## 4.5. INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Effect of co-administered medicinal products on rosuvastatin**

*In vitro* and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer). Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin 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 1, and sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

**Ticagrelor:** Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. 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):

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

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of rosuvastatin should not exceed 5 mg once daily. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 5 mg dose of rosuvastatin with ciclosporin (7.1-fold increase in exposure), a 10 mg dose of rosuvastatin with ritonavir/atazanavir combination (3.1-fold increase) and a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase).

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 rosuvastatin dose above 20mg.

**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 Table1). 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 1: Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials**

**2-fold or greater than 2-fold increase in AUC of rosuvastatin**

| Interacting drug dose regimen | Rosuvastatin dose regimen | Change in rosuvastatin AUC* |
|---|---|---|
| Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days | 10 mg single dose | 7.39-fold ↑ |
| Ciclosporin 75 mg BID to 200 mg BID, 6 months | 10 mg OD, 10 days | 7.1-fold ↑ |
| Darolutamide 600 mg BID, 5 days | 5 mg, single dose | 5.2-fold ↑ |
| Regorafenib 160 mg OD, 14 days | 5 mg single dose | 3.8 -fold ↑ |
| Atazanavir 300 mg/ritonavir 100 mg OD, 8 days | 10 mg, single dose | 3.1-fold ↑ |
| Simeprevir 150 mg OD, 7 days | 10 mg, single dose | 2.8-fold ↑ |
| Roxadustat 200 mg QOD | 10 mg, single dose | 2.9-fold ↑ |
| Velpatasvir 100 mg OD | 10 mg, single dose | 2.69 -fold ↑ |
| Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg/dasabuvir 400 mg BID | 5 mg single dose | 2.59-fold ↑ |
| Teriflunomide | Not available | 2.51-fold ↑ |
| Enasidenib 100 mg OD, 28 days | 10 mg, single dose | 2.4-fold ↑ |
| Grazoprevir 200 mg/elbasvir 50 mg OD | 10 mg single dose | 2.26-fold ↑ |
| Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days | 5mg once daily | 2.2-fold ↑ |
| Lopinavir 400 mg/ritonavir 100 mg BID, 17 days | 20 mg OD, 7 days | 2.1-fold ↑ |
| Capmatinib 400 mg BID | 10 mg, single dose | 2.08-fold ↑ |
| Clopidogrel 300 mg loading, followed by 75 mg at 24 hours | 20 mg single dose | 2-fold ↑ |

| **Less than 2-fold increase in AUC of rosuvastatin** | | |
|---|---|---|
| **Interacting drug dose regimen** | **Rosuvastatin dose regimen** | **Change in rosuvastatin AUC*** |
| Tafamidis 61 mg BID on Days 1 & 2, followed by OD on Days 3 to 9 | 10 mg, single dose | 1.97-fold ↑ |
| Fostamatinib 100 mg BID | 20 mg, single dose | 1.96-fold↑ |
| Febuxostat 120 mg OD | 10 mg, single dose | 1.9-fold ↑ |
| Gemfibrozil 600 mg BID, 7 days | 80 mg, single dose | 1.9-fold ↑ |
| Eltrombopag 75 mg OD, 5 days | 10 mg, single dose | 1.6-fold ↑ |
| Darunavir 600 mg/ritonavir 100 mg BID, 7 days | 10 mg OD, 7 days | 1.5-fold ↑ |
| Tipranavir 500 mg/ritonavir 200 mg BID, 11 days | 10 mg, single dose | 1.4-fold ↑ |
| Dronedarone 400 mg BID | Not available | 1.4-fold ↑ |
| Itraconazole 200 mg OD, 5 days | 10 mg or 80 mg, single dose | 1.4-fold ↑ |
| Ezetimibe 10 mg OD, 14 days | 10 mg, OD, 14 days | 1.2-fold ↑ |
| **Decrease in AUC of rosuvastatin** | | |
| **Interacting drug dose regimen** | **Rosuvastatin dose regimen** | **Change in rosuvastatin AUC*** |
| Erythromycin 500 mg QID, 7 days | 80 mg, single dose | 20% ↓ |
| 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 "↑", decrease as "↓".
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

The following medicinal product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:

Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

Other interacting medicinal products

**Antacid**: The simultaneous dosing of rosuvastatin 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 rosuvastatin. The clinical relevance of this interaction has not been studied.

**Fusidic Acid**: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

**Effect of rosuvastatin on co-administered medicinal products**

Warfarin:

The pharmacokinetics of warfarin are not significantly affected following co-administration with rosuvastatin. However, as with other HMG-CoA reductase inhibitors, co-administration of rosuvastatin and warfarin may result in a rise in INR compared to warfarin alone. In patients taking vitamin K antagonists monitoring of INR is recommended both at initiation or cessation of therapy with rosuvastatin or following dose adjustment.

Fenofibrates/fibric acid derivatives:

Although no pharmacokinetic interaction between rosuvastatin and fenofibrate was observed; 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.

Other medications:

There were no clinically significant interactions with an oral contraceptive, digoxin or fenofibrate.

In clinical studies rosuvastatin was co-administered with antihypertensive agents, antidiabetic agents and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

## 4.6. FERTILITY, PREGNANCY AND LACTATION

The safety of Rosuvastatin Sandoz during pregnancy and whilst breast feeding has not been established. However, due to rosuvastatin's mechanism of action, there is a potential risk for adverse reactions in the foetus. Women of child-bearing potential should use appropriate contraceptive measures (see section 4.3 Contraindications). If a pregnant woman is exposed to rosuvastatin 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.

Breastfeeding is not recommended during treatment with rosuvastatin. 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.

### 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pharmacology testing revealed no evidence of a sedative effect of Rosuvastatin Sandoz. From the safety profile, Rosuvastatin Sandoz is not expected to adversely affect the ability to drive or use machines.

### 4.8. 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.

| | |
|---|---|
| **Common** (>1/100, <1/10) | Headache, myalgia, asthenia, constipation, dizziness, nausea, abdominal pain, diabetes mellitus*. |
| **Uncommon** (>1/1000, <1/100) | Pruritus, rash and urticaria. |
| **Rare** (>1/10,000, <1/1000) | Myopathy (including myositis), hypersensitivity reactions (including angioedema), rhabdomyolysis, pancreatitis. |

* Observed in the JUPITER study (reported overall frequency 2.8% in rosuvastatin and 2.3% in placebo) primarily in patients already at high risk for developing diabetes (See section 4.4 Special Warnings and Precautions for Use and 5.1 Pharmacodynamic Properties).

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 and with other marketed statins.

**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. Increases in HbA1c have also been observed in patients treated with rosuvastatin (See sections 4.4 Special warnings and precautions for use – Diabetes Mellitus and 5.2 Pharmacokinetic properties). Abnormal urinalysis testing (Dipstick positive proteinuria) has been seen in a small number of patients taking rosuvastatin and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

In the JUPITER study, occurrences of diabetes mellitus as a pre-specified secondary outcome were reported more frequently in the rosuvastatin -treated patients (2.8%) than in placebo (2.3%) and a slight increase in the number of subjects whose fasting glucose levels increased to ≥ 7.0 mmol/L (126 mg/dL) was observed in subjects treated with rosuvastatin. There was a 0.1% increase in mean HbA1c with rosuvastatin compared to placebo.

**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:

*Eye disorders: Frequency known:* ocular myasthenia

*Haematological disorders: Frequency unknown:* thrombocytopenia

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

*Musculoskeletal disorders:* Frequency unknown: immune-mediated necrotising myopathy. *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.

*Nervous system disorders: Very rare:* memory loss, *frequency unknown:* peripheral neuropathy, 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 disorder: Frequency unknown:* drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption.

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy.

**Children and adolescents 6 to 17 years of age**

The safety profile of rosuvastatin is similar in children or adolescent patients and adults although CK elevations >10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in a clinical trial of children and adolescents. However, the same warnings and precautions for use in adults also apply to children and adolescents (See section 4.4 Special warnings and precautions for use).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s/.

### 4.9. OVERDOSE

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Haemodialysis is unlikely to be of benefit.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES

**Pharmacotherapeutic group:** HMG-CoA reductase inhibitors

**ATC code:** C10A A07

**Mechanism of action:**

Rosuvastatin is a selective, potent and 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 things, 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, TG, 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 lowering of non-HDL (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

**Clinical Efficacy and Safety**

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I (See Table 2 and Table 3).

Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's.

The clinical trial program showed that rosuvastatin is effective in a wide variety of patient populations, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

A therapeutic response 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.

**Table 2: Dose Response in Patients with Primary Hypercholesterolaemia (Type IIa and IIb) (Adjusted mean % change from baseline)**

| Dose | N | LDL-C | Total-C | HDL-C | TG | Non HLD-C | ApoB | ApoA-I |
|---|---|---|---|---|---|---|---|---|
| **Placebo** | 13 | -7 | -5 | 3 | -3 | -7 | -3 | 0 |
| **5** | 17 | -45 | -33 | 13 | -35 | -44 | -38 | 4 |
| **10** | 17 | -52 | -36 | 14 | -10 | -48 | -42 | 4 |
| **20** | 17 | -55 | -40 | 8 | -23 | -51 | -46 | 5 |
| **40** | 18 | -63 | -46 | 10 | -28 | -60 | -54 | 0 |

**Table 3** **Dose Response in Patients with Hypercholesterolaemia (Type IIb and Type IV) (Median % change from baseline)**

| Dose | N | TG | LDL-C | Total-C | HLD-C | Non HLD-C | VLDL-C | VLDL-TG |
|---|---|---|---|---|---|---|---|---|
| **Placebo** | 26 | 1 | 5 | 1 | -3 | 2 | 2 | 6 |
| **5** | 25 | -21 | -28 | -24 | 3 | -29 | -25 | -24 |
| **10** | 23 | -37 | -45 | -40 | 8 | -49 | -48 | -39 |
| **20** | 27 | -37 | -31 | -34 | 22 | -43 | -49 | -40 |
| **40** | 25 | -43 | -43 | -40 | 17 | -51 | -56 | -48 |

The data in Table 2 and Table 3 are confirmed by the broader clinical programme of over 5,300 patients given rosuvastatin.

In a study of patients with heterozygous familial hypercholesterolaemia, 435 subjects were given rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses of rosuvastatin 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%.

In a force-titration open label study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 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 of less than 15%, 3 had no response or an increase in LDL-C.

Active-Controlled Study: Rosuvastatin 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 rosuvastatin, atorvastatin, simvastatin or pravastatin (Figure 1) and Table 4). 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**

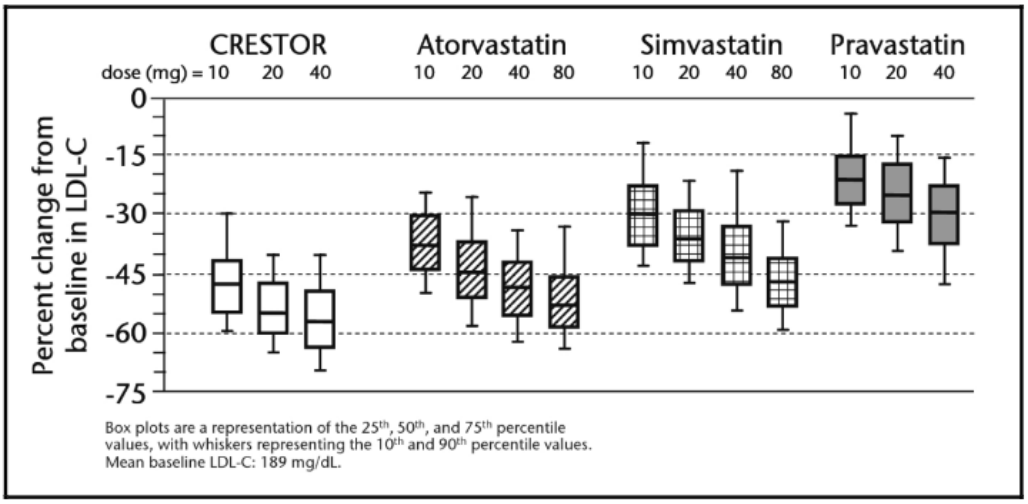



**Table 4 LS Mean§ % change in LDL-C from baseline to Week 6 for each statin treatment group. N = number of patients at each dose of each statin.**

| | TREATMENT DAILY DOSE | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment | 10 mg | | 20 mg | | 40 mg | | 80 mg | |
| | N | Mean (95% Cl) | N | Mean (95% Cl) | N | Mean (95% Cl) | N | Mean (95% Cl) |
| Rosuvastatin | 156 | -46* (-48, -44) | 160 | -52† (-54, -50) | 156 | -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. ($p<0.002$)

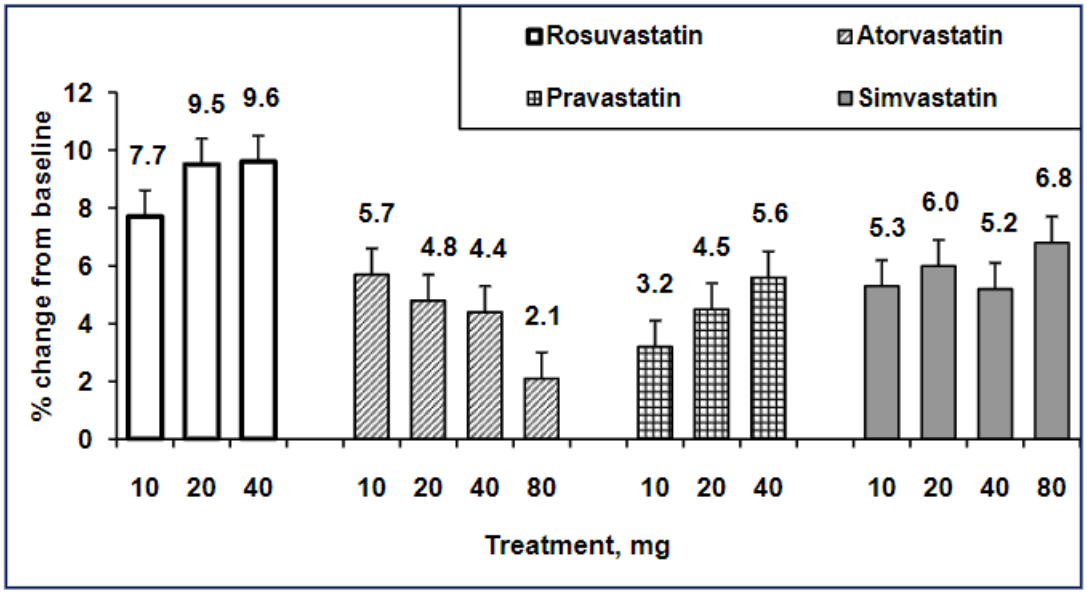
† Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. ($p<0.002$)

‡ 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 represent in Figure 2 is summarised with 95% Cl in Table 5.

**Table 5 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% Cl) | N | Mean (95% Cl) | N | Mean (95% Cl) | N | Mean (95% Cl) |
| Rosuvastatin | 156 | 8 (6, 9) | 160 | 9 (8, 11) | 156 | 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 (6, 8) | 158 | 5 (4, 6) | 163 | 7 (5, 8) |

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, rosuvastatin given as a single daily dose (5 to 40 mg) over 6 weeks significantly reduced serum TG levels (Table 6).

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

| Dose | Placebo N = 26 | Rosuvastatin5 mg N = 25 | Rosuvastatin1 0 mg N = 23 | Rosuvastatin 20 mg N = 27 | Rosuvastatin 40 mg N = 25 |
|---|---|---|---|---|---|
| Triglycerides | 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) |

**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 7 summarises the results for the mean percentage change from baseline at 8 weeks in lipid and lipoprotein variables.

**Table 7 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] |
| Non-HDL-C | -50.75 | -48.27 | -2.48 | -4.25 to –0.72 | 0.006 |
| Apo B | -44.64 | -42.29 | -2.35 | -4.17 to –0.52 | 0.012 |
| Apo-AI | 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

**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 (rosuvatatin: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 rosuvastatin 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 Major Cardiovascular Events**

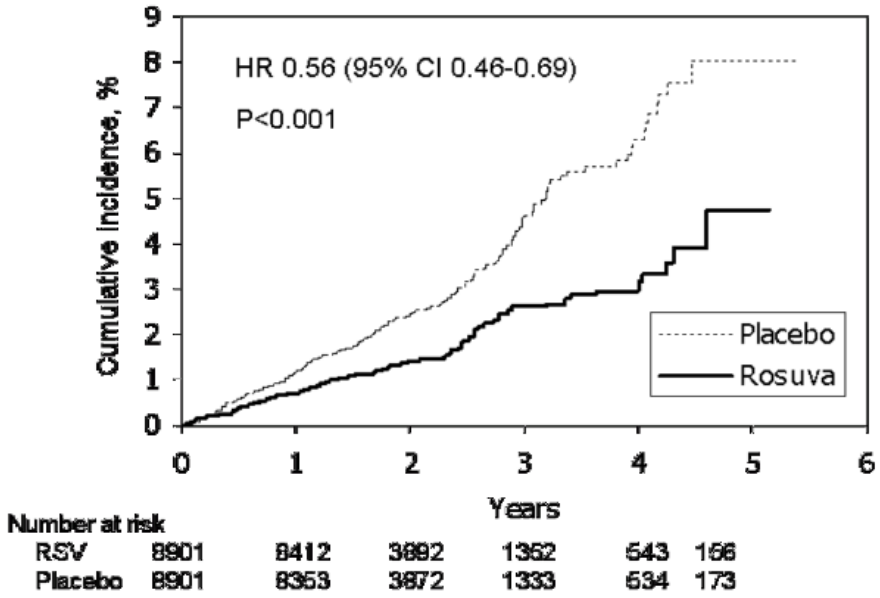
In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, the effect of rosuvastatin (rosuvastatin calcium) on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no established cardiovascular disease, LDL-C levels < 130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.3% 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 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 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, unstable angina or an arterial revascularization 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% (see Figure 3). The benefit was apparent within the first 6 months of treatment. 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. There was a statistically significant 48% reduction in the combined endpoint of CV death, stroke and myocardial infarction (HR: 0.52, 95% 95% CI: 0.40-0.68, p<0.001), a 54% reduction in fatal or nonfatal myocardial infarction (HR: 0.46, 95% CI: 0.30-0.70) and a 48% reduction in fatal

or nonfatal stroke. Total mortality was reduced 20% in the rosuvastatin group (HR: 0.80, 95% CI: 0.67- 0.97, p=0.02).

**Figure 3: Time to occurrence of major cardiovascular events in JUPITER**




The safety profile for subjects taking rosuvastatin 20 mg was generally similar to that of subjects taking placebo. There were 1.6% of rosuvastatin and 1.8% of placebo subjects who withdrew from the trial 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). Adverse reactions reported in ≥ 2% of patients and at a rate greater than or equal to placebo were myalgia (7.6% rosuvastatin, 6.6% placebo), constipation (3.3% rosuvastatin, 3.0% placebo) and nausea (2.4% rosuvastatin, 2.3% placebo).

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%. A post hoc analysis of this study suggests that the risk of development of diabetes on rosuvastatin therapy is limited to patients already at high risk of developing diabetes. The cardiovascular and mortality benefits of rosuvastatin therapy exceeded the diabetes hazard in the trial population as a whole as well as in participants at increased risk of developing diabetes (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

**Children and Adolescents with Hypercholesterolaemia**

In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n = 176, 97 male and 79 female) followed by a 40-week (n = 173, 96 male and 77 female), open label, rosuvastatin dose titration phase, patients 10 – 17 years of age (Tanner stage II-V, females at least 1 year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 – 13 years and approximately 17%, 18%, 40% and 25% were Tanner stage II, III, IV and V respectively.

Rosuvastatin reduced LDL-C (primary end point), total cholesterol and ApoB levels. Results are shown in Table 8 below.

**Table 8 Lipid-modifying effects of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia (least-squares mean percent change from baseline to week 12)**

| Dose (mg) | N | LDL-C | HDL-C | Total-C | TG | Non-HLD-C | ApoB | ApoA-1 |
|---|---|---|---|---|---|---|---|---|
| **Placebo** | 46 | -0.7 | 6.9 | -0.0 | 5.1 | -0.9 | -1.7 | 2.8 |
| **5** | 42 | -38.3 | 4.2 | -29.9 | 0.3 | -36.1 | -31.7 | 1.8 |
| **10** | 44 | -44.6 | 11.2 | -34.2 | -13.6 | -43.0 | -38.1 | 5.4 |
| **20** | 44 | -50.0 | 8.9 | -38.7 | -8.1 | -47.5 | -40.7 | 4.0 |

At the end of the 40 week, open label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 110 mg/dL (2.8 mmol/L).

After 52 weeks of study treatment, no effect on growth or sexual maturation was detected (See section 4.4 Special warnings and precautions for use).

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After treatment, 74 of 197 patients (37.6%) in this study achieved the LDL-C goal of less than 110 mg/dL (2.8 mmol/L). All age groups showed statistically significant reductions in LDL-C from baseline values.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth or sexual maturation was detected after 24 months of treatment.

## 5.2. PHARMACOKINETIC PROPERTIES

Rosuvastatin is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Exposure increases linearly over the dose range. The half life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20%. There is minimal accumulation on repeated once daily dosing.

Rosuvastatin undergoes first pass extraction in the liver which is the primary site of cholesterol synthesis and LDL-C clearance.

Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. The parent compound accounts for greater than 90% of the circulating active HMG CoA reductase inhibitor activity.

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.

**Special populations:**

Age and sex:

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race:

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and $C_{max}$ in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Renal insufficiency:

In a study in subjects with varying degrees of renal impairment, 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.

Hepatic insufficiency:

In a study in subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in the 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.

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. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold higher rosuvastatin exposure (AUC) or 2.4-fold higher exposure, respectively, compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

## 5.3. PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS

**Tablet core:**

- Lactose
- Colloidal anhydrous silica
- Silicified microcrystalline cellulose
- Maize Starch
- Purified talc
- Sodium stearylfumarate

**Tablet coat:**

- Hypromellose
- Mannitol
- Macrogol 6000
- Purified talc
- Titanium dioxide
- Ferric oxide, red (10 mg, 20 mg, 40 mg only)
- Ferric oxide, yellow (5 mg only)

## 6.2. INCOMPATIBILITIES

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

## 6.3. SHELF LIFE

2 years

## 6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

## 6.5. NATURE AND CONTENTS OF CONTAINER

Available in blister packs of 30 and 90 tablets.

Available in bottles of 30 and 90 tablets.

*Not all presentations may be marketed*

## 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

# 7. MEDICINE SCHEDULE

Prescription Only Medicine

## 8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Tel: 0800 726 369

## 9. DATE OF FIRST APPROVAL

15/12/2022

## 10. DATE OF REVISION OF THE TEXT

17/11/2025

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **4.3** | Minor editorial change |
| **4.5** | Addition of drug-drug interaction with ticagrelor |
| **4.8** | Update to adverse reaction reporting URL |
| **4.9** | Addition of risk assessment wording |
| **8** | Change in Sponsor details |