NEW ZEALAND DATA SHEET

ROSUVASTATIN MYLAN

1. Product Name

Rosuvastatin Mylan, 5 mg, 10 mg, 20 mg & 40 mg, film coated tablet.

2. Qualitative and Quantitative Composition

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

Excipients with known effect: lactose.

Allergen declaration: Contains sugars as lactose.

Each Rosuvastatin Mylan 5 mg film coated tablet contains 23 mg of lactose.

Each Rosuvastatin Mylan 10 mg film coated tablet contains 46 mg of lactose.

Each Rosuvastatin Mylan 20 mg film coated tablet contains 93 mg of lactose.

Each Rosuvastatin Mylan 40 mg film coated tablet contains 185 mg of lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Rosuvastatin Mylan 5 mg: A yellow coloured, round, film-coated tablet, debossed with "5" on one side and “R” on the other side.

Rosuvastatin Mylan 10 mg: A pink coloured, round, film-coated tablet, debossed with “10” on one side and “R” on the other side.

Rosuvastatin Mylan 20 mg: A pink coloured, round, film-coated tablet, debossed with "20" on one side and “R” on the other side.

Rosuvastatin Mylan 40 mg: A pink coloured, round, film-coated tablet, debossed with "40" on one side and "R" on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Rosuvastatin Mylan 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), Rosuvastatin Mylan 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 Mylan 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 Mylan 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 Mylan, 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

The dosage of Rosuvastatin Mylan 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).

Patients with risk factors for myopathy or rhabdomyolysis (such as elderly patients, severe renal impairment, severe hepatic impairment, individuals of Asian origin) should initially start on 5 mg once daily and increase as necessary (see further information under special populations below)

Dose

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 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 when necessary. The usual maximum dose of rosuvastatin is 20 mg once per day.

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 Mylan.

Specialist supervision should be considered when the dose is titrated to 40 mg.

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

As stated above, the usual start dose is 5 mg or 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.

Special populations

Use in the elderly

A start dose of 5 mg is recommended in patients > 70 years. No other dose adjustment is necessary in relation to age.

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).

Renal impairment

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

For patients with severe renal impairment the dose of Rosuvastatin Mylan should be started at 5 mg once daily and not exceed 10 mg once daily (see section 4.3 and 5.2).

Hepatic impairment

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

Patients with severe hepatic impairment should start therapy with Rosuvastatin Mylan 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above Rosuvastatin Mylan 10 mg should be carefully considered (see section 5.2).

Race

A 5 mg starting dose of Rosuvastatin Mylan should be considered for Asian patients. Increased plasma concentration of rosuvastatin has been seen in Asian subjects (see section 4.4 and 5.2). 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 Mylan is recommended (see section 4.4, 4.5 and 5.2).

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 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; see section 4.4 and 4.5). It is recommended that prescribers consult the relevant product information when considering administration of such products together with Rosuvastatin Mylan. Whenever possible, alternative medications should be considered, and if necessary, consider temporarily discontinuing rosuvastatin therapy. In situations where co-administration of these medicinal products with rosuvastatin is unavoidable, the benefit and the risk of concurrent treatment and Rosuvastatin Mylan dosing adjustments should be carefully considered (see section 4.5).

Concomitant therapy with ciclosporin

In patients taking ciclosporin, Rosuvastatin Mylan dosage should be limited to 5 mg once daily (see section 4.5).

Concomitant therapy with gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant Rosuvastatin Mylan and gemfibrozil (see section 4.5). If Rosuvastatin Mylan is used in combination with gemfibrozil, the dose of Rosuvastatin Mylan should be limited to 10 mg once daily.

Method of administration

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

4.3 Contraindications

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

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

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

Rosuvastatin Mylan is contraindicated in concomitant use of fusidic acid (see section 4.4 and 4.5).

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

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

Consequently:

1. 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 section 4.5 and 5.2)
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 (> 10xULN) 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 4.4 and 4.5). The benefit of further alterations in lipid levels by the combined used 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 section 4.2 and 4.5).
5. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances that increase rosuvastatin medicine levels (see section 5.2).
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) 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 included 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 derivates, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics (see section 4.2 and 4.5).

Fusidic acid must not be co-administered with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination (see section 4.3, 4.5 and 4.8). 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 patients 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.

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 and 5.1).

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see section 4.2 and 5.2).

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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).

Excipient(s) with known effect

Rosuvastatin Mylan contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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 section 4.2 and 4.4).

Ticagrelor: Ticagrelor has been shown to increase rosuvastatin AUC by 2.3-fold, 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 20 mg.

Protease inhibitors

Co-administration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold (see Table 1). Dose adjustments are needed depending on the level of effect on rosuvastatin exposure (see section 4.2 and 4.4)

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) OD 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↑
Belumosudil 200 mg QD, 8 days	10 mg, single dose on 2 separate days	4.6-fold↑
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8-fold↑
Enasidenib 100 mg OD, 28 days	10 mg, single dose	3.4-fold↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Roxadustat 200 mg QOD	10 mg, single dose	2.9-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg single dose	2.8-fold↑
Momelotinib 200 mg OD, 5 days	10 mg single dose	2.7-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↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10 mg single dose	2.26-fold↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5 mg once daily	2.2-fold↑

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
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↑
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		
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; QOD = every other day, 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 co-administration:
Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200 mg 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.

Physiologically-based pharmacokinetic modelling (PBPK) predicts no clinically relevant DDI between clopidogrel and rosuvastatin based on a dosage regimen of clopidogrel 300 mg loading dose, followed by 75 mg once a day (QD) maintenance dose.

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

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administrations 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, 4.4 and 4.8).

Effect of Rosuvastatin on co-administered medicinal products

Warfarin

The pharmacokinetics of warfarin are not significantly affected following coadministration 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).

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

Pregnancy

The safety of rosuvastatin during pregnancy and whilst breastfeeding 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). 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

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. From the safety profile, rosuvastatin 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 a clinical 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 and 5.1)

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 section 4.4 and 5.2). 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 a clinical 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 unknown: ocular myasthenia

Haematological disorders: Frequency unknown: thrombocytopenia

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

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 disorders: 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 clinical trials of children and adolescents. However, the same warnings and precautions for use in adults also apply to children and adolescents (see section 4.4).

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**Error! Hyperlink reference not valid.** 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 management of overdose please contact the National Poisons Centre 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10AA07

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 Tables 2 and 3).

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

The reported clinical trials showed rosuvastatin to be 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	NonHDL-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 hypertriglyceridaemia (Type IIb or Type IV) (Median % change from baseline)

Dose	N	TG	LDL-C	Total-C	HDL-C	nonHDL-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 Tables 2 and 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.

An active controlled study where rosuvastatin was compared with the HMG-CoA reductase inhibitors atorvastatin, pravastatin and simvastatin in a multicentre, 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 rosuvastatin, atorvastatin, simvastatin or pravastatin (Figure 1 and Table 4). The primary endpoint for this study was percent change from baseline in LDL-C at week 6.

Figure 1. Percent LDL-C change by dose of rosuvastatin, atorvastatin, simvastatin and pravastatin at week 6 in patients with Type IIa/IIb dyslipidaemia

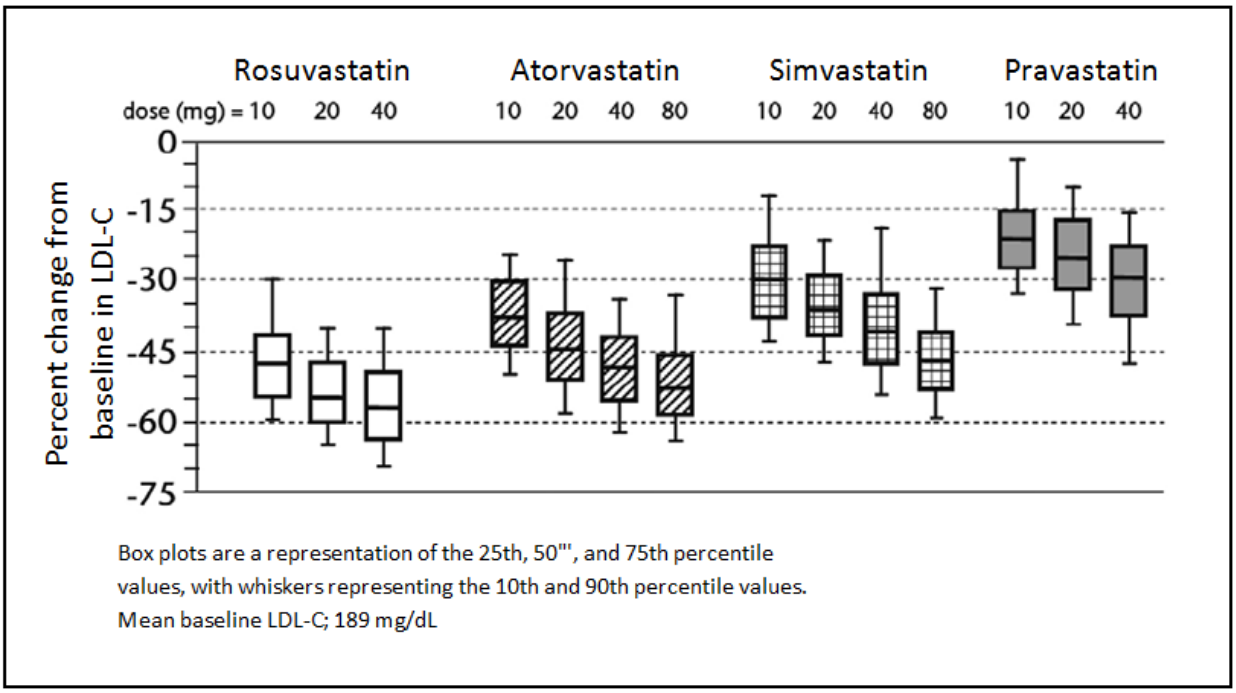


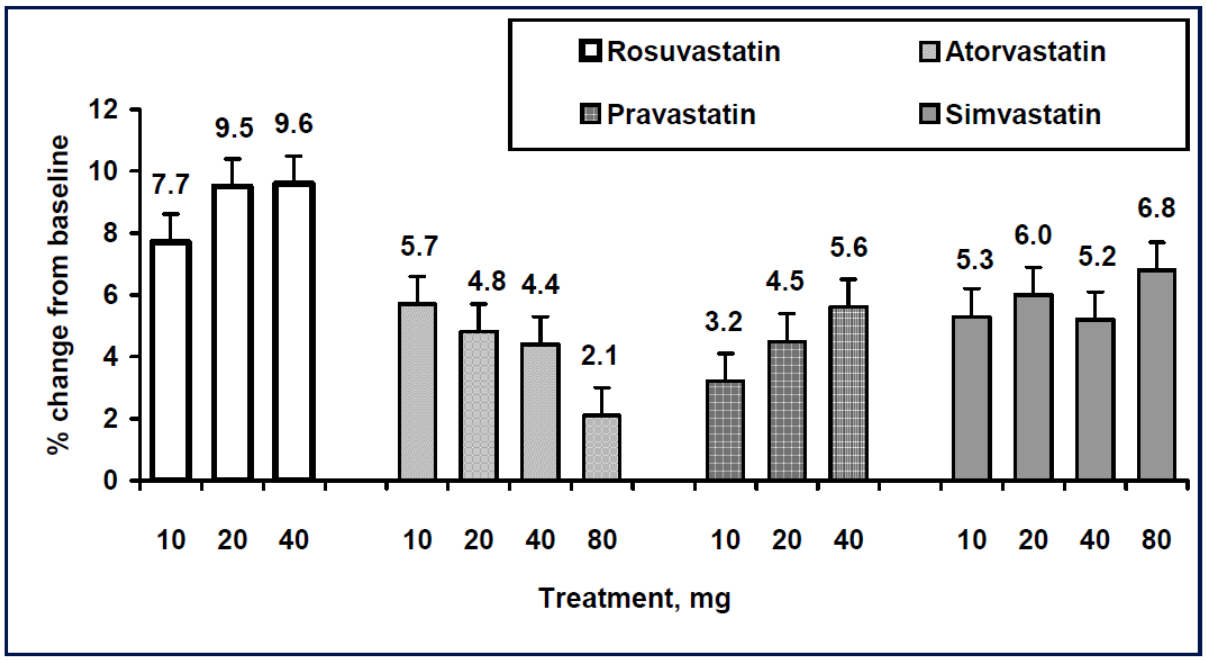
Table 4. LS Mean§ % change in LDL-C from baseline to week 6 for each statin treatment group

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

N = number of patients at each dose of each statin.
* Rosuvastatin 10 mg reduced LDL-C significantly more than atorvastatin 10 mg; pravastatin 10mg, 20 mg, and 40 mg; simvastatin 10 mg, 20 mg, and 40 mg. (p<0.002)
† Rosuvastatin 20 mg reduced LDL-C significantly more than atorvastatin 20 mg and 40 mg; pravastatin 20 mg, and 40 mg; simvastatin 20 mg, 40 mg, and 80 mg. (p<0.002)
‡ Rosuvastatin 40 mg reduced LDL-C significantly more than atorvastatin 40 mg; pravastatin 40 mg; simvastatin 40 mg, and 80 mg (p<0.002)
§ Corresponding standard errors are approximately 1.00

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

Figure 2. Mean (LS mean) percent change from baseline in HDL-C to week 6



p < 0.002 Rosuvastatin 10 mg vs Pravastatin 10 mg
p < 0.002 Rosuvastatin 20 mg vs Atorvastatin 20 mg, 40 mg, 80 mg; Pravastatin 20 mg, 40 mg; Simvastatin 40 mg
p < 0.002 Rosuvastatin 40 mg vs Atorvastatin 40 mg, 80 mg; Pravastatin 40 mg; Simvastatin 40 mg
Data presented as LS means ± SE

The mean percent change in HDL-C from baseline to Week 6 for each statin treatment group represented in Figure 2 is summarised with 95% CI in Table 5.

Table 5. LS Mean % change in HDL-C from baseline to week 6 for each statin treatment group

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

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

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	Rosuvastatin 5 mg N=25	Rosuvastatin 10 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, 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 was measured using B-mode ultrasonography)) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years, using a 5:2 randomised 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 this clinical trial 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).

Prevention of major cardiovascular events

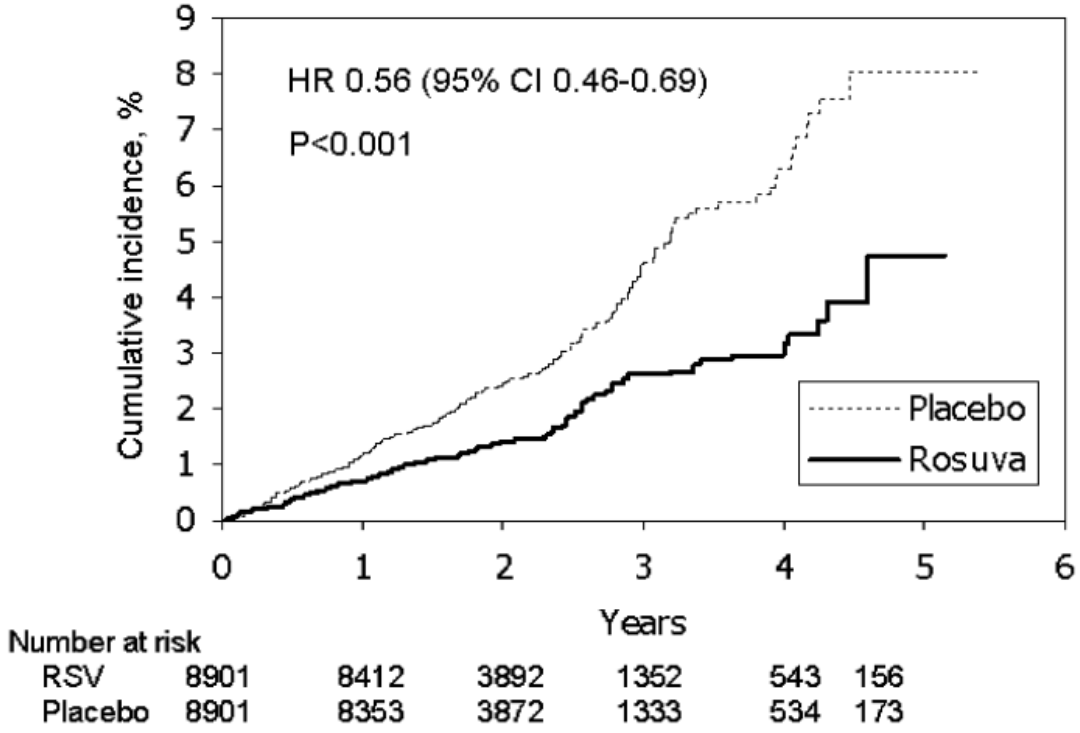
In another study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥ 50 years) and women (≥ 60 years) who had no established cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥ 2 mg/L. The 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% 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 this study.



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, placebo, 2.3%).

In this study 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).

In this study 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 suggested that the risk of developing 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 section 4.4 and 4.8).

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-HDL-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 the study treatment, no effect on growth or sexual maturation was detected (see section 4.4).

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 (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 (2.8mmol/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

Absorption

Rosuvastatin is administered orally in the active form with peak plasma levels occurring 5 hours after dosing. Absorption 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.

Distribution

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.

Biotransformation

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

Elimination

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

Rosuvastatin Mylan film coated tablet also contains:

Tablet core:
- crospovidone
- lactose monohydrate
- microcrystalline cellulose
- megulamine
- magnesium stearate
- pregelatinised starch

Film coating:
- titanium dioxide
- iron oxide red (10 mg, 20 mg and 40 mg tablet only)
- iron oxide yellow (5 mg only)
- triacetin
- lactose monohydrate
- hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle. Pack size of 30, 100, 500 and 1000 film coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

10. Date of Revision of the Text

19 May 2026

Summary table of changes

Section	Summary of new information
	New