

Rosuvastatin (Crestor) for dyslipidaemia

(roh-SOO-vah-stat-in)

Summary

- Choose any of the available statins when initiating treatment to reduce low-density lipoprotein-cholesterol (LDL-C) level; there is no clinical outcome evidence to suggest that one statin is better than another.
- If existing treatment with a statin achieves target LDL-C level, there is no need to switch to another statin, including rosuvastatin.
- Rosuvastatin may have a place for patients who cannot achieve target LDL-C levels. Higher doses of rosuvastatin (20–40 mg) achieve reductions in LDL-C that are not possible with most recommended doses of other statins.
- Start with 5 mg and titrate when necessary to achieve treatment goals (usual dose 5–20 mg once daily). Daily doses above 20 mg should be used with caution.
- The full adverse-effect profile for rosuvastatin is not yet known; however, rosuvastatin toxicity appears to be similar to other statins.

PBS listing

Rosuvastatin is listed on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit for patients who meet the criteria set out in the General Statement for Lipid Lowering Drugs described in the *Schedule of Pharmaceutical Benefits*.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended rosuvastatin for listing on a cost-minimisation basis compared with atorvastatin, with an equi-effective dose of rosuvastatin to atorvastatin of 1:3.¹

This recommendation was based on clinical trials that compared low-density lipoprotein-cholesterol (LDL-C) lowering with rosuvastatin and atorvastatin. There are currently no head-to-head studies comparing clinical outcomes with rosuvastatin at equipotent doses of other statins.

Place in therapy

Rosuvastatin is an HMG-CoA reductase inhibitor (statin) that lowers LDL-C levels.² Statins are first line for the treatment of hypercholesterolaemia.^{3,4} Aim for a target LDL-C level < 2.5 mmol/L (total cholesterol < 4 mmol/L).^{5,6} Any step towards the target is likely to be beneficial.

Lowering LDL-C level

Choose any of the available statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin or simvastatin) when initiating treatment to reduce LDL-C level in patients already compliant with lifestyle changes (such as diet and exercise). There is no clinical outcome evidence to suggest that one statin is better than another. If maximum recommended doses do not achieve treatment goals, switch to a statin that is more potent at lowering LDL-C. Alternatively, combining a statin with another lipid-modifying (non-statin) drug can also help reduce LDL-C.^{3–5}

If changing from other statins to rosuvastatin

Before switching treatment to rosuvastatin, check that the patient has been compliant with taking their statin treatment and with lifestyle changes (such as diet and exercise). Monitor the patient for adverse effects, which can occur when treatments change, especially if titrating rosuvastatin to a higher dose.

Rosuvastatin lowers LDL-C levels across its dose range

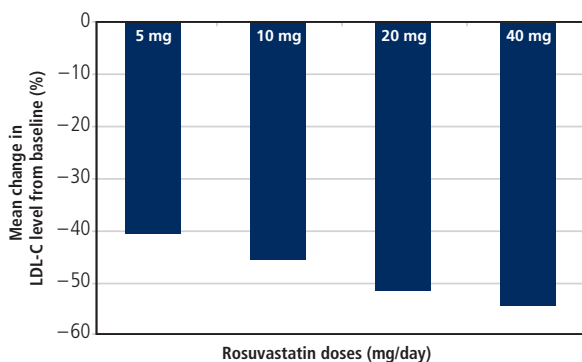
Rosuvastatin is more potent at lowering LDL-C on a milligram-for-milligram basis compared with other statins⁷⁻⁹; dose equivalencies are outlined in Table 1.

Higher doses of rosuvastatin (20–40 mg) achieve reductions in LDL-C not possible with other statins at most doses approved for use in Australia.^{8,9} Increasing the dose of rosuvastatin from 20 mg to 40 mg provides marginal additional reduction in LDL-C level. Mean percentage change in LDL-C levels from baseline⁷⁻⁹ are shown in Figure 1.

Table 1: LDL-C-lowering dose equivalence for approved statin doses

Statin	Dose equivalence			
Rosuvastatin	5 mg	10 mg	20 mg	40 mg
Atorvastatin	15 mg	30 mg	60 mg	—
Simvastatin	40 mg	80 mg	—	—

Figure 1: Mean percentage change in LDL-C levels from baseline



Safety issues

Rosuvastatin's adverse-effect profile is similar to that of other statins. However, its full adverse-effect profile will only be established after more widespread and long-term use in a broader patient population. As with any new drug, use rosuvastatin with caution until more experience accumulates.

Rosuvastatin's adverse effects include myalgia, asthenia, mild gastrointestinal symptoms, dizziness and headache. Rarely, myopathy, rhabdomyolysis, pancreatitis, and hepatic and skin hypersensitivity reactions can occur.² Recommended adverse-event monitoring is outlined in Box 1.

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Familiar statin adverse effects

Pre-registration clinical trials focus on efficacy and so are limited in their ability to detect rare or long-term adverse effects. Postmarketing reports of adverse events can be critical in determining the safety of new drugs, as

Box 1: Recommended adverse-event monitoring with statins^{2,3}

Statin pose a risk of myopathy and rhabdomyolysis

Stop treatment with rosuvastatin if patients develop unexplained muscle aches, mild to severe pain, or stiffness or weakness, even when plasma creatine kinase levels are normal. Monitor creatine kinase at baseline and repeat during treatment if clinically indicated or with any increase in dose.

Monitor liver transaminases, particularly at higher doses

Elevations in liver transaminase levels (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) with statins are dose dependent but uncommon and rarely develop into serious hepatic reactions (e.g. cholestatic jaundice).

Perform liver function tests before initiating rosuvastatin and periodically thereafter. Stop rosuvastatin if ALT and/or AST levels are persistently 3 or more times the upper limit of normal.

experience with cerivastatin has shown (withdrawn from worldwide markets August 2001 because of serious muscle-related adverse effects).¹⁰

Myopathy rates reported in rosuvastatin clinical trials were similar to those of other statins^{11,12} and initial postmarketing reports overseas have shown the incidence of rosuvastatin-associated rhabdomyolysis to be similar to other statins.¹² However, there have been public statements and analyses questioning rosuvastatin's toxicity.^{13,14} In response to this, the US Food and Drug Administration (FDA) conducted a review of muscle and renal adverse-event reports for all statins.¹⁵ During the first 6 months of each drug's availability in the US, a myopathy/rhabdomyolysis reporting rate (per 100 000 prescriptions) of 0.3 for rosuvastatin compared with 0.06 for atorvastatin was observed — rates that are a magnitude less than that reported for cerivastatin. The FDA proposed reasons for the observed difference, including the possibility of enhanced reporting of adverse events following the withdrawal of cerivastatin, and acknowledged the small number of cases (2 cases for rosuvastatin and one for atorvastatin). Therefore the FDA concluded that there was no evidence that rosuvastatin posed any greater risk of muscle toxicity than other statins.

The incidence of dipstick proteinuria for rosuvastatin doses < 20 mg was similar to that for other statins and placebo^{13,16,17} and the FDA concluded that there was no convincing evidence that rosuvastatin posed a risk of renal toxicity.¹⁵

Postmarketing adverse-event reports are limited by variable information quality and the tendency in clinical practice to under-report adverse events, particularly less serious ones; these reports do not reflect the true adverse event incidence rate. While it is too early to draw definitive conclusions about rosuvastatin's overall safety profile relative to that of other statins, such conclusions must include all the evidence available from pre-registration clinical trials, ongoing clinical trials and postmarketing reports.

Rosuvastatin interacts with cyclosporin, gemfibrozil and warfarin

Rosuvastatin dose adjustment is required with concurrent cyclosporin (maximum rosuvastatin dose 5 mg daily) or gemfibrozil (maximum rosuvastatin dose 10 mg daily).²

Monitor for increased INR in patients taking warfarin. Refer to the approved product information for further drug interaction information.² Unlike atorvastatin and simvastatin, rosuvastatin clearance is not dependent on cytochrome P450 3A4 enzyme metabolism.^{2,3,11,18} As such, there are no interactions between rosuvastatin and cytochrome P450 3A4 inhibitors such as erythromycin, fluconazole, itraconazole and ketoconazole.

Dosing issues

Start with 5 mg and titrate if necessary to achieve treatment goals (dose range 5–20 mg once daily). Patients of Asian descent require lower doses. Measure the LDL-C level within 4 weeks of initiating rosuvastatin, or after dose titration. Rosuvastatin can be taken at any time of the day, with or without food.^{2,3,19}

Consider specialist supervision when prescribing rosuvastatin above 20 mg daily

Higher doses (20–40 mg) may be required to reduce LDL-C levels. The 40 mg dose should only be considered for patients who are still at high cardiovascular risk after their response to 20 mg daily is assessed and in whom regular follow-up is planned.^{2,3,19} Do not exceed the 40 mg dose in any patient and do not use this dose in patients of Asian descent.²

Information for patients

Advise patients that:

- rosuvastatin must be taken every day, together with lifestyle changes such as diet and exercise
- adverse effects of the muscle or liver are rare but are more likely to occur if blood levels of rosuvastatin are increased (e.g. by interaction with drugs such as cyclosporin and gemfibrozil)
- persistent muscle aches, mild to severe pain, or stiffness or weakness must be reported promptly, especially after any change in treatment.

Suggest or provide the consumer medicine information (CMI) when prescribing or supplying rosuvastatin.

References

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.