

NEW DRUG EVALUATION

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ROSUVASTATIN

Rosuvastatin is an HMG-CoA reductase inhibitor ('statin') licensed for the treatment of hypercholesterolaemia and mixed dyslipidaemia. Results of comparative trials suggest that it is more potent than atorvastatin, simvastatin, and pravastatin. The adverse effects associated with rosuvastatin are similar to those of the other statins. There are no long-term safety data or clinical outcome data for rosuvastatin and it is not licensed for the prevention of cardiovascular events. At present, rosuvastatin should be reserved for patients who are poorly controlled on, or unable to tolerate high doses of the other statins available.

What is it?

Rosuvastatin (Crestor[®], AstraZeneca) is an HMG-CoA reductase inhibitor ('statin') licensed for the treatment of hypercholesterolaemia, and mixed dyslipidaemia. The recommended starting dose is 10 mg daily. The dose may be increased to 20 mg daily after 4 weeks if required. The maximum daily dose is 40 mg daily.¹ The manufacturer claims that, in comparison to the currently available statins, rosuvastatin produces a greater reduction in LDL-cholesterol (LDL-C), a greater rise in HDL-cholesterol (HDL-C), and enables most patients to reach their LDL-C target level at the lowest dose of 10 mg daily.

How effective is it?

There are 3 randomised, double-blind trials that have compared rosuvastatin with atorvastatin, one of which has not been published.^{2,3,4} In pooled analyses of the 12 week results, rosuvastatin 10 mg daily (n=389), compared with atorvastatin 10 mg daily (n=393), produced greater reductions in LDL-C (47% vs 36%, p<0.001), total cholesterol (33% vs 27%, p<0.001), and triglycerides (19% vs 18%, p=ns).^{5,6} Rosuvastatin was more effective than atorvastatin in raising HDL-C (8.9% vs 5.5%, p<0.001).⁵ More patients treated with rosuvastatin, compared with atorvastatin, reached the LDL-C target of <3.0 mmol/L consistent with that described in the Coronary Heart Disease National Service Framework (82% vs 51%, p<0.001).⁶

There are 2 randomised, double-blind trials that have compared rosuvastatin with simvastatin and pravastatin.^{7,8} In pooled analyses of the 12 week results, rosuvastatin 10 mg daily (n=226), compared with simvastatin 20 mg daily (n=249) or pravastatin 20 mg daily (n=252), produced greater reductions in LDL-C (48% vs 36% vs 27%, p<0.001), total cholesterol (34% vs 25% vs 19%, p<0.001), and triglycerides (20% vs 12% vs 12%, p<0.01).^{5,6} The increase in HDL-C was greater with rosuvastatin than with simvastatin or pravastatin (9.1% vs 6.2% vs 6.2%, p<0.05).⁵ More

patients treated with rosuvastatin reached the LDL-C target of <3.0 mmol/L compared with simvastatin or pravastatin (80% vs 48% vs 16%, p<0.001).⁶

Two of the above studies^{4,8} included 40 weeks of dose titration following the 12 week fixed-dose period. Rosuvastatin continued to show greater potency in reducing LDL-C than atorvastatin, simvastatin, or pravastatin.

In a 6 week, randomised, double-blind, parallel-group study (n=374), rosuvastatin (5, 10, 20, 40, or 80 mg daily) compared with atorvastatin (10, 20, 40, or 80 mg daily) produced an 8.4% greater reduction in LDL-C across the dose range studied (p<0.001).⁹

In a 6 week, open-label, parallel-group study published in abstract form only, 2431 patients were randomised to rosuvastatin, atorvastatin, simvastatin (10, 20, 40, or 80 mg daily), or pravastatin (10, 20 or 40 mg daily). Rosuvastatin 10 mg daily produced a significantly greater reduction in LDL-C than simvastatin 10, 20, or 40 mg daily, pravastatin 10, 20 or 40 mg daily, or atorvastatin 10 mg daily (p<0.002).¹⁰

How safe is it?

The incidence of adverse drug reactions with rosuvastatin is dose-dependent, as with other statins.¹ The most common adverse effects (>1% and <10%) reported were headache, dizziness, gastrointestinal effects, myalgia, and asthenia.¹ In clinical trials, the incidence of clinically significant increases in alanine aminotransferase (ALT) was <0.1%, and the incidence of myopathy was <0.01%, comparable to that seen with other statins.¹¹ Rare cases of rhabdomyolysis have been reported in patients on the unlicensed dose of 80 mg daily.¹ Proteinuria, mostly tubular in origin, was reported in <1% of patients on rosuvastatin 10 or 20 mg daily, and approximately 3% of patients on the 40 mg daily dose.¹ The proteinuria was reversible in most cases and was not predictive of renal disease.¹

What other options are there?

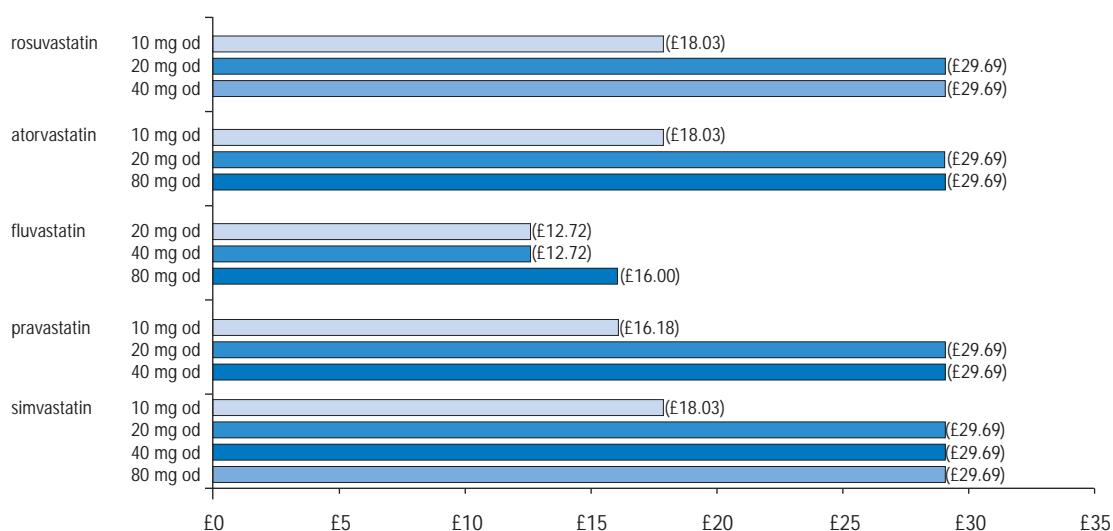
There are currently four other statins licensed in the UK; atorvastatin, fluvastatin, pravastatin, and simvastatin. There has been a recent review of these statins.¹² Although long-term clinical outcome data are emerging for atorvastatin,¹³ simvastatin and pravastatin are currently the only statins with significant long-term morbidity and mortality data that are licensed for both the primary and secondary prevention of cardiovascular events.¹² Simvastatin has just recently come off patent, and can reasonably be expected to show a significant price decrease.¹⁴

When should it be used?

There are no long-term safety data or clinical outcome data for rosuvastatin and it is not currently licensed for the prevention of cardiovascular events. Although rosuvastatin is more potent than other available statins, this in itself does not constitute a significant benefit. When treating with statins, it is important to review therapy regularly and increase the dose as necessary to achieve target cholesterol levels. At present, rosuvastatin may be considered as an alternative for patients who are poorly controlled on, or unable to tolerate high doses of the other statins available.

How much does it cost?

Cost for 28 days treatment (prices from MIMS/Drug Tariff May 2003)



NB Doses shown are for general comparison only and do not imply therapeutic equivalence.

REFERENCES

- 1 Rosuvastatin. Summary of Product Characteristics, AstraZeneca, March 2003.
- 2 Davidson et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002;89:268-275. (RCT)
- 3 AstraZeneca UK Ltd, Data on File CRE/010/FEB2003. (U)
- 4 Olsson AG et al. Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolaemia. *Am Heart J* 2002;144:1044-1051. (RCT)
- 5 Blasetto JW et al. Efficacy of rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *Am J Cardiol* 2003;91(suppl):3C-10C. (MA)
- 6 Shepherd J et al. Guidelines for lowering lipids to reduce coronary artery disease risk: A comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol* 2003;91(suppl):11C-19C. (MA)
- 7 Paoletti et al. Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolaemic patients: a randomised, double-blind study. *J Cardiovasc Risk* 2001;8:383-390. (RCT)
- 8 Brown WV et al. Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolaemia: A randomized, double-blind, 52-week trial. *Am Heart J* 2002;144:1036-1043. (RCT)
- 9 Schneck DW et al. Comparative effects of rosuvastatin and atorvastatin across their dose ranges in patients with hypercholesterolaemia and without active arterial disease. *Am J Cardiol* 2003;91:33-41. (RCT)
- 10 Jones PH for the STELLAR Study group. Statin therapies for elevated lipid levels compared across dose ranges to rosuvastatin: low-density lipoprotein cholesterol and high-density lipoprotein cholesterol results. *J Am Coll Cardiol* 2003;41(6 supplA):315A-316A, Abs 876-2. (A)
- 11 Shepherd J et al. Summary of the benefit-risk profile of rosuvastatin 10-40mg from an international clinical trial programme. *Circulation* 2003;17:e148, Abs P14. (A)
- 12 Regional Drug and Therapeutics Centre. Statins. Drug Update. November 2002. No. 22. (R)
- 13 Sever PS et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-1158. (RCT)
- 14 Anon. First statin expires amid OTC speculation. *Pharm J* 2003;270:603.

KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial