PUBLIC SUMMARY DOCUMENT

Product: Rosuvastatin Calcium, tablets, 5 mg, 10 mg, 20 mg, 40 mg, Crestor®

Sponsor: AstraZeneca Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The application sought a restricted benefit listing of rosuvastatin for the treatment of hypercholesterolaemia.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Crestor is registered by the TGA as an adjunct to diet when the response to diet and exercise is inadequate for the treatment of hypercholesterolaemia (including familial hypercholesterolaemia). Prior to initiating therapy with Crestor, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.

4. Listing requested and PBAC's View

A PBS listing comparable to that of the other HMG CoA reductase inhibitors was requested as shown below.

Restricted Benefit
For use in patients that meet the criteria set out in the General Statement for Lipid Lowering Drugs.

The PBAC's view was that a NOTE be included in the PBS listing, indicating that the highest strength, 40 mg, should be prescribed with caution as described in the approved Product Information.

For the PBAC's view see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Rosuvastatin is a member of the HMG CoA reductase inhibitor (statin) class of drugs. It provides an alternative treatment option to other members of this class for the lowering of lipid levels.

6. Comparator

The submission nominated atorvastatin and simvastatin as the comparators. The PBAC considered atorvastatin was the most appropriate, as this is the drug that will principally be replaced in practice.

7. Clinical trials

The submission presented a series of meta-analyses of 29 randomised trials comparing rosuvastatin with either atorvastatin or simvastatin.

Trial/First author	Protocol/Publication title	Publication citation
SOLAR/ Insull JW et al	Effect of three statins at starting dose on achieving national LDL-C goals in hypercholesterolaemic patients with or without diabetes in a managed-care setting.	Diabetes 2005;54(Suppl:1):1-O.
MERCURY II/ Ballantyne CM et al	Achievement of non-hdl-c and apo B goals in high-risk patients who achieve their atp III LDL-C goal: mercury II trial.	Atherosclerosis Supplements 2005;6(1):W16-004.
Ballantyne CM	Effect of switching high- and very high-risk patients to rosuvastatin from atorvastatin or simvastatin on achievement of new ATP III goals: Mercury II.	Atherosclerosis Supplements 2005;6(1):W16-003.
STELLAR/ Deedwania PC et al	Effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia in patients with characteristics of the metabolic syndrome.	American Journal of Cardiology 2005 Vol 95(3): 360-366.
Jones PH et al	Statin therapies for elevated lipid levels compared across doses to rosuvastatin (STELLAR): LDL-C goal achievement with new NCEP ATP III recommendations.	Atherosclerosis Supplements 2005;6(1):W16-040.
Welty FK et al	Women achieve American Heart Association optimal lipid goals with statin therapy.	Circulation 2005;111(4):E62.
URANUS/ Sorof J et al	Renal safety of rosuvastatin and atorvastatin in type 2 diabetic patients.	Atherosclerosis Supplements 2005;(1):W16-083.
Berne C et al	Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: Results from the URANUS study.	Cardiovascular Diabetology 2005 Vol 4: 11.
ANDROMEDA/ Betteridge DJ et al	Effect of rosuvastatin and atorvastatin on CRP levels in patients with type 2 diabetes: results from the andromeda study. (abstract)	Atherosclerosis Supplements 2005;6(1):W16-007.
DISCOVERY DUTCH/ Bots AFE et al	Achieving lipid goals in real life: the Dutch DISCOVERY Study.	International Journal of Clinical Practice 2005;(12):1387-94.
DISCOVERY PENTA/Fonseca	The discovery penta study: A direct statin comparison of LDL-C value - an	Current Medical Research & Opinion 2005 Vol 21(8):1307-1315

Trial/First author	Protocol/Publication title	Publication citation
FAH et al	evaluation of rosuvastatin therapy compared with atorvastatin.	
Fonseca FAH et al	Comparison of the efficacy and tolerability of rosuvastatin with atorvastatin in patients with hypercholesterolaemia: the discovery penta study.	Atherosclerosis Supplements 2005;6(1):W16-029.
MERCURY I/ Schuster H et al	Measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY I): Achievement of LDL-C goals with updated ATP III recommendations.	Atherosclerosis Supplements 2005;6(1):W16-079.
Stender S	Comparison of rosuvastatin with atorvastatin, simvastatin and pravastatin in achieving cholesterol goals and improving plasma lipids in hypercholesterolaemic patients with or without the metabolic syndrome in the MERCURY I trial.	Diabetes, Obesity & Metabolism 2005 Vol 7(4):430-438,
Cheung RC	Effects of switching statins on lipid and apolipoprotein ratios in the MERCURY I study.	International Journal of Cardiology 100(2):309-16, 2005 Apr 20.
PULSAR/ Clearfield M et al	Efficacy and safety of rosuvastatin 10 mg versus atorvastatin 20 mg: results of the pulsar study.	Atherosclerosis Supplements 2005;6(1):W16-014.
RADAR/ Dallinga TM et al	Effect of rosuvastatin and atorvastatin treatment on LPAI and LPAI:AII in patients with coronary artery disease and low HDL cholesterol.	Atherosclerosis Supplements 2005;6(1):49.
Jukema JW et al	LDL-C/HDL-C ratio in subjects with cardiovascular disease and a low HDL-C: results of the RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study.	Current Medical Research & Opinion 2005;21(11):1865-74.
ARIES/ Ferdinand K et al	Effect of Statin Therapy on C-Reactive Protein Levels Among African American Patients with Hypercholesterolemia: Results of Aries Trial.	Journal of the American College of Cardiology 2005;45(3):A437-5.
Ferdinand KC	Comparison of efficacy and safety of rosuvastatin versus atorvastatin in african-american patients in a six-week trial.	American Journal of Cardiology 2006;229-35.
DISCOVERY CANADA/ Gupta M et al	Direct statin comparison of LDL-C values: an evaluation of rosuvastatin therapy (discovery - Canada).	Atherosclerosis Supplements 2005;6(1):W16-033.
POLARIS/ Leiter LA et al	Efficacy of rosuvastatin 40 mg versus atorvastatin 80 mg in patients with the metabolic syndrome: results from a subgroup of the POLARIS study.	Diabetologia 2005;48(Suppl:1):1.
Leiter LA et al	Rosuvastatin 40 mg versus	European Heart Journal

Trial/First author	Protocol/Publication title	Publication citation
	atorvastatin 80 mg in high-risk patients with hypercholesterolaemia: results of the POLARIS study at 8 and 26 weeks.	2005;26(Abstract:Supplement):
Leiter LA et al	Rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolaemia: early results of the polaris study.	Atherosclerosis Supplements 2005;6(1):W16-051.
Miller PSJ et al	Rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolaemia: economic analysis of the polaris study.	Atherosclerosis Supplements 2005;6(1):W16-055.
COMETS/ Stalenhoef AFH et al	A COmparative study with rosuvastatin in subjects with METabolic Syndrome: Results of the COMETS study.	European Heart Journal 2005 Vol 26(24): 2664-2672)
Stalenhoef AFH et al	Effect of rosuvastatin and atorvastatin on LDC-C and CRP levels in patients with the metabolic syndrome: results from the comets study.	Atherosclerosis Supplements 2005;6(1):W12-071.
Stalenhoef AFH et al	Rosuvastatin has greater beneficial effects than atorvastatin on LDL-C, HDL-C and apolipoproteins A-i and B in subjects with the metabolic syndrome.	International Journal of Clinical Practice 2005;59(Suppl:148):148-4.
DISCOVERY TRIPLE COUNTRY/ Strandberg TE et al	Discovery: a comparison of efficacy and safety of rosuvastatin and atorvastatin in high-risk subjects with hypercholesterolaemia.	International Journal of Clinical Practice 2005;59(Suppl:148):148.
CORALL/ Wolffenbuttel BHR et al	Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes - CORALL study.	Journal of Internal Medicine 2005 Vol 257(6): 531-539).

8. Results of trials

The submission stated that the results of the meta-analyses supported the conclusion that rosuvastatin gave rise to a statistically significantly larger % reduction in LDL-C than twice the strength of atorvastatin and that there was no statistically significant difference between rosuvastatin and four times the atorvastatin strength. This analysis suggested that the rosuvastatin: atorvastatin equivalent dose ratio was greater than 1:2, but less than 1:4. The PBAC agreed that this conclusion appeared consistent with the results of meta-analyses that were produced during the evaluation.

A meta-analysis comparing rosuvastatin 10 mg and simvastatin 20 mg was also presented. The results of the meta-analysis conducted during the evaluation were consistent with the results of the submission's meta analysis, that rosuvastatin gave rise to a statistically significantly larger % reduction in LDL-C than twice the strength of simvastatin. No statistically significant heterogeneity was observed across simvastatin trials.

9. Clinical Claim

The submission claimed that rosuvastatin is no worse, in terms of LDL-C lowering efficacy and safety, than atorvastatin, when compared assuming a therapeutic relativity of rosuvastatin 1 mg: atorvastatin 3 mg.

10. Economic analysis

A preliminary economic evaluation was presented. The choice of a cost-minimisation approach was valid. The resources included were drug costs.

A modelled economic evaluation was appropriately not presented.

11. Estimated PBS Usage and Financial Implications:

The overall statin market was not expected to grow more rapidly as a result of listing rosuvastatin.

12. Recommendations and Reasons

The PBAC recommended listing on a cost-minimisation basis with atorvastatin, with the ratio of equi-effective doses being rosuvastatin to atorvastatin1:3. This recommendation is based on the series of meta-analyses presented in the submission of 29 randomised trials comparing rosuvastatin with atorvastatin or simvastatin. The PBAC agreed that atorvastatin was the most appropriate comparator, as this is the drug that will principally be replaced in practice.

The PBAC considered it appropriate that a NOTE be included in the PBS listing, indicating that the highest strength, 40 mg, should be prescribed with caution as described in the approved Product Information. The PBAC requested that the National Prescribing Service considers developing a RADAR article on this product to highlight this issue. The PBAC also requested that the sponsor develop a QUM strategy to address this issue.

Recommendation
Rosuvastatin calcium, tablets, 5 mg, 10 mg, 20 mg, 40 mg

Restricted Benefit
For use in patients that meet the criteria set out in the General Statement for Lipid Lowering Drugs.

Note: Doses higher than 20 mg per day should be used with caution. See Product Information.

Maximum quantity: 30
Repeats: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Rosuvastatin was the subject of a pre-registration development and safety program, which exceeded that of all the other statins combined. The available evidence shows that rosuvastatin provides superior LDL-C lowering efficacy and the toxicity profile is not different than that of the other listed statins. These data also show that the toxicity profile of the highest dose of rosuvastatin is no different than that of the highest doses of the other statins. All high dose statins should be used with caution.