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Ms Naomi Bleeser
Committee Secretary
Senate Community Affairs References Committee
PO Box 6100
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CANBERRA ACT 2600

14 April 2010

Via email: community.affairs.sen@aph.gov.au

Dear Ms Bleeser

On 25 November 2009, the Senate referred the issue of 'consumer access to pharmaceutical benefits and the creation of new therapeutic groups through the Pharmaceutical Benefits Scheme' to the Community Affairs References Committee for inquiry. The referral directed that the Inquiry was to report by 30 June 2010.

By way of this letter, AstraZeneca seeks to contribute to the Inquiry and the subsequent report. This contribution reflects AstraZeneca's views and experience of the impact of the Therapeutic Group Premium (TGP) policy, particularly since the 2007 PBS Reforms. Specifically, this submission is about the impact of the Therapeutic Group Premium policy on the people taking these medicines.

EXECUTIVE SUMMARY

It is AstraZeneca's view and experience, that the Therapeutic Group Premium (TGP) Policy will have a negative impact on people who need these medicines.

1. The TGP policy negatively impacts Australians by risking **access** to new medicines:
    - It contradicts the intention of PBS Reform, and threatens a key objective of the Reform : timely access to new medicines
    - It has created uncertainty and will lead to delays in access, or can prevent access to new medicines.
2. The TGP policy increases the risk of **patient harm**:
    - the data used to justify formation of therapeutic groups are incomplete and inappropriate
    - Each strength/form of medicine within a therapeutic group does not have an alternative which is interchangeable.
        a. not all medicines within a therapeutic group have been approved by TGA for the same usage
        b. some strengths/forms of medicines within a TG do not have a safe or equivalently effective alternative:
            i. use of a less effective medicine exposes a person to long term health risks
            ii. use of a medicine with greater adverse events exposes a person to increased risk

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3. Over and above TG Premiums, the TGP policy can increase the **financial impact** for people using these medicines. To achieve the equi-effective dose may require an additional prescription.

Context and Background

The 2007 Reforms to the PBS are, of course, an important context to this inquiry.

The objective of the Reforms was to ensure a sustainable PBS with the capacity to provide Australians with timely access to new medicines without an increase in costs to patients. This objective was to be accomplished by achieving significant savings in off-patent[1] medicines.

AstraZeneca agreed with the objective of PBS Reform and subsequently prepared for significant reductions in off patent medicines, and the launch of new medicines in anticipation of a more certain future environment.

However, an unexpected barrier to the achievement of the PBS Reform objective has arisen. While the Reforms sought to separate on-patent (single brand) and off-patent (multi brand) medicines[2], the Therapeutic Group Premium policy is being used to unite single and multiple branded medicines.

Thus the TGP policy, which is being used without consultation with any industry, medical or patient stakeholders, appears to takes precedence over the intention of PBS Reform.

AstraZeneca has first-hand experience of the use of the Policy to disrupt implementation of the legislation. This experience has informed AstraZeneca's view of the TGP policy, it's effect on the future certainty of our environment, and it's subsequent impacts in the short and long term on Australians. This view is presented below in the context of selected, relevant terms of reference of the inquiry.

Term a) the impact of new therapeutic groups on consumer access to existing PBS drugs, vaccines and future drugs, particularly high cost drugs;

New therapeutic groups risk timely access to future medicines

AstraZeneca's single brand rosuvastatin (CRESTOR®) and Pfizer's single brand atorvastatin are two important medicines in the prevention of first and subsequent cardiovascular events in people at moderate to high risk. These two medicines were allocated to the single brand (F1) formulary as per the legislation, and in consultation with AstraZeneca.

The TGP policy has now been used to create a therapeutic group of these medicines without consultation with any physician or patient group. AstraZeneca was similarly not consulted and, in fact, was notified of the formation of the group just hours prior to the release of the details within the 2009 Federal Budget[3].

It is evident that this group was formed as a cost control mechanism; both medicines will be subject to the multi-brand formulary (F2) price reductions at the same time as the PBS listing of the first alternative brand of either medicine, even if still single branded.

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[1] multiple branded

[2] By establishing the F1 formulary (single brands) and the F2 formulary (multiple brands)

[3] This lack of consultation is disturbing, given that the formation of this group was considered by government as early as November 2008, according to information obtained via Freedom of Information.

Impacts such as this highlight the growing, unanticipated, uncertainty of the post PBS Reform environment. Because Australia is used as a reference for other countries, there is a risk that access to new medicines in Australia will be delayed to reduce the impact on other countries. This is termed "launch sequencing" (and AstraZeneca is experiencing this effect with one new product at present).

In the next two years, AstraZeneca Australia intends to build cases to pursue registration and reimbursement for 5-6 new medicines in the clinical areas of pain, cardiovascular disease, and cancer. There is no doubt that the case to pursue access in Australia is at risk because of the threat of the unpredictable formation of Therapeutic Groups. TG formation could link a new single brand medicine with older multiple branded medicines.

In the best case, access will be delayed. However, the risk that some new medicines will not be made available to Australians cannot be dismissed.

New therapeutic groups risk timely access to new medicines.

Term b) the criteria and clinical evidence used to qualify drugs as interchangeable at a patient level

There is no certainty that medicines in a therapeutic group can be used interchangeably and without adverse health outcome in a single person

Despite requests on behalf of it's member companies, Medicines Australia has been unable to secure any clarity around the meaning of "interchangeable at the patient level". Interchangeability is a key matter (but not the only matter) in the determination of a therapeutic group.

In practice, interchangeability is being determined on the basis of inappropriate data. These determinations lead to conclusions that one proven medicine is interchangeable with another which has not been proven to be safe and efficacious. This has the potential to create confusion and to increase risk to people using these medicines.

The available evidence is not an appropriate basis upon which to conclude patient level interchangeability

Regardless of the detailed criteria which may at some point be revealed, it is clear that recommendations of interchangeability at the patient level are being made on the basis of studies which were not designed to answer the question of interchangeability.

AstraZeneca's CRESTOR was recommended for PBS listing by PBAC in 2006 on the basis of >20 head to head studies. PBAC agreed with AstraZeneca that CRESTOR reduces LDL-c (bad cholesterol) to the same extent as a three times higher dose of atorvastatin (the so-called "1:3 relativity" : see the rosuvastatin Public Summary Document, [Attachment 1], the National Prescribing Service's RADAR [Attachment 2] and the PBPA Relativity sheets [Attachment 3].)

Importantly, of this large number of clinical studies only two[4] studied the impact on people of switching between these two medicines. These data would be the appropriate type of evidence to conclude patient-level interchangeability.

The two studies which did examine the effect of switching concluded that switching a person from atorvastatin to the same dose of CRESTOR lead to improved effects : more people achieved the LDL-c target levels, and they experienced a larger reduction in LDL-c.

[4] MERCURY I and MERCURY II

Because of the lack of appropriate evidence upon which a conclusion of interchangeability can be based, there is no certainty that CRESTOR and atorvastatin are interchangeable in the same person. The PBAC have nevertheless recommended that the two medicines are interchangeable at the patient level.

Economic, safety and efficacy criteria define a medicine as interchangeable with another medicine

We continue to use the CRESTOR example to illustrate this issue.

When one considers the accepted "1:3 relativity" described above, it becomes clear that CRESTOR and atorvastatin are not interchangeable for i) economic reasons, ii) safety reasons and iii) efficacy reasons.

Economic reasons

To ensure, as much as possible, that there is no change to health impact when switching between CRESTOR and atorvastatin, one would need to utilise doses consistent with the 1:3 clinical relativity.

For example, using the 1:3 relativity a 20mg dose of CRESTOR is clinically equivalent to 60mg atorvastatin. This is the dose which would ensure, as much as possible, that health outcome would not change if switching to atorvastatin from 20mg CRESTOR.

However, a 60mg dose of atorvastatin does not exist. To access such a dose, two existing strengths of atorvastatin (40mg and 20mg) would need to be combined on a prescription. To the patient, this likely represents an increase in costs from one copayment to two (for a general patient an increase in costs from $33.30 to $66.60. For concessional patients, from $5.40 to $10.80).

The less costly, practical alternative for a physician and patient is to use an existing, but non-equivalent strength of atorvastatin. A non-equivalent strength will have a different health outcome and is therefore non interchangeable.

Safety reasons

Considering a situation in which a person is using the highest strength of CRESTOR (40mg), the dose of atorvastatin required to elicit the same reduction in LDL cholesterol is 120mg.

In addition to the fact that a daily dose of 120 mg does not exist and would likely double the cost to patient[5], it is beyond the range of dosing permitted by TGA and would contradict the TGA approved product information for atorvastatin. Indeed, 80 mg is the maximum allowable daily dose for atorvastatin according to the literature and many other regulatory/reimbursement agencies including the NICE (The National Institute of Clinical Excellence, UK).

This means that there are no data that have established that this dose of atorvastatin is safe for use.

Thus, there are safety reasons which lead to the conclusion that CRESTOR and atorvastatin are not interchangeable for an individual.

[5] It would likely double the cost to patient because to access 120mg atorvastatin, two existing strengths of atorvastatin (40mg and 80mg) would need to be combined on a prescription. To the patient, this likely represents an increase in costs from one copayment to two (for a general patient an increase in costs from $33.30 to $66.60).

Efficacy reasons

Because, as is detailed above, there is no existing interchangeable atorvastatin dose for any strength of CRESTOR, a physician would likely switch to either i) the same dose (mg:mg), or ii) the nearest equivalent dose.

In either of these scenarios, switching from CRESTOR to the non-equivalent dose of atorvastatin will lead to different health outcomes:

- Switching to the same mg dose of atorvastatin will lead to a loss of LDL-c control and an increase in the risk of cardiovascular outcomes.

- Switching to the nearest dose will lead to a loss of LDL-c control, or, as is described above in the 40mg example, will lead to an increase in risk of adverse safety event.

Taking the above economic, safety and efficacy reasons together leads one to the conclusion that CRESTOR is not interchangeable with atorvastatin from the perspective of the individual patient.

It is uncertain that a medicine is interchangeable with another medicine for a use for which there is no evidence of safety or efficacy

It is noteworthy that uncertain interchangeability also exists when Therapeutic Groups are formed between medicines with different TGA registered indications.

A TGA registered indication signifies that a careful assessment of safety and efficacy in a specific population (and sometimes a specific dose) has been undertaken, and that safety and efficacy have been demonstrated.

CRESTOR represents an emerging example of this situation. A landmark clinical study[6] of 18,000 patients has been conducted to examine the ability of the 20mg dose of CRESTOR to reduce cardiovascular events in people who aren't routinely treated with statin medicines. The study successfully illustrated that these patients benefit from treatment with CRESTOR 20mg : there was a 44% reduction in risk for the primary study outcome (one of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina, or revascularisation). All cause mortality was also significantly reduced by 20%.

Though there is no proof that any other dose of any other statin can provide this protection, the formation of the therapeutic group suggests that CRESTOR is interchangeable with atorvastatin and that atorvastatin can be used for this purpose.

There is no certainty that one medicine which has been assessed and been proven to work at a specific dose in a specific population, can be safely exchanged for another medicine which has not been the subject of any assessment by TGA.

Inconsistent messages to prescribers in regard to relative safety and efficacy

There are a number of public expressions of the accepted relative efficacy and safety between medicines.

Using the example of CRESTOR and atorvastatin, the "1:3 relativity" is detailed in the Public Summary Document [Attachment 1], the National Prescribing Service's RADAR [Attachment 2] and the PBPA Relativity sheets [Attachment 3]. Once again, this 1:3 relativity means that the equivalent dose of CRESTOR 40mg is a 120mg dose of atorvastatin ; this dose is not recommended and there are no supporting safety and efficacy data.

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[6] The JUPITER study. Submissions are under consideration by TGA and PBAC.

At the same time, the formation of the Therapeutic Group relays the clear acceptance that the two medicines are interchangeable for any individual person.

A physician prescribing according to the interchangeability principle may feasibly assume that any strength of CRESTOR is interchangeable with an equivalent dose of atorvastatin – this is not the case and the risk (eg. increased adverse events) of such an assumption is borne solely by the person who needs the medicine.

Term d) consultation undertaken in the development of new therapeutic groups;

No consultation occurred to ensure that all relevant stakeholders, and information, were considered – conclusions of interchangeability are uncertain

As described previously, the TGP policy was used to counteract the PBS Reform legislation and form a Therapeutic Group including AstraZeneca's single brand rosuvastatin (CRESTOR®) and Pfizer's single brand atorvastatin.

There was no consultation whatsoever with AstraZeneca. Information accessed by AstraZeneca via the Freedom of Information Act reveals that planning for the formation of the group began in November 2008 at the latest.

There was no consultation, to AstraZeneca's knowledge, with any physician group.

There was no consultation with any focus groups or any other research into the effect that this action may have at the individual patient level.

This lack of consultation means that no action was taken to ensure that a recommendation was based on all relevant information.

The lack of consultation increases the risk that the recommendation is incorrect. Subsequently, a conclusion that CRESTOR and atorvastatin are interchangeable is uncertain.

Term e) the impact of new therapeutic groups on the classification of medicines in F1 and F2 formularies;

Use of the TGP policy to interfere with F1/F2 classification threatens timely access to new medicines

As described previously, a key aspect of the PBS Reform legislation was to achieving significant savings in off-patent medicines. This was to be accomplished by allocation of multiple branded medicines to a separate formulary (F2) and, following a mandatory price reduction (12.5%), subjecting them to market based competition.

This competition would ensure a sustainable PBS and ensure timely access to new medicines.

AstraZeneca agreed with the objective of PBS Reform and subsequently prepared for significant reductions in off patent medicines, and launch of new medicines in a more certain environment.

However, the TGP policy is now being used to counteract formulary (F1 and F) allocations as per the legislation. This is evident in AstraZeneca's experience with CRESTOR, and is also evident in the recently announced therapeutic groups. In each case, the intention of the creation of the Therapeutic Group is to elicit the transition of a single brand, patented F1 medicine to the multi-brand (F2) formulary.

There is no doubt that any case to pursue access in Australia is at risk because of the threat of the unpredictable formation of Therapeutic Groups and subsequent pricing uncertainty. In the best case, access will be delayed but the risk that some new medicines will not be made available to Australians cannot be dismissed.

The TGP policy has been superseded by PBS Reform and yet continues to exert significant interference with the implementation of the Reforms. Such interference threatens a key objective of the Reforms: timely access to new medicines for Australians.

Term g) the process and timing of consideration by Cabinet of high cost drugs and vaccines; and

AstraZeneca's comments to this term of reference support the Medicines Australia submission to this inquiry, and reflect our concern for the future in regard to timely access to new medicines.

AstraZeneca anticipates that at least two of it's medicines in the next 3 years will require Cabinet approval under the current process and net-cost threshold.

These medicines, consistent with most medicines considered by the Cabinet, are proven to extend life, avoid severe adverse health outcomes and increase quality of life.

Delays to such medicines which have been recommended by the PBAC is detrimental to health.

An increase in the Cabinet threshold will undoubtedly avoid some delay for some medicines.

Additionally, the process can be expedited by clarification of the decision making criteria used by the Cabinet. With this clarity, companies such as AstraZeneca can provide further information to increase certainty and expedite decisions on these important new medicines.

Term h) any other related matters

Expanding use of the Therapeutic Group Premium policy is a process which comes at a risk to people who take these medicines.

The use of the TGP policy to undermine PBS Reforms is expanding. While, to present, the policy has been applied to groups of single-drug medicines, it has recently been used to group single drug medicines with fixed dose, multi-drug medicines (osteoporosis bisphosphonate group).

The risk of this practice of Policy expansion and the uncertainty of conclusions of interchangeability is ultimately borne by the individual person who takes a medicine.

This risk will only increase if the use of the Policy is permitted to expand further to include other therapeutic areas such as asthma, mental health and oncology.

AstraZeneca's submission to PBAC

In May 2009, AstraZeneca attempted to highlight to PBAC the lack of interchangeability of CRESTOR 40mg and atorvastatin in a minor submission (Attachment 4).

The submission was based on the concern that a 120mg dose of atorvastatin, which is equivalent to CRESTOR 40mg, is outside of dosing recommendations both in Australia and globally and, as such has no established safety or efficacy profile. The submission also pointed out that a 120mg dose is not a cheaper alternative to CRESTOR 40 mg (because two prescriptions of LIPITOR would be required to make up the 120 mg dose).

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The extract of the PBAC minutes (Attachment 5) reveals that PBAC did not contradict AstraZeneca's assertion that CRESTOR 40mg is not interchangeable with atorvastatin. The PBAC instead focussed on its interpretation that the legislation did not oblige PBAC to consider the interchangeability of specific pharmaceutical items (i.e. the interchangeability of one strength for another).

Subsequently, while there is no evidence that PBAC disagreed that CRESTOR 40mg was not interchangeable with atorvastatin, PBAC concluded that CRESTOR and atorvastatin are interchangeable.

Conclusion : AstraZeneca's view

AstraZeneca supports the PBS Reforms and its objectives, as previously agreed. However, the implementation of the Reform is being disrupted by the expanding and non consultative use of the TGP Policy.

This practice will continue to apply unanticipated pressure to AstraZeneca and other companies. This pressure threatens the timely access to new medicines in Australia.

This practice of TGP policy expansion is based on uncertain and incomplete information. Thus there is no certainty that patient health outcomes will be unchanged on the basis of a recommendation that two medicines are interchangeable.

In AstraZeneca's view, this situation can be largely alleviated by clarification that the PBS Reforms will be implemented without interference by the TGP Policy – single brand medicines should be allocated to the single brand formulary.

In regard to the process and timing of Cabinet consideration, an increase to the Cabinet threshold will reduce the delays for some medicines. Additionally, clarification of the decision criteria and processes will enhance and expedite decision making.

AstraZeneca appreciates the opportunity to contribute to this critical inquiry and I invite you to contact me directly for any further information or assistance.

Yours sincerely,
AstraZeneca Pty Ltd

Jose Vieira
Managing Director

AstraZeneca

Attachment 1 – CRESTOR (rosuvastatin) Public Summary Document

[Electronic Attachment : "Rosuvastatin Public Summary document.")

(Accessed 26 March 2010 : http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-rosuvastatin-july06)

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.

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Attachment 2 - CRESTOR (rosuvastatin) NPS RADAR document

[Electronic Attachment : "rosuvastatin RADAR.pdf")

(Accessed 26 March 2010 : http://www.nps.org.au/__data/assets/pdf_file/0004/23728/rosuvastatin.pdf)

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

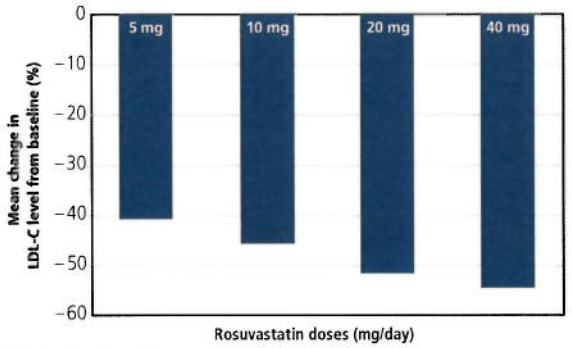
Rosuvastatin is more potent at lowering LDL-C on a milligram-for-milligram basis compared with other statins[7–9]; dose equivalencies are outlined in Table 1.

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 baseline[7-9] 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]

Statins 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.

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Date prepared: December 2006

AstraZeneca

Attachment 3 - PBPA Relativity Sheets* – January 2010

(Accessed 26 March 2010 -
http://www.health.gov.au/internet/main/publishing.nsf/Content/79FFCFDE3F916A41CA256F180046E3EF/$File/Relativity%20Sheets%20-%201%20January%202010.pdf)

PHARMACEUTICAL BENEFITS PRICING AUTHORITY

Therapeutic Relativity Sheets

ATC C10 – Lipid Modifying Agents	Effective Date: 12/07	Page 2 of 2

8. Ezetimibe with simvastatin (Vytorin®) was recommended on a cost minimisation basis compared to the sum of the corresponding strengths of the individual components in patients with coronary heart disease, patients with diabetes mellitus and patients with homozygous familial hypercholesterolemia. The price for the simvastatin component of the combination tablet will be maintained at the same price as that of simvastatin. Special pricing arrangements apply to ezetimibe with simvastatin.

9. Rosuvastatin calcium was recommended on a cost minimisation basis compared to atorvastatin, with the ratio of equi-effective doses being rosuvastatin to atorvastatin 1:3.

10. Amlodipine besylate with atorvastatin calcium tablet, Caduet®, was recommended on a cost minimisation basis compared with the corresponding strengths of the amlodipine and atorvastatin components. Also refer to ATC C08 – Calcium Channel Blockers.

AstraZeneca

Attachment 4 - May 2009 submission to PBAC

CRESTOR minor sub 25May09.doc

Minor submission- CRESTOR (rosuvastatin) 40mg tablets

Background

One of the measures announced in the 2009 Federal Budget is "Extending the therapeutic group premium policy" to place CRESTOR (rosuvastatin) and LIPITOR (atorvastatin) in a new therapeutic group.

According to sections 84AG and 101[3BA], therapeutic groups are groups of drugs that are interchangeable on an individual patient basis.

The PBAC recommended CRESTOR (rosuvastatin) 5 mg, 10 mg, 20 mg and 40 mg tablets for listing on a cost-minimisation basis compared with atorvastatin, with an equi-effective dose of rosuvastatin to atorvastatin being 1:3 at its July 2006 meeting.

Purpose of this submission

The purpose of this submission is to illustrate that it is not appropriate to include CRESTOR 40 mg in a therapeutic group on the basis that it is not safely interchangeable with any dose of atorvastatin.

Summary of evidence supporting this submission

AstraZeneca appreciates the importance of maintaining the sustainability of the PBS. AstraZeneca also understands the rationale of reference pricing including the therapeutic premium policy and that the Government intends to pay the same price for similar health outcomes. The company is however, concerned with the inclusion of CRESTOR 40mg tablets in this new therapeutic group (formed between rosuvastatin and atorvastatin) because the theoretically equivalent atorvastatin 120 mg (a) is outside of dosing recommendations both in Australia and globally (b) would not be expected to achieve equivalent LDL-C reduction (c) has no established safety profile and (d) is not a cheaper alternative to CRESTOR 40 mg (two prescriptions of LIPITOR would be required to make up the 120 mg dose).

Therefore, AstraZeneca believes the proposed exclusion of CRESTOR 40mg tablets from the new therapeutic group is consistent with section 84 (AH) of the ACT, quality use of medicine, the TGA approved doses of rosuvastatin and atorvastatin.

Please see below the full details of our justification in support of this application: -

Evidence supporting this submission (in full details)

1. The equipotent LDL-C lowering dose of CRESTOR 40mg is outside the TGA approved atorvastatin dose

Based on the July 2006 PBAC recommendation for CRESTOR tablets, the equi-effective dose ratio for rosuvastatin to atorvastatin was 1:3. Therefore, the theoretical equipotent LDL-C-lowering dose for rosuvastatin 40 mg is atorvastatin 120 mg. However, a daily dose of 120 mg is outside the maximum dose of 80 mg approved by

the TGA for LIPITOR (atorvastatin) tablets[1]. Indeed, 80 mg is the maximum allowable daily dose for atorvastatin according to the literature (e.g. Martindale) and many other regulatory/reimbursement agencies including the NICE.[2] Therefore, although theoretically the equi effective dose of rosuvastatin 40mg is atorvastatin 120 mg, it is outside the PI-recommended maximum dose for atorvastatin.

The lack of equipotent dose for CRESTOR 40mg was further supported by a RADAR review on rosuvastatin. In December 2006, the National Prescribing Service (NPS) released a RADAR review of rosuvastatin that emphasized the relative difference in potency of rosuvastatin to other statins including atorvastatin [3] The review included a table outlining the LDL-C lowering dose equivalence for approved atorvastatin and rosuvastatin doses. According to the RADAR review, there is no equivalent CRESTOR 40mg dose for approved atorvastatin dose (see Table 1).

Table 1: LDL-C-lowering dose equivalence for approved rosuvastatin and atorvastatin doses

Statin	Dose equivalence			
Rosuvastatin	5mg	10mg	20mg	40mg
Atorvastatin	15mg	30mg	60mg	-----

Source: NPS RADAR review of rosuvastatin[3]

2. 2006 ESC Advice accepted the claim of unequalled LDL-C reduction by rosuvastatin 40 mg

The ESC Advice dated 21 June 2006 received during evaluation of the original CRESTOR PBAC submission accepted the claim that rosuvastatin 40mg is unequalled by any strength of any other statin in terms of LDL-C reduction.[4]

This was in response to the arguments presented in our pre-SubCommittee response, which led to the acceptance by ESC that there is no equivalent dose for CRESTOR 40 mg.

The ESC Advice stated the following:

"Other issues include:

……

- whether the submission provides sufficient evidence to support the claim that rosuvastatin 40mg elicits a response, in terms of LDL-C reduction, which is unequalled in any strength of any other statin. This is addressed appropriately by the Pre-Sub-Committee Response."

3. Minimal efficacy and safety data available for atorvastatin at 120 mg per day

As discussed above, daily doses of atorvastatin above 80mg are outside TGA recommended dosages.

The body of evidence to date consist mainly of data on 10-80 mg atorvastatin. There is limited published data on safety and efficacy of atorvastatin doses above 80mg. Given that dose dependent liver adverse effects is well recognised and a key clinical consideration when prescribing statins, this lack of safety data precludes clinicians in considering use of atorvastatin above 80 mg. These concerns have also been expressed by a leading international lipids specialist who has been involved in and served as a steering committee in key atorvastatin trials.

Below is a summary of the limited published data on safety and efficacy of atorvastatin doses above the TGA approved 80 mg dose:

- in a study by Raal et al, [5] 120 mg/day (in 20 subjects) and 160 mg/day (in 13 subjects) were studied and a dose-dependent liver toxicity was observed, with increases in ALT and AST upon dose increases.

- in a phase 1 study conducted by Posvar et al [6] evaluating the tolerance and pharmacokinetics of atorvastatin at doses between 0.5 mg to 120 mg, dose-limiting symptoms were observed after single administration of 120 mg of atorvastatin solution.

- - a study conducted by Raal et al [5] showed that increasing the dose of atorvastatin to 120 and 160 mg per day did not result in any further reduction in LDL-C, suggesting a "plateau" effect.

The risk/benefit consideration for atorvastatin doses above 80 mg have not been established and these doses cannot be considered a viable alternative to CRESTOR 40 mg. Hypercholesterolemia is a chronic condition that often requires lifelong treatment and an established positive safety profile is a key consideration when treating this condition. Whilst the efficacy and safety of CRESTOR 40 mg has been evaluated and confirmed by the TGA, randomized clinical trials and meta-analysis, the safety profile of atorvastatin doses above 80mg have not been established.

4. No atorvastatin 120 mg dose form available in Australia and worldwide

Notwithstanding the issues discussed above concerning dose equivalency and the safety profile of atorvastatin 120 mg daily dose, there is no LIPITOR (atorvastatin) 120 mg single tablet available on the PBS.

In the Therapeutic Group Premium (TGP) system, the criterion of "individual interchangeability" assists patients wishing to obtain an alternative to a drug in one of these groups whose price has a high additional premium. The TGP policy while allowing pharmaceutical companies to charge a premium for drugs that are included in a therapeutic group, it also provides an assurance that no patients need to pay extra if their doctor chooses to prescribe a clinically equivalent, cheaper alternative.

To illustrate our argument, we refer to a hypothetical situation where a therapeutic group premium of 5 cents was applied to CRESTOR 40mg tablets. Therefore, in order to meet the "individual interchangeability" criterion, a clinically equivalent, cheaper alternative (i.e. atorvastatin 120 mg tablets) would need to be available on the PBS for patients and doctors to choose. However, the current situation does not provide this clinically equivalent, cheaper alternative option. At present, in order for a patient to receive a daily dose of atorvastatin 120 mg, this dosage would need to be made up by taking 2 separate LIPITOR tablets i.e. one tablet each of the 40 mg and 80 mg tablets. Therefore, making this a more expensive alternative because patients will need to pay for two prescriptions instead of one.

Conclusion

Interchangeability, in the designation of a therapeutic group remains central to the issues raised by AstraZeneca, in this submission to the PBAC.

The Minister, the Hon Nicola Roxon, MP has stated that within the newly created rosuvastatin and atorvastatin therapeutic group, the patient will always have an interchangeable cheaper alternative. This statement mirrors the laid down Therapeutic Group Policy.

The test for interchangeability is therefore determined by the availability of a safe, approved alternative to Crestor 40 mg which provides at least the same level of efficacy, at no higher risk of adverse events (and at no higher cost to the patient).

For Crestor 40 mg, there is no safe approved alternative. In addition potency of Crestor 40 mg is such that the theoretically equivalent atorvastatin 120 mg would not achieve the equivalent LD-C reduction. At the Crestor 40 mg dose, these two drugs (in the therapeutic group) are not equivalent or interchangeable.

We therefore seek the PBAC's agreement to remove Crestor 40mg from the new therapeutic group formed between atorvastatin and rosuvastatin.

References

1. Approved Australian Product Information for LIPITOR

2. NICE guidance for statins for the prevention of cardiovascular events dated November 2008

3. NPS RADAR review- Rosuvastatin (Crestor) for dyslipidaemia. December 2006

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Attachment 5 - PBAC minutes – response to AstraZeneca's minor submission

Electronic attachment: "2009-09-21, CRESTOR, from PBA(

Pharmaceutical Benefits Advisory Committee

Telephone: (02) 6289 7099
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Address all mail to:
THE SECRETARY
PBAC
GPO Box 9848
Canberra ACT 2601

The Managing Director

Dear Sir/Madam

Attached for your information is a copy of extracts, relevant to your company, from the ratified minutes of the July 2009 meeting of the Pharmaceutical Benefits Advisory Committee.

Yours faithfully

Diana K. MacDonell

Diana MacDonell
Secretary
21 September 2009

8.10 ROSUVASTATIN CALCIUM, tablet 40 mg (rosuvastatin), Crestor®, AstraZeneca Pty Ltd

Purpose of Application:
To exclude the 40 mg strength of rosuvastatin from the new therapeutic group containing rosuvastatin and atorvastatin, announced in the 2009/2010 Budget, on the basis that it was not safely interchangeable with any available strength of atorvastatin.

Background:
At its July 2006 meeting, the PBAC recommended listing of rosuvastatin on a cost-minimisation basis with atorvastatin, with the ratio of equi-effective doses being rosuvastatin to atorvastatin 1:3.

The PBAC accepted the advice in the pre-PBAC response that the ESC advice in relation to the safety review undertaken by TGA was out of date, and was superseded by a more recent TGA safety review undertaken in 2005. The Committee considered that a remaining issue of concern was an apparent dose-related proteinuria, but noted that this adverse event had been transient in all but one report.

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 considered 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.

At the November 2006 PBAC meeting, the sponsor sought a listing consistent with the other PBS listed high dose HMG CoA reductase inhibitors (statins), by removal of the NOTE applying to the 40 mg dose. The PBAC recommended removing the cautionary note regarding doses higher than 20 mg from the PBS restriction for rosuvastatin recommended at the July 2006 meeting. The Committee accepted that based on a further review of the evidence, there was insufficient justification for concluding that a 40 mg dose of rosuvastatin represented a higher risk of toxicity than the highest doses of other statins.

2009-2010 Budget
Under the heading of maintaining the sustainability of the PBS, the Government announced that it will place two cholesterol lowering medicines – atorvastatin calcium (Lipitor®) and rosuvastatin calcium (Crestor®) – in a new therapeutic group. The formation of the therapeutic group was on advice from the PBAC.

The outcome was that the price of these two medicines will be referenced to each other, which will result in the price paid by the Australia Government for the more expensive medicine reducing to a level relative to the cheaper medicine. These changes will be implemented in consultation with the affected manufacturers. The new therapeutic group will be subject to an annual Weighted Average Monthly Treatment Cost (WAMTC) review consistent with reference pricing policy.

Dosage:
Rosuvastatin

Prior to initiating rosuvastatin, the patient should be placed on a standard cholesterol lowering diet. The recommended starting dose is 5mg 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 as well as the potential risk for adverse reactions. A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of rosuvastatin is 20 mg once per day.

A dose of 40 mg once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. 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. Specialist supervision should be considered when the dose is titrated to 40 mg.

Atorvastatin

Atovastatin can be administered within the dosage range of 10 to 80 mg/day as a single daily dose. Atorvastatin can be taken at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy and the patient's response. After initiation and/or upon titration of atorvastatin, lipid levels should be reanalysed within four weeks and dosage adjusted according to the patient's response.

Summary of Submission and Findings:

8.10.1 The submission claimed that there was no approved atorvastatin alternative to rosuvastatin 40 mg which provided the same level of efficacy at no higher risk or cost to the patient.

8.10.2 The justification to support this claim was based on the following points:

- The equi-potent LDL-C lowering dose of rosuvastatin 40 mg was outside the TGA approved atorvastatin dose.
- The ESC Advice to the July 2006 PBAC that stated the sponsor's Pre-PBAC Response had addressed appropriately the issue of providing sufficient evidence to support the claim that rosuvastatin 40 mg elicited a response, in terms of LDL-C reduction, which was unequalled in any strength of any other statin.
- Minimal efficacy and safety data were available for atorvastatin at 120 mg per day
- No atorvastatin 120 mg dose form was available in Australia or worldwide.

Recommendation and Reasons:

In accordance with subsection 101(4AA) of the *National Health Act 1953*, PBAC reiterated its advice to the Minister that the two drugs atorvastatin and rosuvastatin should together comprise a new therapeutic group. In doing so, and in accordance with subsection 101(3BA), PBAC also advised that the Committee is of the opinion that these two drugs are interchangeable on an individual patient basis.

In relation to the submission's request to consider the interchangeability of a specific pharmaceutical item of rosuvastatin (the 40 mg strength tablet) with pharmaceutical items of atorvastatin, the PBAC formed the view that the legislation obliged the Committee to consider the interchangeability on an individual patient basis of the drugs forming a

therapeutic group, ie not necessarily the interchangeability on an individual patient basis of each individual pharmaceutical item of these drugs. The PBAC retained its view that, consistent with the overall policy for therapeutic groups and when considering all pharmaceutical items of both drugs, the two drugs rosuvastatin and atorvastatin are interchangeable on an individual patient basis.

In relation to the overall policy for therapeutic groups, the PBAC further noted that the need for an individual prescriber to consider interchangeability on an individual patient basis would only arise in the event that a therapeutic group premium were to be imposed on a particular item in order to increase its price above the corresponding prices for the base-priced drug. In the event that this should happen at some time in the future for rosuvastatin 40 mg tablet, an individual patient may ask the prescriber to prescribe atorvastatin at the base price as an alternative. If the prescriber formed the view that to do so the patient would require a higher than TGA-approved dose of atorvastatin, but that this might be unsafe, then under the therapeutic group policy, the prescriber could exercise the option of seeking authorisation from Medicare Australia to continue to prescribe rosuvastatin 40 mg without the patient having to pay the therapeutic group premium. The PBAC was therefore satisfied that the overall implementation of the therapeutic group policy was able to accommodate the clinical concerns raised in the submission.