PUBLIC SUMMARY DOCUMENT

Product: Amlodipine Besylate with Atorvastatin Calcium, tablets, 5 mg (base)-10 mg, 5 mg (base)-20 mg, 5 mg (base)-40 mg, 5 mg (base)-80 mg, 10 mg (base)-10 mg, 10 mg (base)-20mg, 10 mg (base)-40 mg, 10 mg (base) – 80 mg, Caduet®

Sponsor: Pfizer Australia Pty Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought a restricted benefit listing for a fixed combination of amlodipine besylate and atorvastatin calcium for a subset of patients with concomitant hypertension and dyslipidaemia or concomitant angina and dyslipidaemia.

2. Background

This fixed combination had not previously been considered by the PBAC.

3. Registration Status

Caduet was registered on the 14 July 2005 for patients in whom treatment with amlodipine and atorvastatin is appropriate at the doses presented.

4. Requested Listing and PBAC's view

Restricted benefit

For use in patients who have hypertension and/or angina and who meet the criteria set out in the General Statement for Lipid-Lowering Drugs, and:
(a) Who are currently receiving treatment with a dihydropyridine calcium channel blocker;
OR
(b) Whose blood pressure and/or angina is inadequately controlled with other classes of antihypertensive and/or anti-anginal agent, and in whom adjunctive therapy with a dihydropyridine calcium channel blocker would be appropriate;
OR
(c) Who are intolerant of the side effects of other classes of antihypertensive and/or anti-anginal agent, and in whom replacement therapy with a dihydropyridine calcium channel blocker would be appropriate.

For the PBAC's view, see Recommendation and Reasons

5. Clinical place for the proposed therapy

Caduet will be used predominantly by patients who are currently treated with concomitant amlodipine and atorvastatin for the treatment of hypertension and dyslipidaemia.

6. Comparator

The submission nominated amlodipine co-administered with atorvastatin as the comparator. The PBAC accepted this as appropriate.

7. Clinical trials

The submission presented one non-randomised, non-comparative, open-label study of amlodipine + atorvastatin fixed dose combination tablets 5 mg/10 mg, 5 mg /20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg in patients with hypertension and dyslipidaemia over 14 weeks (hereafter referred to as the GEMINI study) and data from eight bioequivalence studies. The Gemini study was published at the time of the submission as follows:

Trial/First author	Study Name	Publication citation
GEMINI/ Blank et al.	Single-pill therapy in the treatment of concomitant hypertension and dyslipidaemia (the amlodipine/atorvastatin Gemini study)	J Clin Hypertens 2005; 7:264-273.

8. Results of trials

The key results of the GEMINI study are summarised in the table below.

Attainment of lipid and/or blood pressure goals in the GEMINI study

Outcome	All patients	Group I*	Group II†	Group III‡
ITT population				
Lipid + blood pressure goals	692/1199 (57.7%)	125/162 (77.2%)	354/465 (76.1%)	213/572 (37.2%)
Blood pressure goal alone	790/1207 (65.5%)	126/163 (77.3%)	373/468 (79.7%)	291/576 (50.5%)
Lipid goal alone	985/1200 (82.1%)	158/162 (97.5%)	437/465 (94.0%)	390/573 (68.1%)
Patients with uncontrolled LDL-C at baseline				
Lipid + blood pressure goals	389/749 (51.9%)	48/67 (71.6%)	214/281 (76.2%)	127/401 (31.7%)
Blood pressure goal alone	470/750 (62.7%)	49/67 (73.1%)	224/281 (79.7%)	197/402 (49.0%)
Lipid goal alone	560/750 (74.7%)	64/67 (95.5%)	261/281 (92.9%)	235/402 (58.5%)

* Group I: hypertension and dyslipidaemia with no additional cardiovascular (CV) risk factors.
† Group II: hypertension and dyslipidaemia with at least one additional CV risk factor excluding coronary heart disease (CHD) and diabetes mellitus (DM).
‡ Group III: hypertension and dyslipidaemia with CHD or CHD risk equivalent (DM or other atherosclerotic disease.

The primary efficacy results were analyses for all patients and by cardiovascular risk groups. At end point, 57.7% of patients treated with amlodipine + atorvastatin fixed dose combination tablets attained both their blood pressure and lipid goals. Attainment of both goals was highest in Group I and II (77.2% and 76.1% respectively) and lowest in Group III (35.3%) indicating that patients with 0-1 additional cardiovascular risk factor (excluding coronary heart disease and diabetes) had the highest rate of attainment. When each treatment goal was considered separately, a similar pattern was observed, although more patients achieved their lipid goal than blood pressure goal (82.1% versus 65.5%). When efficacy data on patients with LDL-C uncontrolled at baseline were analysed

separately, results obtained suggest that the pattern of goal attainment was similar to that observed in the ITT population, although the difference in the proportion of patients who achieved lipid goal versus proportion of patients who reached blood pressure goal was smaller.

Results from the eight bioequivalence studies, presented as supportive evidence, suggested that, in young healthy volunteers, the systemic bioavailability of amlodipine and atorvastatin components from the combination tablets 5 mg/10 mg, 10 mg/40 mg and 10 mg/80 mg was similar to that from the co-administration of the corresponding monotherapies.

In the GEMINI study 64.1% of patients reported at least one adverse event. The most commonly reported adverse events were respiratory tract infection (11.9%), peripheral oedema (8.8%), headache (5.4%) and myalgia (4.2%). The incidence of serious adverse events during the study appeared to be low (2.7%) with no events attributable to the study drug. There were no serious events that correlated with myopathy, myositis, rhabdomyolysis or abnormal/increased in alanine aminotransferase, aspartate aminotransferase or creatine phosphokinase.

9. Clinical Claim

The submission claimed that the amlodipine + atorvastatin fixed dose combination tablets are no worse than the corresponding strengths of amlodipine co-administered with atorvastatin in terms of effectiveness and toxicity.

10. Economic Analysis

The submission presented a cost-minimisation analysis. The PBAC considered the choice of a cost-minimisation approach valid.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 4 of listing the likely number of patients treated would be between 10,000 and 50,000 per year and the financial cost per year to the PBS would be < $10 million.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis compared with the corresponding strengths of the amlodipine and atorvastatin constituents. The PBAC noted the sponsor had agreed to remove the Therapeutic Group premium that currently applies to the amlodipine single agent product from the combination amlodipine with atorvastatin product.

The Committee requested that the DUSC monitor usage.

The PBAC recommended the 20 day safety net rule should apply.

Recommendation
Amlodipine Besylate with Atorvastatin Calcium**,** tablet, 5 mg (base)-10 mg, 5 mg (base)-20 mg, 5 mg (base)-40 mg, 5 mg (base)-80 mg, 10 mg (base)-10 mg, 10 mg (base)-20mg, 10 mg (base)-40 mg, 10 mg (base) - 80 mg

Restriction: Restricted benefit
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OR
(c) who are intolerant of the side effects of other classes of antihypertensive and/or anti-anginal agent, and in whom replacement therapy with a dihydropyridine calcium channel blocker would be appropriate.

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.

Sponsor's Comment:
Pfizer Australia (the Sponsor) welcomes the PBAC recommendation to list Caduet on the PBS. The Sponsor believes the availability of the fixed combination will allow prescribers to simplify and integrate the management of a patients overall cardiovascular risk.