

PUBLIC SUMMARY DOCUMENT

Product: PERINDOPRIL ARGININE with AMLODIPINE BESYLATE, tablet,
5 mg-5 mg, 5 mg-10 mg, 10 mg-5 mg and 10 mg-10 mg, Coveram[®]

Sponsor: Servier Laboratories (Australia) Pty Ltd

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought a Restricted benefit listing for substitution therapy in patients stabilised on perindopril and amlodipine given concomitantly.

2. Background

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

3. Registration Status

Perindopril arginine with amlodipine besylate tablets were registered by the Therapeutic Goods Administration (TGA) on 11 January 2010 and are indicated as substitution therapy for the treatment of hypertension and/or stable coronary heart disease in patients already controlled with separate doses of perindopril and amlodipine, given concurrently at the same dose level. Treatment should not be initiated with this combination.

4. Listing Requested and PBAC's View

Restricted benefit

Substitution therapy in patients who are stabilised on treatment with perindopril and amlodipine, given concurrently at the same dose level. Treatment should not be initiated with this combination.

The PBAC noted that perindopril with amlodipine is only registered for use as substitution therapy. However, the PBAC considered that titration would occur in clinical practice and the restriction for the hypertension indication should be consistent with the changes recommended for the angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist (ACEI/ATRA) with diuretic combination products and the ACEI/ATRA with calcium channel blocker. The PBAC was of the view that all ACEI or ATRA calcium channel blocker (CCB) combinations should have the same restriction for hypertension.

5. Clinical Place for the Proposed Therapy

Perindopril with amlodipine would provide a fourth angiotensin converting enzyme inhibitor with calcium channel blocker combination product treatment option on the Pharmaceutical Benefits Scheme (PBS).

6. Comparator

The submission nominated perindopril arginine and amlodipine besylate given concomitantly as the comparator. The PBAC considered that this was the appropriate comparator.

7. Clinical Trials

The basis of the submission was three bioequivalence studies comparing fixed-dose combinations of perindopril arginine and amlodipine (10 mg/10 mg, 10 mg/5 mg and 5mg/10 mg) with perindopril erbumine and amlodipine combinations (8 mg/10 mg, 8 mg/5 mg and 4 mg/10 mg) given concomitantly in healthy volunteers.

One small (n = 26) randomised controlled crossover trial (Stokes et al. 1998) was also presented. The trial examined the effect of the addition of amlodipine to perindopril monotherapy and the addition of perindopril to amlodipine monotherapy using lower doses than those present in the fixed dose combination formulations proposed for listing on the PBS. The PBAC noted that the trial was conducted in a relatively young population (average age approximately 55 years), used a lower dose of perindopril and amlodipine than requested for this listing (2 mg perindopril erbumine (equiv 2.5 mg perindopril arginine)/2.5 mg amlodipine besylate) and that the primary outcome was in terms of blood pressure not coronary heart disease. Further, the results were presented in graphical format only, so their significance could not be verified.

Details of the Stokes et al. (1998) trial are shown below:

| Trial ID / First author | Protocol title / Publication title | Publication citation |
|-------------------------|---|---|
| Stokes GS et al. (1998) | Double-blind crossover study of the interaction between perindopril and amlodipine on blood pressure and hormones related to fluid and electrolyte balance in patients with essential hypertension. | <i>Journal of Human Hypertension</i> 1998; 12: 129-134. |

8. Results of Trials

Three bio-equivalence studies established bioequivalence of the combination product (Coveram[®]) with its perindopril and amlodipine components administered concomitantly.

The Stokes trial examined the effect of the addition of amlodipine to perindopril monotherapy. There was no statistically significant difference in the reduction of mean blood pressure (BP) or systolic blood pressure (SBP) with the addition of amlodipine (2.5 mg) or placebo to established perindopril (2 mg) therapy. Adding perindopril (2 mg) to established amlodipine (2.5 mg) therapy produced a statistically significant reduction in mean BP compared to amlodipine alone.

There were some differences in BP measures at clinic visits. The low doses of perindopril and amlodipine (doses used for titration in clinical practice), and the small study size, limited the clinical inferences that may could be drawn from this study.

A meta-analysis conducted by Wald et al. (2009) was presented as evidence that adding a second drug from another therapeutic class is approximately 5 times more effective than doubling the dose of a monotherapy agent and the effect from the combination therapy is additive (including ACEI + CCB combinations). This meta-analysis did not include studies examining the combination of perindopril and amlodipine.

The PBAC agreed that the data presented in the studies were difficult to interpret with confidence and that even though the PBAC had previously relied on bioequivalence studies for the listing of a combination product, the currently listed ACEI with CCB combinations had also provided data on efficacy and safety, in addition to bioequivalence, for the combination compared to the individual monotherapies for each of the combinations. Nonetheless, the PBAC accepted that perindopril with amlodipine was non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over perindopril and amlodipine monotherapies.

The most commonly reported adverse events associated with the perindopril/amlodipine treatment regimen were cough, peripheral oedema, joint swelling and dizziness.

9. Clinical Claim

The submission described Coveram[®] as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over perindopril and amlodipine monotherapies.

The PBAC accepted that perindopril with amlodipine was non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over perindopril and amlodipine monotherapies.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as:

- Coveram[®] 5 mg/5 mg equivalent to perindopril 4 mg/5 mg (erbumine/arginine) plus amlodipine 5 mg
- Coveram[®] 5 mg/10 mg equivalent to perindopril 4 mg/5 mg (erbumine/arginine) plus amlodipine 10 mg
- Coveram[®] 10 mg/5 mg equivalent to perindopril 8 mg/10 mg (erbumine/arginine) plus amlodipine 5 mg
- Coveram[®] 10 mg/10 mg equivalent to perindopril 8 mg/10 mg (erbumine/arginine) plus amlodipine 10 mg

11. Estimated PBS Usage and Financial Implications

The likely number of scripts/year estimated in the submission was in the range of 10,000 – 50,000 scripts in Year 5 for the 5 mg/5 mg and 5 mg/10 mg perindopril/amlodipine strengths and in the range of 100,000 – 200,000 scripts in Year 5 for the 10 mg/5 mg and 10 mg/ 10 mg perindopril/amlodipine strengths.

The estimated financial savings/year to the PBS were initially estimated by the submission to be less than \$15,000 in Year 5. Revised estimates correcting for perindopril and amlodipine used in other combination products such as Coversyl Plus[®] (perindopril plus indapamide) and Caduet[®] (amlodipine plus atorvastatin) indicated savings in the range of \$45,000 - \$75,000 in Year 5.

12. Recommendation and Reasons

The PBAC recommended the restricted benefit listing of perindopril with amlodipine in accordance with the combination guidelines, on a cost-minimisation basis compared with the corresponding strengths of its constituent components, perindopril (erbumine/arginine) and amlodipine given concomitantly.

The PBAC agreed that the data presented in the studies were difficult to interpret with confidence and that even though the PBAC had previously relied on bioequivalence studies for the listing of a combination product, the currently listed ACEI with CCB combinations had also provided data on efficacy and safety, in addition to bioequivalence, for the combination compared to the individual monotherapies for each of the combinations. Nonetheless, the PBAC accepted that perindopril with amlodipine was

non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over perindopril and amlodipine monotherapies.

The PBAC noted the sponsor's comments that perindopril with amlodipine was only registered for use as substitution therapy. However, the PBAC considered that titration would occur in clinical practice and the restriction for the hypertension indication should be consistent with the changes recommended for the ACEI/ATRA with diuretic combination products and the ACEI/ATRA with calcium channel blocker. The PBAC was of the view that all ACEI or ATRA CCB combinations should have the same restriction for hypertension.

Recommendation:

PERINDOPRIL ARGININE with AMLODIPINE BESYLATE, tablets, 5 mg – 5 mg, 5 mg – 10 mg, 10 mg – 5 mg and 10 mg – 10 mg

Restriction:

Restricted benefit

Hypertension in a patient who is not adequately controlled with either of the drugs in the combination.

Stable coronary heart disease in a patient who is stabilised on treatment with perindopril and amlodipine at the same doses.

CAUTION:

Use of ACE inhibitors during pregnancy is contraindicated since these drugs have been associated with foetal death in utero.

NOTE:

Treatment should not be initiated with this combination.

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

Servier supports the decision to list with the same restriction as other ACEI/ATRA/CCB products.