

## **PUBLIC SUMMARY DOCUMENT**

**Product:** OLMESARTAN MEDOXOMIL with AMLODIPINE (as besylate), tablets, 20 mg-5 mg, 20 mg-10 mg, 40 mg-5 mg and 40 mg-10 mg, Sevika<sup>®</sup>

**Sponsor:** Schering-Plough Pty Ltd

**Date of PBAC Consideration:** July 2010

### **1. Purpose of Application**

The submission sought a restricted benefit listing for hypertension in patients who are not adequately controlled with either angiotensin II receptor antagonist (AIIRA) or dihydropyridine calcium channel blocker (CCB) monotherapy.

### **2. Background**

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

### **3. Registration Status**

Olmesartan with amlodipine was TGA registered on 14 May 2010 for the treatment of hypertension. Treatment should not be initiated with this fixed dose combination.

### **4. Listing Requested and PBAC's View**

#### Restricted benefit

Hypertension in patients who are not adequately controlled with either angiotensin II receptor antagonist or dihydropyridine calcium channel blocker monotherapy.

*For PBAC's view, see Recommendation and Reasons.*

### **5. Clinical Place for the Proposed Therapy**

Olmesartan with amlodipine will provide an alternative choice of an angiotensin II antagonist/CCB combination product for the treatment of hypertension in patients who have trialled and failed monotherapy with either olmesartan or amlodipine.

### **6. Comparator**

The submission appropriately nominated the individual components of the combination, olmesartan and amlodipine as the main comparators.

### **7. Clinical Trials**

The submission presented one randomised trial comparing amlodipine (5 mg and 10 mg) add-on therapy with placebo add-on in hypertensive patients who failed to respond adequately to olmesartan medoxomil 20 mg monotherapy (Trial 302); and one randomised trial comparing olmesartan medoxomil (10 mg, 20 mg and 40 mg) add-on therapy with placebo add-on in hypertensive patients who failed to respond adequately to amlodipine 5 mg monotherapy, with a blinded up-titration period if necessary (Trial 303).

The submission also presented a factorial-design placebo-controlled trial comparing differing doses of olmesartan medoxomil (10 mg, 20 mg, and 40 mg), amlodipine (5 mg, and 20 mg), each of the possible combinations of olmesartan medoxomil plus amlodipine and placebo in hypertensive patients as supportive evidence (COACH trial).

The published trials presented in the submission are shown in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
<b>Direct randomised trials</b>		
Trial 302 Barrios V et al. (2009)	Olmesartan medoxomil plus amlodipine increases efficacy in patients with moderate-to-severe hypertension after monotherapy: a randomized, double-blind, parallel-group, multicentre study	Clinical Drug Investigation 2009; 29(7):427-439
Trial 303 Mourad J-J et al. (2009)  Volpe M et al. (2009)  Volpe M et al. (2009)	Effective systolic blood pressure reduction with olmesartan medoxomil/amlodipine combination therapy: Post hoc analysis of data from a randomized, double-blind, parallel-group, multicentre study.  Efficacy and safety of a stepped-care regimen using olmesartan medoxomil, amlodipine and hydrochlorothiazide in patients with moderate-to-severe hypertension: an open-label, long-term study.  Efficacy and tolerability of olmesartan medoxomil combined with amlodipine in patients with moderate to severe hypertension after amlodipine monotherapy: a randomized, double-blind, parallel-group, multicentre study.	Clinical Drug Investigation 2009; 29(6):419-425  Clinical Drug Investigation 2009; 29(6):381-391  Clinical Drug Investigation 2009; 29(1):11-25
COACH Chrysant SG et al. (2008)  Oparil S et al. (2009)	The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study.  Subgroup analyses of an efficacy and safety study of concomitant of amlodipine besylate and olmesartan medoxomil: evaluation by baseline hypertension stage and prior antihypertensive medication use (publication identified during the evaluation).	Clinical Therapeutics 2008; 30(4):587-604  Journal of Cardiovascular Pharmacology 2009; 54(5):427-436

## 8. Results of Trials

The primary outcome measure of Trials 302 and 303 was mean change in sitting diastolic blood pressure (DBP).

In Trial 302, the addition of amlodipine (5 mg and 10 mg) to olmesartan medoxomil monotherapy resulted in a statistically significant additional reduction in mean sitting DBP compared to add-on placebo in patients inadequately controlled by olmesartan 20 mg monotherapy (-2.7 [95%CI: -4.4, -1.1] and -3.2 [95% CI: -4.9, -1.5] respectively). However, the upper limits of the 95% confidence intervals for the change in mean sitting DBP indicated a reduction less than 2.0 mmHg (which the European Medicines Agency guidelines for the clinical investigation of medicinal products in the treatment of hypertension suggest is a clinically relevant change for sitting DBP).

In Trial 303 Period II, the addition of olmesartan medoxomil (10 mg, 20 mg, and 40 mg) resulted in statistically significant reductions in sitting DBP when compared to add-on

placebo in patients whose blood pressure was inadequately controlled by amlodipine 5 mg monotherapy (-2.0 [95%CI: -3.7, -0.2]; -3.7 [95%CI -5.4, -2.0] and -3.8 [95%CI -5.5, -2.1] respectively). The upper limits of the 95% confidence intervals for the reduction in mean sitting DBP were around 2.0 mmHg for both the proposed olmesartan medoxomil plus amlodipine proprietary products of 20 mg/5 mg and 40 mg/5 mg.

In the factorial design COACH trial, there was a statistically significant reduction in sitting DBP from baseline for all groups including placebo. The numerical reductions in the placebo-adjusted mean sitting DBP were greatest for the combination therapy groups (-10.8 mmHg to -15.9 mmHg), compared to olmesartan medoxomil monotherapy (-5.3 mmHg to -7.4 mmHg) and amlodipine monotherapy (-6.5 mmHg and -9.9 mmHg). The upper limit of the 95% confidence interval for the placebo-adjusted least squares mean change was consistent with blood pressure reductions greater than 2.0 mmHg for all groups. There appeared to be dose-response relationships, as increasing doses of amlodipine or olmesartan medoxomil resulted in numerically larger reductions in sitting DBP.

The mean reduction in mean sitting DBP was statistically significantly higher for each combination therapy in the COACH trial when compared to the respective olmesartan medoxomil monotherapy or amlodipine monotherapy. The upper limit of the 95% confidence interval for the least squares mean difference was consistent with a mean sitting DBP reduction of less than 2.0 mmHg only for olmesartan medoxomil 10 mg plus amlodipine 10 mg compared to amlodipine 10 mg monotherapy. There is no olmesartan medoxomil 10 mg combination therapy proposed for the Australian market.

The submission presented subgroup analyses for the COACH trial based on prior use of antihypertensives (naïve or non-naïve), as this trial did not specifically recruit patients who had failed monotherapy antihypertensive treatment. The submission argued that a significant proportion of non-antihypertensive naïve patients would match the proposed PBS restrictions. In general, these data suggest that prior treatment with antihypertensives does not affect the reduction in mean sitting DBP. However, of the proposed proprietary products, the upper limit of the 95% confidence interval indicates a reduction in sitting DBP of less than 2.0 mmHg for the olmesartan medoxomil 20 mg plus amlodipine 10 mg combination compared to amlodipine 10 mg monotherapy only.

The submission stated that no additional safety signals or significant changes to the risk-benefit ratio of olmesartan medoxomil with amlodipine have been observed in post-marketing surveillance.

Overall, the safety profile of olmesartan medoxomil with amlodipine combination is similar to the component monotherapies.

*For PBAC's view of these results, see Recommendation and Reasons.*

## **9. Clinical Claim**

The submission described olmesartan medoxomil with amlodipine as significantly more efficacious than treatment with either olmesartan medoxomil or amlodipine used as monotherapy and similar in terms toxicity.

*For PBAC's view, see Recommendation and Reasons.*

## **10. Economic Analysis**

The submission presented a cost minimisation analysis of olmesartan medoxomil plus amlodipine combination against the individual component products at the current price to pharmacist level.

## **11. Estimated PBS Usage and Financial Implications**

The likely number of patients per year was estimated by the submission to be between 10,000 and 50,000 in Year 5. The PBAC considered the submission's estimate to be uncertain because of uncertainty in the extent of uptake of olmesartan/amlodipine.

The net financial cost per year to the PBS was estimated by the submission to be less than \$10 million in Year 5. The PBAC considered the submission's estimate a likely overestimate as the change in use of other AIIRA/CCBs has been underestimated. It is unlikely that listing a fixed-combination product would result in a large net cost to the PBS/RPBS when the price is based on a cost-minimisation approach using the price-to-pharmacist for the individual components.

## **12. Recommendation and Reasons**

The PBAC recommended the listing of olmesartan with amlodipine 20 mg-5 mg, 40 mg-5 mg and 40 mg-10 mg tablets in accordance with the combination guidelines, on a cost-minimisation basis compared with the corresponding strengths of the constituent components, amlodipine and olmesartan given concomitantly.

The PBAC agreed that the restriction for this angiotensin II receptor antagonist (AIIRA)/calcium channel blocker (CCB) combination product should be "*hypertension in a patient who is not adequately controlled with either of the drugs in the combination*", consistent with its March 2010 recommendation that this restriction wording be applied to all AIIRA/CCB and angiotensin converting enzyme inhibitor (ACEI)/CCB combination products for the treatment of hypertension.

The PBAC agreed with the ESC that the data presented in the submission adequately demonstrates that olmesartan with amlodipine is significantly more efficacious than treatment with either olmesartan or amlodipine used as monotherapy and similar in terms toxicity.

The PBAC further agreed with the ESC that the submission's estimate of the increase in net cost to the PBS/RPBS that would result from the listing of this combination product is unlikely to be realised.

The PBAC noted some with concern that the sponsor had advised in the pre-subcommittee response that it will not proceed with the listing of the olmesartan 20 mg – amlodipine 10 mg combination tablet. This means that a patient whose hypertension is uncontrolled with the 20 mg – 5 mg tablet who wishes to continue to use the combination only has the option of increasing the olmesartan dose by moving to the 40 mg - 5 mg strength. The dose of amlodipine alone cannot be increased from 5 mg to 10 mg with the combination strengths available. The PBAC noted that the sponsor had provided no explanation for its decision not to proceed with the 20 mg – 10 mg product and requested the Secretariat seek an explanation for the Committee.

The PBAC decided it was not satisfied as required by section 101 (4AC) of the *National Health Act 1953* ('the Act') and therefore it will not provide advice to the Minister under that section in relation to the following combination item: olmesartan medoxomil with amlodipine (as besylate), tablets, 20 mg-5 mg, 40 mg-5 mg and 40 mg-10 mg which have the brand name Sevikar<sup>®</sup>. The PBAC noted there was no basis to conclude that these combination items have any significant improvement in compliance, efficacy or reduction in toxicity, over their alternative therapies for some patients.

***Recommendation:***

OLMESARTAN MEDOXOMIL with AMLODIPINE (as besylate), tablets, 20 mg-5 mg, 40 mg-5 mg and 40 mg-10 mg

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

Maximum quantity:    30

**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**

The sponsor has no comment.