PUBLIC SUMMARY DOCUMENT
Product: Amlodipine besylate with Valsartan, tablet, 5 mg-80 mg, 5 mg-160 mg, 10 mg-160 mg, Exforge® 5/80, Exforge®5/160, Exforge®10/160
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application
To seek a restricted benefit listing for hypertension in patients who are not adequately controlled with either amlodipine or valsartan monotherapy.

2. Background
This combination drug had not previously been considered by the PBAC. Amlodipine is an unrestricted benefit and has been listed on the PBS since August 1993, while valsartan has been recommended for PBS listing on a number of occasions.

3. Registration Status
Exforge was registered by the TGA on 5 February 2008 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 amlodipine or valsartan monotherapy

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
The combination of valsartan and amlodipine allows more effective blood pressure reduction than the respective monotherapies, and the fixed combination tablet will reduce the tablet burden in patients requiring different types of anti-hypertensive medications.

6. Comparator
The submission nominated the individual components of the fixed dose combination, i.e. valsartan and amlodipine as the comparator. The PBAC considered this was appropriate.

7. Clinical Trials
The submission presented nine randomised trials comparing fixed dose valsartan/amlodipine (various dose combinations) with corresponding doses of either valsartan or amlodipine monotherapies in patients with hypertension. The submission presented two pharmacokinetic studies comparing fixed combination vs free components.

The trials published at the time if submission are as follows:

Trial/Author	Protocol title/Publication title	Publication citation
Study 2201	Two Multicenter, 8-Week, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Studies Evaluating the Efficacy and Tolerability of Amlodipine and Valsartan in Combination and as Monotherapy in Adult Patients with Mild to Moderate Essential Hypertension.	Philipp T ,et al. Clinical Therapeutics 29(4): 563-580
	Amlodipine and Valsartan Combined and	Smith TR,et al.

Trial/Author	Protocol title/Publication title	Publication citation
	as Monotherapy in Stage 2, Elderly and Black Hypertensive Patients: Subgroup Analyses of 2 Randomised, Placebo-Controlled Studies.	Journal of Clinical Hypertension 9(5): 355-364
Study 2307	A Randomised, Double-Blind, Multi-centre, Multifactorial, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Valsartan (160mg and 320mg) and Amlodipine (10mg) Combined and Alone in Hypertensive Patients. 2005. Novartis Pharmaceuticals.	Same as citations for Study 2201.
Fogari et al, 2007	Effect of Valsartan Addition to Amlodipine on Ankle Oedema and Subcutaneous Tissue Pressure in Hypertensive Patients.	Journal of Human Hypertension 21: 220-224

8. Results of Trials

The key results from the trials evaluating the mean change in blood pressure showed there was a statistically significant difference in diastolic/systolic blood pressure (D/SBP), favouring valsartan/amlodipine combination therapy, compared to either drug alone, which is likely to be clinically important because the trials were generally powered to detect differences ranging from 2mmHg to 3.5mmHg.

The results from the pharmacokinetic studies showed that the valsartan/amlodipine combination product, compared to the products alone could be considered equivalent.

The occurrence of adverse events was low and consistent with the side effect profiles of the two component monotherapies. The most common adverse events were oedema and headache.

For PBAC's comments on these results, see Recommendations and Reasons.

9. Clinical Claim

The submission claimed the fixed combination is as effective as the individual components given concomitantly and also claimed superior efficacy for the combination product compared to constituent monotherapies.

The PBAC noted that there is currently no evidence to support an advantage in efficacy, safety or compliance for this combination product over alternative therapy.

For PBAC's view, see Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as fixed valsartan/amlodipine combination once daily and concomitant valsartan and amlodipine once daily.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS to be less than $10 million per year in Year 4. The PBAC considered this to be an underestimate.

12. Recommendation and Reasons

The PBAC recommended listing of amlodipine with valsartan in accordance with the combination guidelines, on a cost-minimisation basis compared with its constituent components, amlodipine and valsartan at equivalent doses.

The PBAC noted that valsartan will be supplied on the PBS from 1 March 2009 and therefore this combination product can only be listed from that date.

The PBAC also noted that there is currently no evidence to support an advantage in efficacy, safety or compliance for this combination product over alternative therapy in accordance with subsection 101 (4AC) of the National Health Act.

Recommendation

AMLODIPINE BESYLATE with VALSARTAN, tablet, 5 mg-80 mg, 5 mg-160 mg, 10 mg-160 mg

Restriction:	Restricted Benefit Hypertension in patients who are not adequately controlled with either amlodipine or valsartan monotherapy
Maximum quantity:	28
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

The sponsor chose not to comment.