PUBLIC SUMMARY DOCUMENT
Product: Valsartan with hydrochlorothiazide, tablets, 80 mg - 12.5 mg, 160 mg - 12.5 mg and 160 mg – 25 mg Co-Diovan®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application
The submission sought listing of valsartan with hydrochlorothiazide (HCTZ) in fixed dose combination tablets as a restricted benefit for patients with hypertension that is not adequately controlled with either valsartan or HCTZ monotherapy.

2. Background
The combination item containing valsartan with HCTZ had not been considered by the PBAC. HCTZ as a single ingredient product has been listed on the PBS since 1 May 1964. Valsartan as a single ingredient product is not currently listed on the PBS.

3. Registration Status
Valsartan with HCTZ has been TGA registered since 31 May 2005. Valsartan with HCTZ is indicated for the treatment of hypertension. Treatment should not be initiated with the combination products.

4. Listing Requested and PBAC's View
Restricted benefit
Hypertension in patients who are not adequately controlled with either hydrochlorothiazide or valsartan monotherapy.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
The new listing will provide another alternative angiotensin II antagonist with diuretic treatment option for hypertension which is not adequately controlled with monotherapy and lifestyle modifications.

6. Comparator
The submission nominated the following comparators:
a) Each of the individual components (valsartan and hydrochlorothiazide (HCTZ) given alone;
b) Each of the individual components (valsartan and HCTZ) given concomitantly.

The PBAC considered this was appropriate.

7. Clinical Trials
The submission presented 12 randomised trials comparing the fixed dose combination valsartan/HCTZ and the individual components in patients with hypertension. The submission presented three pharmacokinetic studies comparing fixed combination vs. free components.

A list of the trials and associated reports published at the time of submission is as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Study 301 Benz JR et al	Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy.	Journal of Human Hypertension. 1998. 12(12):861-6
Study 2301 Pool JL et al	Comparison of valsartan/hydrochlorothiazide combination therapy at doses up to 320/25 mg versus monotherapy: A double-blind, placebo-controlled study followed by long-term combination therapy in hypertensive adults.	Clinical Therapeutics. 2007. 29(1): 61-73
Study 0201 Carretta R et al	Pulse pressure responses in patients treated with valsartan and hydrochlorothiazide combination therapy.	European Heart Journal. 2002, 236-49.
Carretta R et al	Pulse pressure responses in patients treated with valsartan and hydrochlorothiazide combination therapy.	Journal of International Medical Research. 2003. 31 (5), 370-377.
Mallion J-M et al.	Valsartan/hydrochlorothiazide is effective in hypertensive patients inadequately controlled by valsartan monotherapy.	Blood Pressure, Supplement. 2003, 12 (1), 36-43.
Lacourciere Y et al, 2005	Antihypertensive efficacy and tolerability of two fixed-dose combinations of valsartan and hydrochlorothiazide compared with valsartan monotherapy in patients with stage 2 or 3 systolic hypertension: an 8-week, randomized, doub le-blind, parallel-group trial.	Clinical Therapeutics. 2005. Jul. 27(7):1013-21.
Lacourciere Y et al, 2004	Effective blood-pressure control with valsartan/HCTZ combination therapy in patients with moderate to severe systolic hypertension: The VALOR trial.	American Journal of Hypertension. 2004. 17 (5 PART 2), 115A.
Trenkwalder et al, 2004	Efficacy and safety of valsartan 160mg/hydrochlorothiazide 25mg combination in patients with hypertension not adequately controlled by valsartan 160mg/hydrochlorothiazide 12.5mg.	Clinical Drug Investigation. 2004, 24 (10): 593-602.
Trenkwalder P et al, 2004	Valsartan 160/ HCTZ 25 effectively reduces blood pressure in hypertensive patients not controlled by valsartan 160/ HCTZ 12.5.	Journal of Hypertension. 2004. 22 (SUPPL. 1), S194
Trenkwalder P et al, 2003	Blood pressure reduction with valsartan 160/HCTZ 25 in hypertensive patients uncontrolled by valsartan 160/HCTZ 12.5.	Deutsche Medizinische Wochenschrift. 2003. 128 (SUPPL. 3), S163.
Fogari et al, 2006	Hydrochlorothiazide added to valsartan is more effective than when added to olmesartan in reducing blood pressure in moderately hypertensive patients	Advances in Therapy. 2006 Sep-Oct. 23(5):680-95.

Trial/First author	Protocol title/Publication title	Publication citation
	inadequately controlled by monotherapy.	
Hua and Li, 2004	Efficacy and safety of combination of Valsartan with hydrochlorothiazide in the management of patients with essential hypertension.	American Journal of Hypertension. 2004. 17 (5 PART 2), 111A-112A.
Della Chiesa et al, 2003	Sexual activity in hypertensive men.	Journal of Human Hypertension. 2003. 17 (8), 515-521.
Schmidt et al, 2001	Antihypertensive effects of valsartan/hydrochlorothiazide combination in essential hypertension.	Blood Pressure. 2001, 10(4):230-7.
Waeber et al, 2001	Combination of hydrochlorothiazide or benazepril with valsartan in hypertensive patients unresponsive to valsartan alone.	Journal of Hypertension. 2001. 19 (11), 2097-2104.
Hilleman et al, 2001	Cost-effectiveness evaluation of fixed-dose combination of angiotensin-II receptor blockers with and without hydrochlorothiazide.	American Journal of Hypertension. 2001. 14 (4 Pt 2), 112A-113A (Abs P-250).
Black et al, 2000	Valsartan in combination with hydrochlorothiazide reduces the incidence of diuretic-induced hypokalemia: an integrated analysis of clinical data.	Journal of the Renin-Angiotensin-Aldosterone System. 2000. 1 (1), 102 (Abs PG. 18).

8. Results of Trials

The key results from the published trials and associated reports comparing the effectiveness as measured by mean change in blood pressure (mmHg) showed that there was a statistically significant difference in diastolic/systolic blood pressure (D/SBP), favouring valsartan/HCTZ combination therapy, compared to either drug alone. The PBAC considered that this is likely to be a clinically important difference because of the size of the effect and pharmacological plausibility.

The results from the published pharmacokinetic studies (apart from Study 07) showed that the combination therapy compared with the concomitant administration of the separate components could be considered bioequivalent.

Overall, 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 headaches and dizziness.

9. Clinical Claim

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

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/HCTZ combination once daily and concomitant valsartan and HCTZ once daily.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost/year to the PBS to be less than $10 million in Year 4. The PBAC considered that the submission's estimate to be an underestimate.

12. Recommendation and Reasons

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

VALSARTAN with HYDROCHLOROTHIAZIDE, tablets, 80 mg - 12.5 mg, 160 mg - 12.5 mg and 160 mg – 25 mg.

Restriction:	Restricted benefit Hypertension in patients who are not adequately controlled with either hydrochlorothiazide 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.