PUBLIC SUMMARY DOCUMENT

Product: Olmesartan medoxomil with hydrochlorothiazide, tablet, 20 mg-12.5 mg, 40 g 12.5 mg, 40 mg-25 mg, Olmetec Plus®

Sponsor: Schering-Plough Pty Limited

Date of PBAC Consideration: March 2007

1. Purpose of Application:

The submission sought a restricted listing for the treatment of hypertension in patients who are not adequately controlled with either hydrochlorothiazide or olmesartan monotherapy.

2. Background:

The combination product had not previously been considered by the PBAC.

Olmesartan tablet 10 mg, 20 mg and 40 mg were considered at the November 2005 PBAC meeting following a request from Pfizer Australia Pty Ltd. The PBAC recommended listing on a cost minimisation basis compared to irbesartan with 1 mg olmesartan being equivalent to 7.5 mg irbesartan.

3. Registration Status:

Olmetec Plus was registered by the TGA in June 2006 for: 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 hydrochlorothiazide or olmesartan monotherapy

See Recommendation and Reasons for PBAC's View.

5. Clinical place for the proposed therapy

Olmesartan medoxomil with hydrochlorothiazide will provide another combination of angiotensin II receptor antagonist (ATRA) and diuretic for patients with hypertension unresponsive to monotherapy with either ingredient.

6. Comparator:

The submission nominated olmesartan medoxomil (olmesartan) and hydrochlorothiazide (HCTZ) taken concomitantly as the appropriate comparator.

7. Clinical trials

The scientific basis of comparison consisted of two randomised controlled trials which involved:

a) comparing olmesartan (20 mg) and hydrochlorothiazide (12.5 mg or 25 mg) with olmesartan (20 mg) monotherapy, in patients with diastolic blood pressure (DBP) between 100 and 115mm Hg, over 12 weeks.
b) comparing, in a 12 arm randomisation, olmesartan and hydrochlorothiazide (6 dosage combinations) with olmesartan (10 mg, 20 mg or 40 mg) or hydrochlorothiazide (12.5 mg or 25 mg) monotherapy and placebo, in patients with diastolic BP between 100 and 115mm Hg, over 8 weeks.

The full list of trials forming the basis of the submission is tabulated below

Citations of the relevant randomised trials in the submission

Study	Citation
Sellin et al (2005)	Adding hydrochlorothiazide to olmesartan dose dependently improves 24-h blood pressure and response rates in mild-to-moderate hypertension. Journal of Hypertension 23:2083-2092
Chrysant et al (2004)	Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. American Journal of Hypertension 17:252

8. Results of trials

The results of the key trials are summarised in the table below:

Results of the key trials' primary outcomes: comparison of mean changes in blood pressure between differing dosage combinations

Olmesartan (mg) / HCTZ (mg)	N		Mean difference (95% CI)	p-value
Sellin et al (2005)		Mean change in daytime ambulatory DBP (SD)		
20 mg / placebo	174	– 2.8 (± 8.4)	-2.20 (-3.93,-0.47)	<0.0001
20 mg / 12.5 mg	184	– 5.0 (± 8.3)		
Chrysant et al (2004)		Mean change in trough seated DBP (SD)		
20 mg / placebo	41	–13.8 (± 7.4)	-2.60 (-6.67,1.47)	0.21
20 mg / 12.5 mg	44	–16.4 (± 11.2)		
40 mg / placebo	45	–14.6 (± 7.7)	–2.70 (–5.69, 0.29)	0.08
40 mg / 12.5 mg	42	–17.3 (± 6.4)		
40 mg / 12.5 mg	42	–17.3 (± 6.4)	–4.60 (–7.65, –1.55)	0.003
40 mg / 25 mg	39	–21.9 (± 7.6)		

DPB = diastolic blood pressure

The secondary outcomes, such as the proportions of participants whose blood pressure dropped after treatment to a defined norm, did not show any statistically significant outcomes.

The PBAC noted the sponsor's Pre-PBAC response observed that although not all analyses were statistically significant, this may be explained by the small number of patients in the Chrysant et al Study.

There were no significant differences reported in the treatment groups and the placebo group with respect to adverse events. In Chrysant et al the overall discontinuation rate due to adverse events of patients who received one or both of the active study drugs was 2.0%. The PBAC noted that the toxicity data in the submission was not well documented.

9. Clinical Claim

The submission described all three fixed dose combination of olmesartan and hydrochlorothiazide as having significant advantages in effectiveness over olmesartan or hydrochlorothiazide monotherapy.

See recommendations and Reasons for PBAC's view

10. Economic analysis

A preliminary economic evaluation was presented. The PBAC agreed that a cost-minimisation approach was valid.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated per year was estimated to be between 75,000-105,000 patients in Year 4.

The financial cost to the PBS was expected to be cost neutral, for although the predicted numbers of patients to be treated was deemed to be poorly justified by the ESC, each is individually expected to be cost neutral.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis compared with the corresponding strengths of the hydrochlorothiazide and olmesartan medoxomil components given concomitantly. The Committee noted that the olmesartan monotherapy product, recommended for listing at the November 2005 meeting, will also be listed. This ensures that the combination product meets the PBAC guidelines for fixed combination products.

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

Recommendation

OLMESARTAN with HYDROCHLOROTHIAZIDE tablet, 20 mg-12.5 mg, 40 mg-12.5 mg, 40 mg-25 mg

Restriction:	Restricted benefit Hypertension in a patient not adequately controlled with either hydrochlorothiazide or olmesartan medoxomil monotherapy.
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

Sponsor chose not to make a comment.