PUBLIC SUMMARY DOCUMENT
Product: Lercanidipine with Enalapril, tablets, 10 mg-10 mg, 10 mg-20 mg, Zan Extra®
Sponsor: Solvay Pharmaceuticals
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a Restricted benefit listing for hypertension in patients who are not adequately controlled with either lercanidipine or enalapril monotherapy.

2. Background

The PBAC had not previously considered this combination.

Lercanidipine has been listed on the PBS since November 2001. Enalapril has been listed on the PBS since August 1986 and is available in numerous generic versions.

3. Registration Status

Zan-Extra tablets were registered by the TGA on 14 February 2008 for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

4. Listing Requested and PBAC's View

Restricted benefit
Hypertension in patients who are not adequately controlled with either lercanidipine or enalapril monotherapy.

NOTE:
Treatment should not be initiated with these fixed dose combinations.

The PBAC had no objections to the requested wording of the restriction.

5. Clinical Place for the Proposed Therapy

Zan-Extra is a combination of lercanidipine (a calcium channel blocker) and enalapril (an angiotensin converting enzyme inhibitor) suitable for patients whose hypertension is not adequately controlled by lercanidipine or enalapril monotherapy.

6. Comparator

The submission nominated lercanidipine and enalapril monotherapy as the comparator. The PBAC agreed that this was appropriate.

7. Clinical Trials

The submission presented three key trials and one supportive trial. Two bioequivalence studies were presented as supplementary trials. Details of the trials are in the table below.

Trial ID	Protocol / Title
Key trials	
CPL1-0018	A multi-centre, randomised, parallel group, double-blind phase III trial to study the efficacy and tolerability of a combination of lercanidipine and enalapril in patients with mild to moderate essential hypertension not adequately controlled by lercanidipine treatment (add-on to lercanidipine).
CPL1-0019	A multi-centre, randomised, parallel group, double-blind phase III trial to study the efficacy and tolerability of a combination of lercanidipine and enalapril in

Trial ID	Protocol / Title
	patients with mild to moderate essential hypertension not adequately controlled by enalapril treatment (add-on to enalapril).
IT-CL 0044	A double-blind, placebo controlled, crossover study comparing lercanidipine, enalapril and their combination in the treatment of elderly patients with essential hypertension.
Supportive trial	
CPL2-0008	A multi-centre, randomised, double-blind, parallel group trial to determine the optimal dose combinations of lercanidipine and enalapril in comparison to each component administered alone.
Supplementary trials	
PK 0152	Bioequivalence Study of a fixed combination versus a Combination of Marketed Tablets of Lercanidipine HCl (10 mg) and Enalapril maleate (10 mg).
PK 0159	Bioequivalence Study of a fixed combination versus a Combination of Marketed Tablets of Lercanidipine HCl (10 mg) and Enalapril maleate (20 mg).

8. Results of Trials

The results from the three key trials are shown in the tables below.

Summary of primary and secondary efficacy outcomes for the key trials CPL1-0018 and CPL1-0019

	Trial CPL1-0018			**Trial CPL1-0019**		
	L 10 + E 10 (N = 165)	**L 10 (N = 172)**	**Difference (95% CI)**	**L 10 + E 20 (N = 162)**	**E 20 (N = 163)**	**Difference (95% CI)**
Primary outcome						
Mean change in SDBP (mmHg)	-7.1	-4.3	-2.8 (-1.4, -4.2) p<0.001	-9.2	-7.5	-1.8 (-0.4, -3.2) p=0.015
Secondary outcome						
Mean change in SSBP (mmHg)	-7.7	-2.3	-5.4 (-3.0, -7.8) p<0.001	-9.8	-6.7	-3.1 (-0.7, -5.5) p=0.013

Abbreviations: L + E = lercanidipine + enalapril; L = lercanidipine; E = enalapril; SDBP = sitting diastolic blood pressure; SSBP = sitting systolic blood pressure.

Summary of primary efficacy outcomes for the key trial CL-0044

	Trial CL-0044*		
	L 10mg (N = 66)	**E 20mg (N = 66)**	**L 10mg + E 20mg (N = 68)**
Mean baseline SBP (mmHg)	151	151	151
Mean ± SE 24-h SBP (mmHg)	138 ± 11	133 ± 12	128 ± 10
Change in mean 24-h SBP versus placebo	-6.6 ± 13.4	-11.4 ± 13.0	-16.5 ± 12.7
Least square means SBP unadjusted (mean± SE), (mmHg)	-6.7 ± 1.5 (p<0.0001 vs P)	-11.7 ± 1.5 (p<0.0001 vs P)	-17.0 ± 1.5 (p<0.0001 vs P) (p<0.0001 vs L 10) (p=0.0017 vs E 20)
Least square means adjusted for carry-over (mean±SE), (mmHg)	-7.4 ± 1.6 (p<0.0001 vs P)	-12.7 ± 1.5 (p<0.0001 vs P)	-17.6 ± 1.5 (p<0.0001 vs P) (p<0.0001 vs L 10) (p=0.0017 vs E 20)

Abbreviations: L + E = lercanidipine + enalapril; L = lercanidipine; E = enalapril; P = placebo; SBP = systolic blood pressure, DBP = Diastolic blood pressure.

*Cross-over trial

The key trials, CPL1-0018 and CL-0044 showed the superiority of the combination therapy over monotherapy with the individual components in reducing blood pressure. Trial CPL1-0019 shows non-inferiority of Zan-Extra 10/20 over enalapril 20 mg.

Two bioequivalence studies demonstrated the equivalence of the combination drug with the two monotherapies administered concurrently.

The combination product has similar side effects to its constituent drugs, lercanidipine and enalapril, i.e. dizziness, cough, headache, nasopharyngitis, flushing, vertigo and palpitations.

9. Clinical Claim

The submission claimed lercanidipine with enalapril combination tablet to be equivalent in terms of comparative effectiveness and equivalent in terms of comparative safety over lercanidipine in combination with enalapril. The submission claimed the combination tablet to be superior in terms of comparative effectiveness over lercanidipine and enalapril monotherapies.

Based on the supporting data, the PBAC considered these claims reasonable.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses are estimated as Zan-Extra 10/10 or 10/20 daily over duration of therapy and lercanidipine 10 mg with enalapril 10 mg or 20 mg daily over duration of therapy.

Because of PBS Reform policy, enalapril prices will be reduced by 25% on August 1, 2008. Lercanidipine prices will be reduced by 4% on August 1, 2008 and by a further 7% on August 1, 2011. The submission noted that the mandatory price cuts for lercanidipine and enalapril will extend to Zan-Extra.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of packs dispensed per year would be between 10,000 and 50,000 in the first year, increasing to between 100,000 and 200,000 in year 5. Market gains were predicted to be in exchange for the individually prescribed monotherapies.

The submission estimated an increased cost to the Government in Years 1 and 2 of listing of less than $10 million, and financial savings per year to the PBS of less than $10 million in year 5.

12. Recommendation and Reasons

The PBAC recommended a restricted benefit listing of lercanidipine with enalapril in accordance with the combination guidelines, on a cost-minimisation basis compared with its constituent components, lercanidipine and enalapril, the equi-effective doses being lercanidipine with enalapril 10/10 or 10/20 daily and lercanidipine 10 mg in combination with enalapril 10 mg or 20 mg daily over duration of therapy.

The PBAC also noted that the submission agreed that future price reductions for lercanidipine and enalapril will also flow to the combinations lercanidipine with enalapril 10/10 and 10/20.

Recommendation:
LERCANIDIPINE HYDROCHLORIDE with ENALAPRIL MALEATE, tablets, 10 mg-10 mg, 10 mg-20 mg

Restriction:	Restricted benefit Hypertension in patients who are not adequately controlled with either lercanidipine or enalapril monotherapy. NOTE: Treatment should not be initiated with these fixed dose combinations.
Maximum quantity:	30
Number of 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 has no comments.