PUBLIC SUMMARY DOCUMENT
Product: LOSARTAN, tablets, 25 mg and 50 mg (as potassium), Cozavan®
Sponsor: Alphapharm Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission requested an unrestricted benefit listing, intended for the treatment of hypertension.

2. Background

At the December 1995 meeting, the PBAC recommended an unrestricted listing for losartan potassium 50 mg tablets on a cost-minimisation basis compared with enalapril with the equi-effective doses being 87 mg losartan and 17 mg enalapril. Listing was effective 1 November 1997.

Losartan was deleted from the PBS effective 1 August 1998 due to issues with pricing arrangements.

3. Registration Status

Cozavan 25 mg and 50 mg tablets were TGA registered on 2 February 2010 for the treatment of hypertension, alone or in combination with other antihypertensives.

It is also registered for the treatment of hypertensive type 2 diabetics with proteinuria, defined as urinary albumin creatinine ratio greater than or equal to 300 mg/ g to delay the progression of renal disease.

4. Listing Requested and PBAC's View

Unrestricted benefit.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure may lead to shortened life expectancy.

Losartan will provide an additional choice of angiotensin II receptor antagonist for the treatment of hypertension.

6. Comparator

The submission nominated irbesartan as the main comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented six randomised comparative trials (Oparil 1998, Dang 2006, Fogari 2001, Kassler-Taub 1998, Koh 2004 and Oparil 2001) comparing losartan 50 mg to 100 mg and irbesartan 150 mg to 300 mg in patients with essential hypertension. It also presented two clinical outcome studies, one in hypertensive patients with left ventricular hypertrophy (LIFE), and the other in patients with type 2 diabetes and nephropathy (RENAAL).

The submission presented a published meta-analysis (Conlin 2000) of 43 randomised trials comparing an AIIRA or an AIIRA/hydrochlorothiazide (HCTZ) combination with other AIIRAs, other classes of antihypertensive, or placebo.

During the evaluation two clinical outcome trials (INDT and IRMA-2) were reviewed comparing irbesartan and placebo in hypertension with type 2 diabetic nephropathy. These trials are described in the irbesartan PI.

These trials had been published at the time of the submission as shown in the table below:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Trials measuring changes in blood pressure as outcome		
Optional titration trials measuring blood pressure		
Oparil 1998 Oparil et al.	An optional -titration study of the comparative effectiveness of two angiotensin II-receptor blockers, irbesartan and losartan.	Clin Ther 1998; 20(3):398-409.
Dang 2006 Dang A et al. Dang A et al.	Effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia in Chinese population. The effects of angiotensin II receptor blockers in hypertensive patients complicating hyperuricaemia.	J Hum Hypertens 2006; 20(1):45-50. Zhonghua Xin Xue Guan Bing Za Zhi [Chinese Journal of Cardiovascular Diseases] 2006; 34(10):882-885.
Fogari 2001 Fogari et al.	Effects of four angiotensin II-receptor antagonists on fibrinolysis in postmenopausal women with hypertension.	Curr. Ther. Res. Clin. Exp. 2001; 62(1):68-78.
Fixed dose trials measuring blood pressure		
Kassler-Taub 1998 Kassler-Taub K et al.	Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild-to-moderate hypertension. Irbesartan/Losartan Study Investigators	Amer J Hypertens 1998; 11(4 Pt 1): 445-453.
Koh 2004 Koh K et al.	Comparison of effects of losartan, irbesartan, and candesartan on flow-mediated brachial artery dilation and on inflammatory and thrombolytic markers in patients with systemic hypertension.	Amer J Cardiol 2004; 93(11):1432-1435, a10.
Oparil 2001 Oparil S et al. (2001) Smith D et al. (2005)	Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. Use of 24-hour ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan.	J Clin Hypertens 2001; 3(5):283-291+318. American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions 2005; 5(1):41-50.

Trials with clinical outcomes		
LIFE Dahlof B et al. (2002)	Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol.	Lancet 2002; 359:995-1003.
Okin P et al	Baseline characteristics in relation to electrocardiographic left ventricular hypertrophy in hypertensive patients: the Losartan intervention for endpoint reduction (LIFE) in hypertension study.	Hypertension 2000; 36:766-773
RENAAL Brenner B et al. (2001)	Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.	N Engl J Med 2001; 345:861-869.
Brenner B et al. (2000)	The losartan renal protection study – rationale, study design and baseline characteristics of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.	J Renin-Angiotensin-Aldosterone System 2000; 1(4):328-335.
Published meta-analysis presented in the submission		
Conlin et al (2000)	Meta-analysis of 43 published studies (up to October 1998) investigating the antihypertensive efficacy losartan, irbesartan, valsartan and candesartan. Angiotensin II Antagonists for Hypertension: Are There Any Differences in Efficacy?	American Journal of Hypertension, 2000; 13:418-426

The two clinical outcome trials identified during the evaluation are shown in the table below:

Trials with clinical outcomes identified during the evaluation		
Irbersartan vs Placebo		
IDNT Berl T et al. (2003)	Cardiovascular outcomes in the irbesartan diabetic nephropathy trial of patients with type 2 diabetes and overt nephropathy.	Ann Int Med 138:542-9.
Lewis E et al. (2001)	Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes.	N Engl J Med 345:851-60.
IRMA-2 Parving H et al. (2001)	The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.	N Engl J Med 345:870-8

8. Results of Trials

From the results of change from baseline diastolic blood pressure (DBP) the PBAC noted that in the optional titration trials, two of the three comparisons (Dang 2006, Fogari 2001) showed no statistically significant differences between treatments in diastolic blood pressure (DBP), and one (Oparil 1998) showed a statistically significant difference, with irbesartan producing larger blood pressure reductions than losartan (-10.2 mmHg vs -7.9 mmHg, $p<0.02$). There were four comparisons in the three fixed dose trials (Kassler-Taub 1998 compared losartan

100 mg with irbesartan 300 mg and irbesartan 150 mg). Three of the four comparisons (Kassler-Taub 1998: losartan 100 mg v irbesartan 300 mg, Koh 2004: losartan 100 mg v irbesartan 300 mg, and Oparil 2001: losartan 50 mg v irbesartan 150 mg) used a losartan to irbesartan ratio of 1 to 3. Koh and Oparil (2001) showed no statistically significant difference between treatments and Kassler-Taub (1998; losartan 100 mg v irbesartan 300 mg) showed a statistically significant difference in favour of irbesartan. The fourth comparison (Kassler-Taub 1998: losartan 100 mg v irbesartan 150 mg) used a losartan to irbesartan ratio of 1 to 1.5 and showed no statistically significant difference.

The results of change from baseline systolic blood pressure (SBP) in all three optional titration trials showed no statistically significant differences between losartan and irbesartan in systolic blood pressure (SBP). In the fixed dose trials, three of the four comparisons (Kassler-Taub 1998: losartan 100 mg v irbesartan 300 mg, Koh 2004: losartan 100 mg v irbesartan 300 mg, Oparil 2001: losartan 50 mg v irbesartan 150 mg) used the same dose relativities (1:3) as the optional titration trials. Of these Koh (2004) and Oparil (2001) showed no statistically significant difference and Kassler-Taub (1998; losartan 100 mg v irbesartan 300 mg) showed a statistically significant difference in favour of irbesartan. There was no statistically significant difference in mean reductions in SBP for the fourth comparison (Kassler-Taub 1998; losartan 100 mg v irbesartan 150 mg).

Only two trials (Oparil 1998 and Kassler-Taub 1998) reported the proportion of patients responding, defined as attaining a DBP < 90 mmHg or a DBP reduction of at least 10 mmHg, or proportion normalising DBP, defined as attaining a DBP < 90 mmHg. None of the between-drug comparisons in these analyses showed a statistically significant difference. Only one trial (Oparil 2001) reported ambulatory BP monitoring, showing no statistically significant difference in changes in DBP or SBP between losartan 50 mg and irbesartan 150 mg.

In the Conlin meta-analysis, there were no statistically significant differences in DBP reduction in comparisons of losartan and any of the other three angiotensin II receptor antagonists (AIIRAs). In SBP reduction there was a statistically significant difference in the titrated dose comparison of losartan and irbesartan, favouring irbesartan. Overall, these results show similar DBP and SBP reductions between losartan 50 mg compared to irbesartan 150 mg and between losartan 100 mg and irbesartan 300 mg.

In the LIFE trial, a 4.8-year, randomised trial comparing losartan-based treatment with atenolol-based treatment in 9,193 patients with hypertension and left ventricular hypertrophy, losartan demonstrated a statistically significant benefit compared to atenolol in the composite primary outcome (cardiovascular death, stroke, and myocardial infarction), driven mainly by the 25% risk reduction in stroke (HR 0.75, 95% CI 0.63, 0.88). There was also a statistically significant reduction in new-onset diabetes for patients treated with losartan compared to atenolol. Other events (revascularisation, resuscitated cardiac arrest, hospitalisation for unstable angina, or hospitalisation for heart failure) occurred in 6% or less of patients and showed no difference across arms.

The RENAAL trial was a 3.4-year, randomised trial comparing losartan with placebo in 1513 patients with type 2 diabetes and proteinuria, with or without hypertension (over 90% of patients had a history of hypertension treatment), which demonstrated a statistically significant 16% risk reduction for losartan in the primary composite outcome of creatinine-

doubling, development of end-stage renal disease or death, an effect seen in both creatinine-doubling and development of end-stage renal disease. These results were confirmed by analysis of renal progression and proteinuria. A reduction in cardiovascular events was not demonstrated.

The INDT trial was a 3-arm, 2.6-year, randomised trial comparing irbesartan with amlodipine and placebo in 1715 patients with hypertension and type 2 diabetes with proteinuria which demonstrated a statistically significant 20% risk reduction associated with irbesartan treatment compared to placebo in the same primary composite outcome as used in RENAAL (doubling of baseline creatinine, end-stage renal disease, or death), an effect most pronounced in creatinine-doubling. The results were confirmed by the results of renal progression and proteinuria reduction. Although RENAAL and INDT enlisted somewhat different patient populations and showed different placebo rates for the primary outcome (47.1% v 39%, RENAAL v INDT) and for creatinine-doubling (26.0% v 23.7%), the trials overall suggest similar effects on the delay of renal progression in patients with hypertension and type 2 diabetes.

The IRMA-2 trial was a 24-month randomised trial comparing irbesartan and placebo in 590 patients with hypertension and type 2 diabetes which showed a statistically significant reduction in progression to overt nephropathy for irbesartan 300 mg compared to placebo, supported by statistically significant reductions in urinary albumin excretion. These results are consistent with those of the INDT trial.

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

The PBAC noted that losartan and irbesartan have similar safety profiles as shown in the short term trials measuring blood pressure.

9. Clinical Claim

The submission described losartan as no worse than irbesartan in terms of comparative effectiveness and safety. The PBAC considered this claim to be reasonable.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated by the submission as losartan 100 mg daily and irbesartan 150 mg daily (i.e., a ratio of 1:1.5).

Based on the trial data presented in the submission, between 51.6% and 61% of patients might be expected to be prescribed the 100 mg dose. Based on 2008/2009 Medicare Australia data, the pre-sub-committee response conservatively estimated that 75% of patients will be uptitrated to the 100 mg dose and proposed a weighted price for the 50 mg tablet based on the expected utilisation split between the 50 mg and 100 mg doses.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be greater than 200,000 in Year 5. The PBAC noted there was an error in the submission's calculations that resulted in an underestimate of usage predictions by 10.5%.

The financial savings per year to the PBS were estimated by the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended listing losartan on the PBS as an unrestricted benefit listing on a cost-minimisation basis compared with irbesartan, at the prices proposed by the sponsor. The PBAC accepted the sponsor's pre-Sub Committee response offer of a weighted price to account for patients who require a dose of 100 mg in the absence of a 100 mg strength tablet. This weighted price is based on 75% patients taking a 100 mg dose and 25% taking a 50 mg dose. The sponsor based this on 2008/2009 Medicare Australia data of the utilisation of irbesartan 75 mg and 150mg, which showed that 75% patients within these two strengths were prescribed the higher dose.

The PBAC agreed the approach of the submission for the dose relativity was conservative as the dose relativity implied by the optional titration studies were 1:2.85 (Oparil 1998) and 1:2.6 (Fogari 2001). Overall, the relativity of the equi-effective doses from these trials was accepted as 1:2.8, using the number of participants in each trial still taking the compared drugs at steady state in each trial as the weighting factor.

The PBAC noted that in the optional titration trials, two of the three comparisons (Dang 2006, Fogari 2001) show no statistically significant differences between treatments in diastolic blood pressure (DBP), and one (Oparil 1998) showed a statistically significant difference, with irbesartan producing larger reduction in diastolic blood pressure than losartan. However, there was no statistically significant difference in systolic blood pressure (SBP) in any of these three trials. There were four comparisons in the three fixed dose trials (Kassler-Taub 1998 compared losartan 100mg with irbesartan 300mg and irbesartan 150mg). Three of the four comparisons (Kassler-Taub 1998: losartan 100mg v irbesartan 300mg, Koh 2004: losartan 100mg v irbesartan 300mg, and Oparil 2001: losartan 50mg v irbesartan 150mg) used a losartan to irbesartan ratio of 1:3. Koh and Oparil (2001) showed no statistically significant difference in DBP or SBP between treatments and Kassler-Taub (1998; losartan 100mg v irbesartan 300mg) showed a statistically significant difference in favour of irbesartan for both DBP and SBP. The fourth comparison (Kassler-Taub 1998: losartan 100mg v irbesartan 150mg) used a losartan to irbesartan ratio of 1:1.5 and showed no statistically significant difference in DBP or SBP.

In the Conlin meta-analysis, there were no statistically significant differences in DBP reduction in comparisons of losartan and any of the other three angiotensin II receptor antagonists (AIIRAs). In SBP reduction there was a statistically significant difference in the titrated dose comparison of losartan and irbesartan, favouring irbesartan. Overall, these results show similar DBP and SBP reductions between losartan 50mg compared to irbesartan 150mg and between losartan 100mg and irbesartan 300mg. The authors of the meta-analysis note that, whilst some head-to-head studies comparing losartan with other AIIRAs (including the study reported by Oparil 1998) suggest differences in efficacy between the agents tested, these direct comparative studies contribute only a small proportion of the available evidence,

and that a meta-analysis such as that presented provides a stronger basis for understanding the comparative efficacy of the drugs.

The PBAC also noted that the clinical outcome data of the four trials presented in the submission (LIFE, RENAAL, INDT and IRMA-2) support the conclusion that losartan is similar to other drugs in the AIIRA class in terms of the most clinically relevant outcome of survival. In other published studies, losartan is shown to be superior to atenolol in a composite outcome of stroke, myocardial infarction and death (Dahlof 2002) and similar to enalapril in reduction of all cause mortality (ELITE 2).

The PBAC considered that based on the evidence presented in the submission and the totality of the published literature for blood pressure reduction and long term benefits, the claim that losartan is no worse than irbesartan in terms of comparative effectiveness and safety was reasonable. The longer term risk/benefit of losartan and irbesartan also appeared similar.

The PBAC considered that losartan was clinically similar to the drugs currently in the AIIRA therapeutic group based on the totality of the evidence presented in the submission. The PBAC is therefore of the view that, on the basis of the material available to it at this time, losartan should be treated as interchangeable on an individual patient basis with the AIIRAs candesartan, eprosartan, irbesartan, olmesartan, telmisartan and valsartan. The appropriate delegate may therefore wish to consider it for inclusion in the AIIRA Therapeutic Group.

The PBAC noted that determining equi-effective doses can be difficult for drugs which have a flat dose-response curve, and that this factor may in part explain the statistically significant differences in DBP for irbesartan over losartan in one of the three dose titration studies presented in the submission. The PBAC did however note that there is evidence from the HEAAL *(Konstam M et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009, 374:1840-48)* study that up-titrating doses of losartan beyond 50mg confers additional clinical benefit. In accordance with the Guidelines, the PBAC considered that the direct optional dose titration studies (Oparil 1998 and Fogari 2001) are most appropriate for estimating equi-effective doses. Overall, the PBAC determined that the dose relativity of losartan and irbesartan was 1:2.8 and accepted the price offered by the Sponsor which is less than that based on dose relativity.

The PBAC noted that the sponsor did not market a 100 mg strength tablet but that the trial data showed that between 51.6% and 61% of patients required a dosage of 100 mg. In its Pre-Sub-Committee Response the sponsor offered a weighted price to account for the additional cost of treating patients with 100 mg. The PBAC noted that patients may be financially disadvantaged as those requiring 100 mg per day would require two scripts and hence two co-payments per month as the maximum quantity proposed for the 50 mg tablets is 30. The PBAC therefore considered that the maximum quantity for the 50 mg tablets should be increased to 60 tablets

The PBAC requested the sponsor to provide information regarding whether 100 mg strength tablets could be made available in the future.

The PBAC recommended the Safety Net 20 Day Rule should apply.

Recommendation:
LOSARTAN, tablets, 25 mg and 50 mg (as potassium), Cozavan®

Restriction:	Unrestricted benefit
Maximum quantity:	30 (25 mg) 60 (50 mg)
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 further comment.