PUBLIC SUMMARY DOCUMENT
Product: Paricalcitol, capsules, 1 microgram, 2 micrograms and 4 micrograms, Zemplar®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a Section 85 Authority Required listing for the treatment of patients with end stage chronic renal disease receiving dialysis who have secondary hyperparathyroidism.

2. Background

This was the second submission for paricalcitol. At its July 2007 meeting, the PBAC considered that the evidence from the non-randomised retrospective cohort studies presented did not adequately support the submission's claim of superiority over calcitriol in terms of the outcomes of reduced hospitalisations and survival, and was more suggestive of non-inferiority between paricalcitol and calcitriol.

The PBAC rejected the submission on the grounds of insufficient evidence of superiority over the comparator to support a cost-effectiveness claim.

3. Registration Status

Paricalcitol, 1 microgram, 2 micrograms and 4 micrograms capsules were registered by the TGA on 1 March 2007 for the treatment for the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease, stages 3, 4 and 5.

4. Listing Requested and PBAC's View

Authority required

Treatment by a nephrologist of patients with end stage renal disease receiving dialysis who have secondary hyperparathyroidism (iPTH value > 300 pg/mL (30pmol/L) AND

(i) Phosphate >1.6mmol/L OR
(ii) Ca > 2.4 mmol/L

NB: Intact PTH should be monitored quarterly (measured at least 12 hours post dose) and the dose adjusted as necessary to maintain an appropriate iPTH level.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Paricalcitol, an analogue of calcitriol, the metabolically active form of vitamin D, regulates parathyroid hormone (PTH) levels, improves calcium and phosphate balance, and may prevent or treat metabolic bone disease associated with chronic kidney disease (CKD).

6. Comparator

The submission nominated oral calcitriol as the main comparator. This was previously agreed by the PBAC.

7. Clinical Trials

The re-submission presented new trial data. Two new non-randomised observational studies reported by Kalantar-Zadeh (2006), Lee (2007) (based on the same study) and Young (2006) along with three non-randomised retrospective cohort studies which were presented in the prior submission, are provided in this submission as pivotal evidence. The newly presented publications by Kalantar-Zadeh (2006) and Lee (2007) examined the association between the administration of paricalcitol and mortality in stratified paricalcitol dose groups or subgroups defined by baseline characteristics, respectively. The poster presentation by Young (2006) was new to this submission, which demonstrated survival benefits associated with paricalcitol and/or calcitriol compared to no vitamin D therapy. Neither of the newly included non-randomised studies compared paricalcitol and calcitriol directly. Three previously considered non-randomised observational studies (Dobrez 2004; Teng 2003; Tentori 2006a and 2006b) compared survival and hospitalisation benefits between IV paricalcitol and IV calcitriol.

Seven randomised, placebo-controlled paricalcitol trials and one meta-analysis on calcitriol vs. placebo were new to this submission and served as supportive evidence. Paricalcitol and calcitriol were indirectly compared on controlling iPTH levels in haemodialysis patients.

8. Results of Trials

The key results were unchanged from the previous submission and are summarised in the tables below.

Hazard ratios for all-cause mortality for patients receiving IV paricalcitol compared to IV calcitriol treated patients in Teng (2003) and Tentori (2006b)

Model	Covariates	IV paricalcitol vs. IV calcitriol		
		n	HR (95%CI)	p value
Teng (2003)				
1	Unadjusted	67,399	0.81 (0.78, 0.85)	< 0.001
2	Age, gender, race, diabetes status, duration of dialysis	66,950	0.86 (0.82, 0.89)	< 0.001
3	Model 2 + study-entry period	66,950	0.90 (0.86, 0.95)	< 0.001
4	Model 3 + SMR	66,950	0.89 (0.85, 0.94)	< 0.001
5	Model 4 + dialysis access	66,950	0.89 (0.85, 0.93)	< 0.001
6	Model 5 + albumin, calcium, phosphorus, PTH, ALP, haemoglobin, ferritin, bicarbonate, dialysate calcium and creatinine	30,012	0.84 (0.79, 0.90)	< 0.001
Tentori (2006b)				
1	Unadjusted	7,731	0.78 (0.69, 0.89)	< 0.05
2	Age, gender, race, cause of ESRD, year started HD, time on HD before first vitamin D administration	7,731	0.79 (0.68, 0.92)	< 0.05
3	Model 2 + baseline serum calcium, phosphorus, PTH, albumin,, Kt/V, creatinine, and Hct labs	6,107	0.93 (0.78, 1.11)	NS
4	Model 3 + clinic SMR	6,107	0.94 (0.79, 1.13)	NS
5	Model 4 + time-varying labs	6,107	0.95 (0.79, 1.13)	NS

Hospitalisation effect of IV paricalcitol relative to IV calcitriol in Dobrez 2004

	IV paricalcitol compared to IV calcitriol		p value
	ITT (N=11,443)	Efficacy subset analysis*	
No. of hospital admissions per year	-0.642	-0.846	<0.0001
No. of hospital days per year	-6.84	-9.17	<0.0001
Risk of first all-cause hospitalization	HR: 0.863	-	<0.0001
No. of hyperparathyroidism-related hospital admissions per year	-0.297	-	<0.0001
No. of hyperparathyroidism-related hospital days per year	-4.03	-	<0.01
Risk of first hyperparathyroidism-related hospitalization	HR: 0.878	-	<0.0001

*the subset of patients who remained on their initial vitamin D therapy without switching treatment

The study by Young (2006) demonstrated an informal indirect comparison of mortality associated with paricalcitol and calcitriol, with no vitamin D therapy being the common reference.

Kalantar-Zadeh (2006) and Lee (2007) demonstrated the administration of paricalcitol reduced all-cause mortality compared to patients who did not receive paricalcitol. Young (2006) reported an indirect comparison on survival benefit between IV paricalcitol and oral vitamin D. The adjusted model showed that IV paricalcitol was associated with a significant reduction in all-cause mortality (RR: 0.85 (95% CI: 0.74, 0.97)) whereas no significant reduction is provided by oral vitamin D (RR: 0.95 (95% CI: 0.87, 1.03)). However, the oral vitamin D arm was a mix of oral vitamin D analogues, but largely made up of calcitriol.

In addition, the difference between the two RR estimates was non-significant (p=0.162). Results from Young (2006) indicated that both IV paricalcitol and IV calcitriol significantly reduced all-cause mortality when compared to no vitamin D therapy [RR= 0.85 (95% CI: 0.74, 0.97), RR= 0.91 (95% CI: 0.83, 0.99), respectively].

The above results on the direct and/or indirect comparisons between paricalcitol and calcitriol were all derived from non-randomised observational studies. The PBAC noted non-randomised observational studies are prone to selection bias and other confounders which cannot be fully adjusted for in statistical analyses. The PBAC had previously expressed concerns about the use of non-randomised observational studies as pivotal studies to claim the superiority of paricalcitol over calcitriol.

The Committee agreed that the Teng (2003) study, despite concerns regarding non-randomisation, is supportive of a significant mortality advantage for intravenous paricalcitrol over intravenous calcitriol. As the study is large, the differences in the study populations at baseline are not great, the mortality difference is large and the finding of reduced mortality is supported by other, albeit non-randomised, studies. However, the data provided to support a reduction in hospitalization rates with paricalcitol (Dobrez (2004) was more difficult to interpret and this remained a significant area of uncertainty for the PBAC.

The PBAC also remained concerned that most studies presented examined intravenous (IV) paricalcitol, while the submission requests listing for oral paricalcitol. An indirect comparison based on two meta-analyses showed that oral/intravenous paricalcitol

significantly reduced iPTH compared to placebo (-333.37 pg/ml (95%CI: -385.00, -183.22)), in contrast, calcitriol failed to show a significant reduction in iPTH (-156.00 pg/ml (95% CI: -330.89, 18.89)).

No results on the comparison of oral paricalcitol (the proposed drug) and oral calcitriol (the nominated main comparator) were presented in this re-submission. Although the bioequivalence of IV and oral paricalcitol has been established, the bioequivalence of IV and oral calcitriol remains uncertain. Therefore, the relative effectiveness of oral paricalcitol vs. oral calcitriol was not clear.

No new toxicity data were presented in the re-submission.

Two head-to-head trials on paricalcitol vs. calcitriol showed that paricalcitol had a similar safety profile to calcitriol except for significantly higher nervous system adverse events in paricalcitol patients (p=0.028). No advantage of hypercalcaemia in paricalcitol was evident. However, the PBAC noted, these two trials were relatively short (24-32 weeks) to capture long-term toxicity of paricalcitol therapy in ESRD patients.

9. Clinical Claim

Paricalcitol was described as having significant advantages in effectiveness over calcitriol. No interpretation was made on the comparative safety.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

An updated modelled economic evaluation was presented. The changes to the previous model were to adjust the intravenous paricalcitol dose to oral paricalcitol using a multiplication factor of 1.28 derived from the PI, and update drug costs. The approach to determination of hospitalisation rate had not been updated (the PBAC has previously expressed concerns about the approach).

Over a simulated 5-year horizon, paricalcitol was dominant versus calcitriol. The PBAC noted that the dominance of paricalcitol could only be accepted if the methodology used to determine the paricalcitol hospitalisation rate was accepted.

The model was most sensitive to the hospitalisation rate, hospitalisation costs, the hazard ratio for mortality, and the inclusion of dialysis cost. The result of the sensitivity analysis on the variation of hazard ratio of mortality is counterintuitive. With the increase of the hazard ratio, which means an increase in the paricalcitol mortality rate, paricalcitol becomes even stronger in dominating over calcitriol.

11. Estimated PBS Usage and Financial Implications

The submission estimated likely number of patients was less than 10,000 in Year 5 at a financial cost/year to the PBS of between $10-30 million in Year 5.

12. Recommendation and Reasons

The PBAC noted that this new submission proposed to list oral paricalcitol only. It also provided new clinical evidence in the form of two additional non-randomised cohort studies together with seven randomised placebo-controlled paricalcitol (IV or oral) trials and a meta-

analysis of calcitriol (IV or oral) for an indirect comparison of paricalcitol versus calcitriol on iPTH reduction.

The hearing clarified the clinical place of paricalcitol as a treatment for hyperparathyroidism in a patient with end stage renal disease whose serum calcium is higher than 2.4 mmol per litre but less than 2.8 mmol per litre, at which later point it is appropriate to discontinue treatment with paricalcitol and commence treatment with cinacalcet (noting however that the cinacalcet clinical studies used Vitamin D as an adjunct). The PBAC agreed that this clarification meant it was inappropriate to align the paricalcitol restriction with the cinacalcet one as suggested by the Restrictions Working Group.

However, the PBAC noted that there was a lack of concordance between the submission and the treatment algorithm presented at the hearing with most of the subjects in the large cohort studies presented being not representative of the proposed PBS population, particularly in regards to serum calcium and iPTH levels at baseline, which were lower than those required by the proposed listing restriction.

The Committee agreed that the Teng (2003) study, despite concerns regarding non-randomisation, is supportive of a significant mortality advantage for intravenous paricalcitrol over intravenous calcitriol, as the study is large, the differences in the study populations at baseline are not great, the mortality difference is large and the finding of reduced mortality is supported by other, albeit non-randomised, studies. However, the data provided to support a reduction in hospitalisation rates with paricalcitol (Dobrez (2004)) was more difficult to interpret and this remained a significant area of uncertainty for the PBAC.

The PBAC also remained concerned that most studies presented examined IV paricalcitol, while the submission requests listing for oral paricalcitol. Additionally, although the indirect comparison based on two meta-analyses shows that oral/intravenous paricalcitol significantly reduces iPTH compared to placebo (-333.37 pg/ml (95%CI: -385.00, -183.22)), and in contrast, calcitriol fails to show a significant reduction in iPTH (-156.00 pg/ml (95% CI: -330.89, 18.89)); the results of the indirect comparison are of borderline significance (p=0.057), and the inclusion of the meta-analysis on calcitriol may not be appropriate. Furthermore, no conclusion about comparative safety can be drawn because the presented safety data are based on two short-term trials only.

Many of the issues of economic uncertainty for the PBAC arose from the issues of clinical uncertainty identified above. The Committee noted that the revised submission had not updated the methodological approach used in determining hospitalisation rates about which the PBAC previously expressed concern, and that the model is highly sensitive to the hospitalisation rate. For example, at the hospitalisation rate of 85% used in the base case, paricalcitol is dominant, a reduction in hospitalisation rate to 64% increases the estimated incremental cost effectiveness ratio (ICER) to between $15,000 and $45,000 per extra quality adjusted life year (QALY) gained and decreasing the hospital rate further to 21% increases the ICER to between $105,000 and $200,000 per extra QALY gained.

The PBAC welcomed the sponsor's coverage with evidence development (CED) proposal in principle, but noted that the two randomised trials upon which this proposal was based excluded patients with baseline calcium levels higher that 2.5 or 2.6 mmol per litre, which

means that they will largely exclude patients representative of the PBS population and have very limited usefulness for the proposed CED.

Thus overall, members rejected the application because of continued concerns about the validity of the clinical claim of superiority for paricalcitol over calcitriol and because of the resulting uncertain cost-effectiveness.

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 will work with the PBAC to achieve a successful listing of paricalcitol.