PUBLIC SUMMARY DOCUMENT
Product: Paricalcitol, injection, 2 micrograms in 1 mL and 5 micrograms in 1 mL; capsules, 1 microgram, 2 micrograms, Zemplar®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) Private Hospital Authority Required listing for the oral and IV formulation and Section 85 Authority required listing for the oral formulation for the treatment of patients with end stage renal disease (Stage 5) receiving dialysis who have secondary hyperparathyroidism.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This was the third submission for paricalcitol.

At the July 2007 meeting, the PBAC rejected two submissions for paricalcitol, one for the injection and a minor submission for the capsules, for the treatment by a nephrologist of patients with end stage renal disease receiving dialysis who have secondary hyperparathyroidism on the grounds of insufficient evidence of superiority over the comparator, oral calcitriol, to support a cost-effectiveness claim.

At the March 2008 meeting, the PBAC rejected the application for paricalcitol capsules for the treatment of patients with end stage chronic renal disease receiving dialysis who have secondary hyperparathyroidism 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.

3. Registration Status

Paricalcitol, 1 microgram and 2 micrograms capsules were TGA registered on 21 March 2007 for the treatment of the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease, stages 3, 4 and 5.

Paricalcitol, 5 micrograms in 1ml injection was registered by the TGA on 21 March 2007 for the treatment of the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease, stage 5.

Paricalcitol, 2 micrograms in 1 mL injection was registered by the TGA on 29 October 2008 for the treatment of the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease.

4. Listing Requested and PBAC's View

Section 85 Authority Required (Oral formulation only)
Treatment by a nephrologist of patients with chronic kidney disease (Stage 5) receiving dialysis who have secondary hyperparathyroidism (iPTH value > 300 pg/mL or 31.8 pmol/L)

Section 100 Highly Specialised Drugs (Oral and IV formulations)
Private Hospital Authority Required
Treatment by a nephrologist of patients with chronic kidney disease (Stage 5) receiving dialysis who have secondary hyperparathyroidism (iPTH value > 300 pg/mL or 31.8 pmol/L)

For PBAC's view, see Recommendation and Reasons.

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. The PBAC considered this was appropriate, as previously, if the calcium level was between 2.4mmol/L and 2.8mmol/L.

7. Clinical Trials

The basis of the submission was:

1. For evidence on mortality and hospitalisation: Two pivotal non-randomised cohort studies (Teng 2003 and Dobrez 2004) and four supplementary non-randomised cohort studies.
2. For evidence of (i) a lower rate for paricalcitol of hypercalcaemia and/or elevated calcium-phosphate product, and (ii) similar biochemistry effects generally to support the submission's claim of a mortality and hospitalisation benefit: Four direct randomised comparative trials comparing paricalcitol and calcitriol used for seven meta-analyses and two 'lumped' analyses.
3. For supportive evidence of similar PTH control of paricalcitol and cinacalcet in order to be able to apply the paricalcitol mortality and hospitalisation effects to cinacalcet patients in the model: Twelve randomised comparative trials (seven comparing paricalcitol and placebo, five comparing cinacalcet and placebo) for an indirect analysis of paricalcitol and cinacalcet on control of PTH.
4. For supplementary evidence supporting dosing recommendations and translating intravenous to oral doses because many of the trials were done using the intravenous formulation yet the listing also includes the oral formulation: Two dose strategy trials and four bioequivalence studies.

The trials published at the time of submission are listed below:

Trial ID/First Author	Protocol title/Publication title	Publication citation
Randomised trials of biochemistry outcomes comparing IV paricalcitol vs IV ** calcitriol		
95028 Sprague et al	Suppression of parathyroid hormone section in hemodialysis patients	Am J Kidney Dis 2001;38 (Suppl 5):S51-S56
Cohort studies of survival and hospitalisations		
Primary cohort studies		
Teng (2003)	Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy	NEJM 2003;349:446-456
Dobrez (2004)	Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients	Nephrol Dialysis Transplant 2004;19:1174-1181
Supportive cohort studies		

Trial ID/First Author	Protocol title/Publication title	Publication citation
Tentori (2006)	Mortality risk among hemodialysis patients receiving different vitamin D analogs	Kidney International 2006; 1858-1865.
Kalantar-Zadeh (2005)	Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis	Kidney International 2005; 70,771-780.
Young (2006)	Vit D therapy and mortality in the dialysis outcomes and practice patterns study (DOPPS)	J Am Soc Nephrol 16: 2005 (abstract)
Shinaberger (2008) *	Ratio of paricalcitol dosage to PTH level and survival in maintenance hemodialysis	Clin J Am Soc Nephrol 2008, doi:10.2215/CJN.01760408
Supportive randomised trials of paricalcitol vs placebo		
M03635 (oral) *	Ross: Oral paricalcitol for secondary hyperparathyroidism	Am J Nephrol 2008;28:97-106
Supportive randomised trials of cinacalcet vs placebo		
Trial 173 *	Block: Cinacalcet for secondary hyperparathyroidism	NEJM 2004;350:1516-1525
Trial 182 *		
Trial 188 *	Lindberg: Cinacalcet for secondary hyperparathyroidism – a randomised trial	J Am Soc Nephrol 2005;16:800-807
Trial 141 *	Malluche: An assessment of cinacalcet on bone histology in dialysis patients	Clin Nephrol 2008;69:269-277
Japanese trial *	Fukagama: Cinacalcet decreases PTH in Japanese dialysis patients	Nephrol Dialysis Transplant 2008;23:328-335
Supportive bioequivalence studies		
Mazess(2003) *	A review of intravenous and oral vitamin D hormone therapy in hemodialysis patients.	Clin Nephrol 2003;59:319-325
Levine (1996) *	Pharmacokinetics and efficacy of pulse oral vs intravenous calcitriol in hemodialysis patients	J Am Soc Nephrol 1996;7:488-496

* signifies trials new to this submission

8. Results of Trials

The submission presented the same two pivotal non-randomised cohort studies (Teng 2003 and Dobrez 2004) as in the March 2008 application and four supplementary non-randomised cohort studies as evidence for the claim of improved survival and decreased hospitalisations with paricalcitol over calcitriol.

The results of the survival analysis are unchanged from the previous submission, see March 2008 PSD.

However, the results of hospitalisation rates by multivariate analysis have changed by using the full ITT population instead of the subset used in the previous submission and are shown below:

Hospitalisation by multivariate analysis from the Dobrez (2004) non-randomised study

Hospitalisation outcome measure	Paricalcitol N = 4,611	Calcitriol N = 6,832
No. hospitalisations per patient per year, mean	1.97	2.61
	0.64/yr fewer hospitalisations for paricalcitol	
No. hospital days per patient per year, mean	13.0	19.8
	6.2 fewer hospital days for paricalcitol	

The value of 0.64 fewer hospitalisations per year used in the economic model was in contrast to the value of 0.85 fewer hospitalisations used in the previous two submissions.

The results on the rates of hypercalcaemia and/or elevated calcium phosphate product used for supportive biochemistry evidence are shown below:

Rate of hypercalcaemia and/or elevated calcium-phosphate product in the randomised paricalcitol (P) vs calcitriol (C) trials

Description	Trial included in analysis (+ = yes, - = no)				Result (95% CI) p value	I^2 value* (95% CI)
	95027 IV P v oral C	95028 IV P v IV C	95034 IV P v IV C	M02516 IV P v IV C		
A. Meta-analysis of proportion with hypercalcaemia +/or elevated CP product	-	+	+	+	Paricalcitol 22.6% (=77/340) Calcitriol 30.6% (=106/346**) RR=0.75(0.53,1.04)** P=0.09**	42% (0%, 82%)
B. 'Lumped' analysis of proportion with hypercalcaemia +/or elevated CP product	-	+	+	-	Paricalcitol 24.1% (=55/228) Calcitriol 32.8% (=76/232) RR=0.74(0.57,0.95) NR	Not a meta-analysis
Random effects meta-analysis of analysis B	-	+	+	-	RR=0.74 (0.43, 1.29)	71% (0%, 93%)
Random effects meta-analysis as in A but using initial definition*** of hypercalcaemia and/or elevated calcium-product	-	+	+	+	Paricalcitol 53.5% (=182/340) Calcitriol 53.2% (=184/346) RR=1.01 (0.79, 1.29)	68.1% (0%, 91%)

* Calculated during the evaluation from the data provided in the submission
** The data appear to have been incorrectly transcribed in the submission, so the meta-analysis was conducted during the evaluation
*** The original definition in the trial reports used the first occurrence of hypercalcemia or of the calcium-phosphate product, compared to the definition used in the submission which was two consecutive elevations of calcium and four consecutive evaluations of the calcium-phosphate product The full protocols, amendments, and statistical analysis plans were not provided in the submission.
Abbreviations: CP=calcium-phosphate, NR=not reported, RR=relative risk

The submission presented new toxicity data from the two trials (Trial 95027 and M02516) new to this submission, but the results did not differ from those in the previous submission.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described paricalcitol as superior in terms of comparative effectiveness (survival and hospitalisations) and equivalent in terms of comparative safety over calcitriol. It added that these findings were supported by the biochemistry comparisons of paricalcitol versus calcitriol.

The PBAC did not consider that paricalcitol is superior in terms of comparative effectiveness (survival and hospitalisations) and equivalent in terms of comparative safety over calcitriol as the survival and hospitalisation results, although supportive of the submission's claim, are not conclusive because there are no randomised trial data on survival and hospitalisations.

10. Economic Analysis

An updated modelled economic evaluation was presented which consisted of a cost-utility, single cohort Markov model of two states, dialysis and death, beginning at age 60 and extending over a 10-year horizon in quarterly cycles. Cinacalcet was captured in the current modelling as a sensitivity analysis by switching those patients having hypercalcaemia or elevated calcium-phosphate levels from their initiated therapy (paricalcitol or calcitrol) to cinacalcet.

The sensitivity analyses showed that the mortality treatment effect and its duration and the hospitalisation treatment effect were the most prominent drivers of the model.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5 and the financial cost per year to the PBS was estimated to be in the range of $10 – $30 million in Year 5.

12. Recommendation and Reasons

The PBAC agreed that patients receiving paricalcitol should not have elevated serum calcium and phosphate levels as high serum calcium levels are considered a reason to cease vitamin D supplements (CARI Guidelines, Vitamin D in Dialysis 2006) and considered the restriction as requested on iPTH levels alone to be sufficient.

The submission nominated oral calcitriol as the comparator which was considered appropriate, as previously, if the calcium was between 2.4mmol/L and 2.8mmol/L

As pivotal evidence for the claim of improved survival and decreased hospitalisations with paricalcitol over calcitriol the submission presented the same two non-randomised cohort studies (Teng 2003 and Dobrez 2004) as in the application considered in March 2008 and four supplementary non-randomised cohort studies. The PBAC again considered that the key issue in the submission was the inability to establish whether there was a mortality benefit for paricalcitol over calcitriol in dialysis patients given the use of the large non-randomised study (Teng et al) as evidence. The Committee agreed with the ESC that both observational cohorts had a number of limitations, being susceptible to bias (e.g. lack of control over risk assignment, differential loss to follow-up, differences in the stage of disease) and so did not provide the level of empirical evidence equivalent to that provided by a randomised controlled clinical trial. The PBAC also agreed with the ESC that the reported 16% improvement in overall survival gain was implausibly large in dialysis patients and considered that the Teng Study was hypothesis generating and that a prospective randomised study was needed to confirm the findings of the Teng Study.

The PBAC therefore did not accept the claim in the submission of a 16 % improvement in the survival with paricalcitol over calcitriol, based on the results of Teng et al (2003).

Similarly, the PBAC was unable to ascertain if hospitalisation rates are affected by treatment with paricalcitol compared to calcitriol given the use of a non-randomised study (Dobrez et al, 2004) presented in support of the claim of reduced hospitalisation rates with paricalcitol.

Therefore, the PBAC did not consider that paricalcitol is superior in terms of comparative effectiveness (survival and hospitalisations) and equivalent in terms of comparative safety over calcitriol as the survival and hospitalisation results, although supportive of the submission's claim, are not conclusive because there are no randomised trial data to support these claims on survival and hospitalisations.

For evidence that paricalcitol treatment results in a lower rate of hypercalcaemia and/or elevated calcium-phosphate product and similar biochemistry effects generally, and to support the submission's claim of a mortality and hospitalisation benefit, the submission presents four direct randomised comparative trials comparing paricalcitol and calcitriol, which were used for seven meta-analyses and two 'lumped' analyses.

The PBAC considered that the major use of the results of the randomised trial to determine the rate of switching to cinacalcet triggered by hypercalcaemia and/or calcium-phosphate product (the 22.6% and 30.6% rates for paricalcitol and calcitriol) was uncertain as it relies on analyses that are not statistically significant and entail heterogeneity.

The PBAC also considered the economic evaluation to be uncertain as it relies on the evidence from non-randomised clinical trials. The Committee noted that the mortality treatment effect, its duration and the hospitalisation treatment effect were the most prominent drivers of the model.

The PBAC noted advice from the Highly Specialised Drugs Working Party that paricalcitol did not meet all the criteria for listing under the Highly Specialised Drugs Program.

The PBAC rejected the submission for paricalcitol due to the primary use of non-randomised data to establish the clinical case of superiority of paricalcitol over calcitriol and 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 is working with the PBAC to achieve PBS listing for paricalcitol.