PUBLIC SUMMARY DOCUMENT

Product: Paricalcitol, injection, 5 micrograms in 1 mL and 10 micrograms in 2ml; capsules, 1 microgram, 2 micrograms and 4 micrograms, Zemplar®

Sponsor: Abbott Australasia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a section 100 (Highly Specialised Drug) PBS listing for paricalcitol injection for the treatment by a nephrologist of patients with end stage renal disease 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 drug had not previously been considered by the PBAC.

3. Registration Status

Paricalcitol, 5 micrograms in 1ml and 10 micrograms in 2 mL injections were registered by the TGA on 1 March 2007 for the treatment for the biochemical manifestations of secondary hyperparathyroidism associated with chronic kidney disease, stage 5.

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

Section 100 (Highly Specialised Drug) Private hospital authority required
Treatment by a nephrologist of patients with end stage renal disease receiving dialysis who have secondary hyperparathyroidism (iPTH value > 300 pg/mL).

NOTE: 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

Chronic kidney disease (CKD) can affect all the organs and systems of the body. The disturbances to the body's chemical balance and build-up of waste substances in the blood can have extensive functional consequences, leading to the development of complications and contributes to the high morbidity and mortality of CKD. Stage five CKD, also known as end stage renal disease (ESRD) is characterised by kidney failure and patients require dialysis.

One of the endocrine complications of CKD is vitamin D deficiency which leads to the development of secondary hyperparathyroidism, as vitamin D deficiency promotes

parathyroid gland growth and increased parathyroid hormone (PTH) synthesis. The end result is elevated serum PTH and abnormal calcium and phosphorus balance.

The complications associated with chronic secondary hyperparathyroidism include renal bone disease, cardiovascular complications and less frequently neurotoxicity and endocrinopathy. Renal bone disease includes high turnover bone disease, osteoporosis, osteomalacia and low turnover bone disease.

Paricalcitol is an analogue of calcitriol, the metabolically active form of vitamin D, which regulates PTH levels and improves calcium and phosphate balance.

6. Comparator

The submission nominated oral calcitriol as the main comparator. Calcitriol is neither TGA nor PBS listed for secondary hyperparathyroidism associated with end-stage renal disease (ESRD), but it is commonly used in patients with chronic kidney failure.

The PBAC agreed that oral calcitriol is the appropriate comparator.

7. Clinical Trials

The submission presented three non-randomised retrospective cohort studies as pivotal evidence comparing intravenous paricalcitol with intravenous calcitriol in haemodialysis patients and two randomised controlled trials as supportive evidence comparing intravenous paricalcitol with intravenous calcitriol in haemodialysis patients over 24-32 weeks.

These trials had been published at the time of submission, as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Non-randomised trials – pivotal evidence		
Dobrez D et al 2004	Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings.	Nephrol Dial Transplant 2004, 19(5): 1174-81.
Teng M et al 2003	Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy.	N Engl J Med 2003, 349(5): 446-56.
Tentori F et al 2006	Risk of Hospitalisation is decreased among hemodialysis (HD) patients receiving vitamin D (IVVD) therapy.	American Society of Nephrology (ASN), San Diego. 2006, 14-19 November
Tentori F et al 2006b	Mortality risk among hemodialysis patients receiving different vitamin D analogs.	Kidney Int advance online publication 2006
Randomised trials – supportive evidence		
95028 Sprague S et al 2001	Suppression of parathyroid hormone secretion in haemodialysis patients: Comparison of paricalcitol with calcitriol.	Am J Kid Dis 2001, 38 (5 SUPPL. 5): S51-S56. (subgroup of 38 patients)
95028 Sprague S et al 2003	Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism.	Kid Int 2003, 63(4): 1483-90

8. Results of Trials

The results of the key studies are summarised in the tables below:

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

Model	Covariates	Paricalcitol vs. 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

In Teng et al (2003), the Kaplan-Meier plot showed that a survival difference between paricalcitol (n = 29,021) and calcitriol patients (n = 38,378) was evident at the end of the 36 month follow-up period ($p < 0.001$). The mortality rate was significantly lower in the paricalcitol group (18.0 per 100 patient years) than in the calcitriol group (22.3 per 100 patient years). In both unadjusted and adjusted models, the mortality difference between paricalcitol and calcitriol remained significant.

In Tentori et al (2006b), survival was significantly better in the paricalcitol treatment group compared to the calcitriol treatment group. The mortality rate in the paricalcitol group was 15.3 per 100 patient years compared to 19.6 per 100 patient years in the calcitriol group. However, after adjustment for baseline variables, the differences in survival were not statistically significant and may be smaller than previously reported by Teng et al (2003).

Hospitalisation effect of paricalcitol relative to calcitriol in Dobrez 2004

	Paricalcitol compared with 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 multivariate analysis indicated that patients who started on paricalcitol had 6.84 fewer hospital days per year and 0.642 fewer hospitalisations per year than calcitriol patients ($p < 0.0001$). In addition, patients who started on paricalcitol were 14% less likely to be hospitalised (HR = 0.863; $p < 0.0001$). The results of additional models that explored the effect of vitamin D treatment indicated paricalcitol patients had lower hyperparathyroidism-

related hospitalisation outcomes than calcitriol patients. However, as stated in Dobrez et al (2004), 5.6% of paricalcitol patients switched to other therapy while 41.3% switched therapy in the calcitriol arm during the observation period.

Two supportive trials 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, these two trials were relatively short (24-32 weeks) to capture long-term toxicity of paricalcitol therapy in ESRD patients.

The incidence of hypercalcaemia and/or elevated Ca×P in the randomised supportive trials is reported below:

Proportion of patients who became hypercalcaemic for at least 2 consecutive laboratory draws and/or had a Ca×P>75 at least one period of 4 consecutive laboratory draws

	Paricalcitol n/N (%)	**Calcitriol n/N (%)**	**Relative risk (95% CI)**		**Risk difference (95% CI)**	
95028	24/130 (18.5)	44/133 (33.1)	0.56 (0.36, 0.86)		-14.6 (-25.0, -4.2)	
95034	31/98 (31.6)	32/99 (32.3)	0.98 (0.65, 1.47)		-0.7 (-13.7,12.3)	
Pooled (Fixed or random effect)			**Fixed** 0.74 (0.55, 0.99)	**Random** 0.74 (0.43, 1.29)	**Fixed** -8.7 (-16.8, -0.5)	**Random** -8 (-22, 5)
p value of test for heterogeneity			0.06		0.10	
I^2 statistic			70.9%		62.9%	

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described paricalcitol as having significant advantages in effectiveness over calcitriol.

The PBAC considered that the evidence from the non-randomised retrospective cohort studies presented does not adequately support the submission's claim of superiority over calcitriol in terms of the outcomes of reduced hospitalisations and survival, and may be more suggestive of non-inferiority between paricalcitol and calcitriol.

10. Economic Analysis

The submission presented a modelled economic evaluation. A cost utility approach was used. The resources included in the base case were drug costs and hospitalisation costs.

For the base case modelled incremental discounted cost/extra discounted life year gained or quality adjusted life year (QALY) over a simulated 5-year horizon, the submission concluded that paricalcitol is dominant (ie more effective and less costly) versus calcitriol.

The PBAC noted that dominance of paricalcitol can only be accepted if the methodology used to determine the paricalcitol hospitalisation rate is accepted, as it appears that the resultant hospitalisation costs are the key drivers of the model. Given that the methodology used to determine the paricalcitol hospitalisation rate is not likely to be valid, the results of the model may not reflect the true cost-effectiveness of paricalcitol.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 5 of listing the financial cost/year to the PBS (excluding co-payments) would fall in the range $10 – $30 million.

12. Recommendation and Reasons

The PBAC agreed that oral calcitriol is the appropriate comparator. However the clinical evidence presented compares intravenous paricalcitol against intravenous calcitriol, and the comparative effectiveness of intravenous versus oral calcitriol is unknown. Additionally the only two randomised controlled trials presented (studies 95028 and 95034) only examined the effects of treatment on biochemical endpoints and did not include any relevant clinical endpoints, so it is not known if paricalcitol treatment will improve bone histology and bone mineral density, reduce fracture rates and/or ameliorate other clinical symptoms related to secondary hyperparathyroidism or to a reduced rate of parathyroidectomy. Data relating to quality of life and survival are also not available from these trials.

The PBAC agreed that there was a trend in the results from the randomised controlled trials favouring intravenous paricalcitol over intravenous calcitriol in the proportion of patients who experienced a sustained hypercalcaemic and/or elevated Ca×P event. The PBAC did not accept the submission's claim that this result was statistically significant based on a fixed effect analysis. The Committee agreed with the evaluation that a random effects analysis is more appropriate and that based on the random effects model, the numerical difference in hypercalcaemic and/or elevated Ca×P events between paricalcitol and calcitriol is not significant at $P<0.05$.

The Committee noted that in the absence of clinical endpoint data from direct randomised controlled studies, the submission's therapeutic claim relied upon the results of three non-randomised retrospective cohort studies. The PBAC agreed that selection bias is inherent in such observational studies, and that without supportive evidence from randomised controlled trials (even using surrogate endpoints) the submission's claim of superiority is highly uncertain. The adjusted analysis in one of the retrospective cohort studies was not statistically significant and the supportive evidence from the short randomised controlled trials on biochemical outcomes, such as Ca×P, did not show a benefit for paricalcitol over calcitriol.

Overall the PBAC considered that the evidence from the non-randomised retrospective cohort studies presented does not adequately support the submission's claim of superiority over calcitriol in terms of the outcomes of reduced hospitalisations and survival, and may be more suggestive of non-inferiority between paricalcitol and calcitriol.

The PBAC agreed that there were issues of economic uncertainty. In particular, the dominance of paricalcitol in the model rests on the acceptance of submission's claim of improved survival and reduced hospitalisations, which the PBAC found not to be adequately supported.

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

Recommendation

Reject

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 disappointed with the decision of the PBAC particularly because calcitriol is neither TGA nor PBS approved for the intended listing. The sponsor believes that paricalcitol has significant advantages over the comparator and it will continue to work collaboratively with the PBAC in order to demonstrate this advantage in future submissions.