PUBLIC SUMMARY DOCUMENT
Product: Paricalcitol, capsule, 1 microgram and 2 micrograms, Zemplar®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

The submission sought an Authority Required listing for treatment of secondary hyperparathyroidism in patients with chronic kidney disease where treatment with calcitriol is not appropriate.

2. Background

This was the fourth major submission to the PBAC for paricalcitol.

At the July 2007 meeting, the PBAC considered two submissions, one for the injection and a minor submission for the capsules, seeking 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. The PBAC rejected both submissions on the grounds of insufficient evidence of superiority over the comparator to support a cost-effectiveness claim.

At the March 2008 meeting, the PBAC rejected a submission seeking a Section 85 Authority Required listing 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.

At the March 2009 meeting, the PBAC rejected a submission seeking a Section 100 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 because of the primary use of non-randomised data to establish the clinical case of superiority of paricalcitol over calcitriol and uncertain cost effectiveness.

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 of secondary hyperparathyroidism in patients with chronic kidney disease where treatment with calcitriol is not appropriate.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Chronic kidney disease 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.

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 (hormone imbalance). Renal bone disease includes high turnover bone disease, osteoporosis, osteomalacia and low turnover bone disease.

Paricalcitol, an analogue of calcitriol, the metabolically active form of vitamin D (antiparathyroid agent), regulates PTH levels, improves calcium and phosphate balance, and may prevent or treat metabolic bone disease associated with CKD. Other drugs which are used to treat secondary hyperparathyroidism include calcitriol and cinacalcet.

The submission proposed that the place in therapy of paricalcitol would be in pre-dialysis patients who have been treated with calcitriol and have developed hypercalcaemia, have increasing iPTH levels or have developed an intolerance to calcitriol, and who are not sick enough to commence dialysis and hence qualify for PBS-subsidised treatment with cinacalcet.

6. Comparator

The submission nominated placebo as the main comparator, which the PBAC accepted as appropriate.

For PBAC's view, see Recommendation and Reasons

7. Clinical Trials

The basis of the re-submission was three identical design, direct randomised comparative trials (combined and reported as one) for pre-dialysis CKD comparing paricalcitol and placebo and four randomised comparative trials for end stage renal disease (ESRD) (combined and reported as one) comparing paricalcitol and placebo. The primary outcome was two consecutive decreases from baseline iPTH levels of 30% or greater. The primary and secondary outcomes were surrogate outcomes. The trials did not report final outcomes such as fractures and overall survival. Trials were of short duration with 12 to 24weeks follow up.

For PBAC's view, see Recommendation and Reasons.

The table below details the published trials presented in the submission:

Trial/First author	Protocol title / Publication title	Publication citation
Direct randomised trials		
Predialysis trials		

Trial/First author	Protocol title / Publication title	Publication citation
Coyne D et al	Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD.	Am J Kidney Dis; (2006) 47:263-276.
Abboud H et al	A comparison of dosing regimens of paricalcitol capsule for the treatment of secondary hyperparathyroidism in CKD stages 3 and 4.	Am J Nephrol,(2006); 26:105-114.
Agarwal R et al	Antiproteinuric effect of oral paricalcitol in chronic kidney disease	Kidney Int; (2005) 68:2823-2828.
ESRD trials		
Ross EA et al	Oral paricalcitol for the treatment of secondary hyperparathyroidism in patients on haemodialysis or peritoneal dialysis.	Am J Nephrol; (2007) 28:97-106.
Meta-analyses of direct randomised trials		
Palmer SC et al	Meta-analysis: Vitamin D compounds in chronic kidney disease.	Ann Intern Med, 2007; 147:840-853.
Palmer SC et al	Vitamin D compounds for people with chronic kidney disease requiring dialysis.	Cochrane Database Syst Rev, 2009, no. 4, article number: CD005633.
Palmer SC 2009b	Vitamin D compounds for people with chronic kidney disease not requiring dialysis.	Cochrane Database Syst Rev, 2009, no. 4, article number: CD008175.
Geary DF et al	Interventions for bone disease in children with chronic kidney disease.	Database of Syst Rev, 2010, no. 1, article number: CD008327.

8. Results of Trials

The re-submission presented the results of the trials as a pooled analysis rather than a meta-analysis.

The pooled results of the primary outcome of two consecutive ≥ 30% decreases from baseline in iPTH for the predialysis and ESRD trials indicated paricalcitol is highly effective at reducing levels of iPTH compared with placebo treatment.

The PBAC noted that there were similar proportions of patients experiencing adverse events in the paricalcitol and placebo arms of the trials presented by the re-submission. There were statistically significant differences in rates of fevers, urinary tract infections (higher for paricalcitol) and peripheral vascular disease (higher for placebo) between groups however these were infrequent events and unlikely to represent true systematic differences between the groups.

9. Clinical Claim

The re-submission claimed paricalcitol as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo, which based on the supporting data using levels of iPTH as the primary outcome, the PBAC considered this description was reasonable.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The economic evaluation used a Markov cohort model limited to CKD patients with secondary hyperparathyroidism (SHPT) and Stage 3 or higher disease. The model compared paricalcitol treatment with standard care in the cohort and contained ten health states.

The model cycle length was one year and patients could either remain in their current health state each year or transition to a new health state. Fracture rate was included in the model and varied between treatment groups in ESRD dialysis patients. The time horizon of the model was 10 years.

Along with the progression through the stages of CKD eventually to dialysis, the outcomes used in the economic model included:

- Fracture,
- Non-fatal cardiovascular event,
- Fatal cardiovascular event, and
- Non-cardiovascular related death.

For each of these outcomes and for each stage of CKD the model assigned a weighted relative risk to both the paricalcitol group and the placebo group. Utilities were attached to the CKD stages and a disutility was attached to patients modelled to experience a fracture. Costs were applied according to treatment and whether a non-fatal or fatal cardiovascular event or fracture was experienced.

The incremental cost effectiveness ratio cost per QALY gained was calculated to be less than $15,000.

Overall survival curves were generated by the economic evaluation in the re-submission for both treatment groups, and the difference in survival was underpinned by the assumption that lowering and controlling iPTH levels in patients would reduce the risk of death, which had not been demonstrated in the re-submission.

In a sensitivity analysis, conducted during the evaluation, the relative risk for all-cause mortality in the paricalcitol arm had been set equal to the risk in the placebo arm for Stages 3 and 4 CKD. Also, the treatment cost reductions had been removed. This resulted in an ICER of between $15,000-$45,000 per QALY and had a significant impact on the incremental health gain reducing it from 0.99 to 0.25.

Setting both the all-cause and cardiovascular mortality risks in CKD Stages 3 and 4 equal to the placebo risks and removing the cost reductions resulted in an ICER of greater than $200,000 per QALY. Other potential areas of health gain were not modelled such as a decrease in utility as CKD progresses or a decrease due to non-fatal cardiovascular events.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the re-submission to be less than 10,000 in Year 5 of listing.

The financial cost per year to the PBS was estimated by the re-submission to be less than $10 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC noted that the requested restriction is not manageable as Medicare Australia has no basis for determining when it is not appropriate to treat a patient with calcitriol.

The PBAC accepted the nominated main comparator of placebo as appropriate in patients with chronic kidney disease (CKD) who are not receiving dialysis for the proposed restriction –'…where treatment with calcitriol is not appropriate'. However, a comparison with calcitriol could still be useful given this is the therapy that could be substituted in practice and the need to support the implicit claims of improved efficacy/reduced hypercalcaemia with paricalcitol, based on the proposed PBS restriction.

The PBAC noted that the primary outcome of the trials was two consecutive decreases from baseline iPTH levels of 30% or greater. The primary and secondary outcomes are surrogate outcomes. The trials did not report demonstrate improvements in clinical outcomes such as fractures, cardiovascular events and overall survival. The trials were of short duration with 12 to 24 weeks follow up.

The PBAC noted that patients with a history of "significant sensitivity" to drugs similar to the study drug were excluded from the trials and that patients with vitamin D deficiency were not excluded from the predialysis trial. In the trials there were trends towards greater increases in calcium and phosphate concentrations in the paricalcitol treated groups, the clinical significance of this is uncertain.

The submission claims paricalcitol is superior in terms of comparative effectiveness and equivalent in terms of comparative safety over placebo. Based on the supporting data using levels of iPTH as the primary outcome, this description was considered reasonable. However, although paricalcitol is highly effective at reducing levels of iPTH, it is unclear how this translates to final outcomes such as reduction in fractures, cardiovascular events or improved survival.

The key concern arising from the premodelling studies undertaken by the re-submission is the use of the distribution of patients within iPTH bands for each stage of CKD from the pivotal trials (not an outcome of the clinical trials) in combination with a collection of cohort studies showing an association between increasing iPTH and increasing risk of event. The result of the pre-modelling study includes the strong assumption that controlling iPTH levels will result in reductions of clinically relevant outcomes such as survival. One of the retrospective cohort studies used (Smith et al., 2009a), concludes that increasing levels of iPTH were associated with a significantly elevated risk of mortality and renal replacement therapy but notes that the study provides no evidence that treating patients for higher levels of iPTH will ameliorate poor outcomes. Smith et al, 2009a further states that it is possible that elevated iPTH may simply be a marker for worsening CKD coincident with changes in iPTH.

The PBAC considered that it is unacceptable to use relative risks taken from selected observational studies (that do not demonstrate that controlling iPTH levels leads to reductions in risk of assessed events) and then apply these relative risks to changes in iPTH levels in the pivotal trial population. It is highly unlikely that the total relative risk reduction associated with differing iPTH levels is 100% attributable to changes in iPTH alone.

The PBAC recalled that the evidence presented for the cinacalcet submission also reported change in iPTH as the primary outcome; however secondary outcomes of CV events, fractures, parathyroidectomy and mortality were also reported in these 26 week trials. The recommendation for cinacalcet also included a request that the sponsor provide ongoing data from the EVOLVE trial when available as this would provide evidence of efficacy in outcomes relevant to patients.

Minimal trial evidence is presented to substantiate the clinical place in therapy or efficacy in the proposed PBS population i.e. that paricalcitol is effective in controlling iPTH and serum Ca×P product when calcitriol has failed. Further, although the submission correctly identifies hypercalcaemia as a reason for ceasing calcitriol, no evidence is provided to demonstrate that paricalcitol vs placebo does not cause hypercalcaemia in this context or evidence that paricalcitol causes fewer episodes of hypercalcaemia than calcitriol (calcitriol, however was not the comparator in this submission). The PBAC considered that if patients have persisting hypercalcaemia after dose reduction of calcitriol the effects of a vitamin D analogue are highly uncertain.

The PBAC considered that there were a number of issues of uncertainty associated with modelled economic evaluation. In particular, it was considered inappropriate to model a difference in overall survival, non-fatal cardiovascular events and fractures between paricalcitol and standard care, derived from the combination of the pivotal trial iPTH level data and the observed association between iPTH and risk of event in certain cohort studies. The Committee was of the view that the re-submission had not demonstrated a causal relationship between controlling iPTH and reducing the risk of mortality yet this factor is the key driver of the model and produces almost all of the health gain. In addition, the modelled gains in survival from paricalcitol treatment were considered to be implausibly large.

The PBAC therefore rejected the submission because of uncertain clinical benefit and uncertain cost effectiveness.

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 has no comment.