PUBLIC SUMMARY DOCUMENT

Product: Cinacalcet Hydrochloride, tablets, 30 mg, 60 mg and 90mg, Sensipar®

Sponsor: Amgen Australia Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The re-submission requested listing as a Section 100 (Highly Specialised Drugs) item for use in patients with end stage renal disease receiving dialysis who have uncontrolled secondary hyperparathyroidism (SHPT), demonstrated by an iPTH value > 53 pmol/L (>500 pg/mL).

2. Background

Cinacalcet was considered by the PBAC at its meeting in November 2005. The Committee rejected the submission because of uncertain extent of clinical benefit and the resultant uncertain, thus inadequately demonstrated, cost-effectiveness. The PBAC recognised that it was unlikely that trials would be continued for a sufficient duration to detect benefits in outcomes which were directly meaningful to the patient and thus suggested that a meeting be held with renal physicians and the sponsor to examine ways in which any relationships between changes in the surrogate measures reported and changes in patient-relevant outcomes may be quantified in a re-submission.

A post-PBAC meeting between the PBAC Chair, the Department and the sponsor with renal physicians in attendance was held on 16 December 2005 to discuss the issues raised at the November 2005 PBAC meeting.

3. Registration Status

Cinacalcet is registered by the TGA as follows:
Cinacalcet may be used to treat the biochemical manifestations of secondary hyperparathyroidism in patients with end stage renal disease, receiving dialysis.
Cinacalcet should be used as adjunctive therapy.
Cinacalcet is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma.
Cinacalcet may be used to treat the biochemical manifestations of primary hyperparathryoidism in patients for whom parathryoidectomy is not a treatment option.

4. Listing requested and PBAC's View

Section 100
Private Hospital Authority Required
Initial treatment (dose titration for up to six months) by a nephrologist of patients with end stage renal disease receiving dialysis who, despite conventional therapy, have uncontrolled secondary hyperparathyroidism, as demonstrated by an iPTH value > 53.0 pmol/L (> 500 pg/mL). Intact PTH should be monitored every four weeks (measured at least 12 hours post dose) and the dose titrated until an appropriate iPTH value is achieved.

During this titration phase, approval will be limited to provide sufficient supply for four weeks of treatment at a time, with doses between 30 mg and 180 mg/day according to the patient's response and tolerability.

Continuing treatment by a nephrologist at the effective dosage determined during the titration phase. Approval will be limited to provide sufficient quantity for one month's treatment and up to five repeats per prescription. 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.

The PBAC's view was that, although the restriction limited use of cinacalcet to patients with an intact parathyroid hormone (iPTH) level of >53 pmol/L (the "53+" subgroup), the results suggested that there was no difference between the estimates for the 53+ and the all patient groups.

5. Clinical place for the proposed therapy

Cinacalcet assists with the management of uncontrolled secondary hypoparathyroidism by reducing parathyroid levels while simultaneously lowering serum calcium and phosphorus levels in chronic kidney disease in patients receiving dialysis.

6. Comparator

The submission nominated placebo for add-on to standard care involving dietary modification, vitamin D products in association with calcium-based phosphate binders and dialysate-based interventions. This was considered appropriate.

7. Clinical Trials

The re-submission presented data collected post hoc from trial records of safety data. Four clinical events (parathyroidectomy, cardiovascular hospitalisation, fracture, and death) were pooled over five trials (the Cunningham trials). Four of these trials were the biochemical endpoint trials from the original submission and one further small trial was added. The trials published at the time of the submission were:

Trial/First author	Protocol/Publication title	Publication citation
Cunningham Trials/ Cunningham, J et al.	Effects of the calcimimetic cinacalcet HCl on cardiovascular disease, fracture, and health-related quality of life in secondary hyperparathyroidism.	Kidney International 2005; 68(4): 1793-1800
Trial 188/ Lindberg	Cinacalcet HCl, an Oral Calcimimetic agent for the Treatment of Secondary Hyperparathyroidism in Hemodialysis and Peritoneal Dialysis: A Randomized, Double-Blind, Multicenter Study.	J Am Soc Nephrol 2005; 16:800-807
Trials 172, 183, and 188/ Moe S et al.	Achieving NKF-K/DOQI bone metabolism and disease treatment goals with Cinacalcet HCl.	Kidney International 2005; 67:760-771.
Trial 141/ Malluche H et al.	Cinacalcet HCL reduced bone turnover and bone marrow fibrosis in hemodialysis patients with secondary	41st Congress. European Renal Association. European Dialysis and Transplantation Association.

Trial/First author	Protocol/Publication title	Publication citation
	hyperparathyroidism (HPT) [*abstract*]	Lisbon, Portugal, May 15-18, 2004.

In the re-submission Cox proportional hazard (CPH) analyses stratified by trial of the four events were reported in Cunningham et al. The re-submission additionally presented hazard ratios for a subgroup defined as patients with a baseline PTH of least 53 pmol/L (the "53+ subgroup") to correspond to the new requested restriction. The re-submission also provided two supportive trials, the SENSOR trial used to support an argument for less intensive dosing, and the OPTIMA trial used to help assign utilities for the economic model. The event-rate treatment effects were derived from post hoc analyses of subgroups from trials not designed with the clinical events as primary or secondary outcomes. Both factors increased uncertainty in any conclusion.

8. Results of Trials

The differences in event rates per 100 patient-years in the four events in the five trials were used in preliminary economic evaluation and the hazard ratios of the time-to-event analyses were used in the modelled economic evaluation of the re-submission.

Most outcomes reached statistical significance based on the results of the hazard ratio, but the results for the rate/100 patient years were not statistically significant. This difference might be explained by the better power of the hazard ratio when measuring survival i.e. time to an event which is a continuous outcome, whereas the rate is a dichotomous variable, or because cinacalcet does not prevent clinically important adverse outcomes, only delay them by a relatively short time frame (6 months was the time frame of the trials).

A recent meta-analysis, Stripoli et al 2006, used mortality data from 5 studies conducted over a period of 0.5 to 6 months, involving 1,285 patients. The RR for mortality was 0.75 (95% CI 0.30 to 1.88), a non-significant result. This estimate was not substantially different to the all patient analysis in this resubmission which concluded a hazard ratio for mortality of 0.81 (95% CI 0.45, 1.45).

An interaction test using the CPH model could not be done during the evaluation because individual patient data were not available. Tests of interaction using proportions of events between treatment and PTH status, <53 versus ≥ 53 pmol/L, were done during the evaluation. The p value for mortality was 0.1378. The actual distribution of events in the 53+ subgroup across trials could not be determined because the breakdown of events by trial was not provided. The analysis of safety data rather than primary endpoint data, and the use of a subgroup not included in the overall alpha calculation made it difficult to conclude a treatment benefit in mortality in the 53+ subgroup compared to the all patient analysis.

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

9. Clinical Claim

The submission described cinacalcet as having significant advantages in effectiveness in the 53+ subgroup and in the all-patient population compared to standard care and having

similar or less toxicity. The PBAC considered this conclusion was not demonstrated by the results because of uncertainty from using a post hoc analysis of safety data. A key issue was the plausibility of the submission's claim that based on trials of six months duration in patients with kidney failure and therefore at very high cardiovascular risk for an extended (pre-dialysis and dialysis) period, within 6 months of the intervention, mortality is reduced substantially by cinacalcet.

10. Economic Analysis

An updated preliminary economic evaluation was presented. The trial-based incremental cost per extra life year saved > $200,000 using the mortality difference of 0.011 calculated during the evaluation based on KM curves for all patients censored at 52 weeks.

A modelled economic evaluation was presented with a base case modelled incremental discounted cost per QALY in the range of $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was up to 1,578 in Year 4 with a financial cost per year to the PBS of up to $16,646,808 in Year 4 for the trial based dosing or up to $12,895,416 in Year 4 for the clinical practice based dosing. Costs offsets due to events averted are $2,777,852 in Year 4 in both cases.

12. Recommendations and Reasons:

The PBAC noted that the submission requested a restriction that limited use of cinacalcet to patients with an intact parathyroid hormone (iPTH) level of >53 pmol/L (the "53+" subgroup). By way of analysis of rate/100 patient years, some of the comparisons in the 53+ subgroup and the all-patient population were not statistically significant. This led to uncertainty about the interpretation of the data for the requested sub-group.

Recognising the reduced power of the chi-squared test (p for mortality was 0.1378), any differences in mortality between the subgroups could have been the result of the play of chance. There is increased uncertainty in the estimates of treatment effects because of the use the analysis of safety data rather than primary endpoint data, and the use of a subgroup not included in the overall alpha calculation make it difficult to conclude a treatment benefit in mortality in the 53+ subgroup compared to the all patient analysis. The PBAC thus considered there was uncertainty about the estimate of the hazard ratio for mortality of 0.4 (95%CI: 0.17, 0.94) in the 53+ sub-group, the main driver in the economic model.

The PBAC considered that the preliminary economic evaluation, which used clinical outcome events and cost offsets from events averted was appropriate and consistent with PBAC concerns with the original submission. However, the value of the mortality difference seen in the Kaplan Meier curves of the Cunningham trials was overestimated in the resubmission at 0.09 as compared with 0.011 calculated during the evaluation. The Pre-Sub-Committee Response acknowledged that the 0.09 presented in the submission was incorrect and by censoring the data at 52 weeks the correct estimate is 0.011. The Response then argued that an alternative approach would be to use the complete set to 65

weeks using individual patient data rather than data from Kaplan Meier curves to 52 weeks. The AUC differences between cinacalcet and placebo became 0.04 for the 53+ subgroup and 0.02 for all patients. The trial-based incremental cost/extra life year saved exceeds $1 million using the mortality difference of 0.011. The Pre-Sub-Committee Response recalculated the ratio based on 65 weeks data as being > $200,000 per LYS for severe patient subgroup and > $200,000 LYS for all patients. However, the time frames for the AUCs (out to 65 weeks) and costs out to 53.2 weeks do not coincide and as the costs were underestimated, the ratio would be biased in favour of cinacalcet**.**

The PBAC agreed that there was considerable uncertainty about the economic model. As noted above, the mortality benefit is uncertain and is the main driver of the model. Further, the submission's claim that, based on trials of six months duration in patients with kidney failure and therefore at very high cardiovascular risk for an extended (pre-dialysis and dialysis) period, within 6 months of the intervention, mortality is reduced substantially by cinacalcet, was not considered plausible.

Further, there was uncertainty involved in using the "clinical practice dosing" for cinacalcet rather than dosing based on the Cunningham trials. The Pre-Sub-Committee Response acknowledged that there is uncertainty in relation to the clinical practice dose in Australia so it proposed to address this through a risk sharing agreement. However, the PBAC was advised that it is not possible to monitor dosing under the Highly Specialised Drug Program, other than for private hospital prescriptions approved by Medicare Australia.

A number of other uncertainties about the model, about its structure (omission of a transplant health state) and inputs (cost offsets) were also noted by the ESC. However, as noted in the PES Commentary, the main drivers of economic model were the mortality estimates and doses of cinacalcet.

The PBAC therefore rejected the submission because of uncertain clinical benefit 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

Although disagreeing with the recent recommendation, the sponsor intends to work collaboratively with the PBAC to find a way to move forward with reimbursement of Cinacalcet. Please refer to Amgen Australia website <http://www.amgen.com.au/public/contact/Sensipar.jsp> for further information.