PUBLIC SUMMARY DOCUMENT
Product: CINACALCET HYDROCHLORIDE, tablets, 30 mg, 60 mg, 90 mg, Sensipar®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

This submission sought a Section 100 listing (Highly Specialised Drugs Program) for the treatment of secondary hyperparathyroidism (SHPT) in patients with end stage renal disease receiving dialysis.

Under Section 100 of the National Health Act 1953, alternative arrangements can be made for the provision of pharmaceuticals. The Highly Specialised Drugs Program allows for supply via the public and private hospital system.

2. Background

This drug has not previously been considered by the PBAC.

3. Registration Status

Sensipar is registered by the TGA for the following indication:

> Sensipar may be used to treat the biochemical manifestations of secondary hyperparathyroidism in patients with end stage renal disease receiving dialysis. Sensipar should be used as adjunctive therapy.
> Sensipar may be used to treat the biochemical manifestations of primary hyperparathyroidism in patients for whom parathyroidectomy is not a treatment option.
> Sensipar is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma.

The PBAC noted the approved Product Information included the following comments:
"Cinacalcet has not been evaluated in patients with chronic kidney disease who do not require dialysis. The pivotal clinical studies were designed to evaluate the effect of cinacalcet on biochemical parameters, including PTH (parathyroid hormone), serum calcium and phosphorus. Clinical outcomes such as quality of life, parathyroidectomy, symptomatic bone disease, hospitalisation, or mortality were not pre-specified endpoints and were not evaluated within individual studies."

4. Listing Requested and PBAC's View

<u>Section 100</u> (Highly Specialised Drugs Program)
Private Hospital Authority Required
1. Initial treatment for up to 6 months, by a nephrologist of patients with end stage renal disease receiving dialysis who, despite conventional therapy (defined as dietary modification, vitamin D products in association with phosphate binders, surgical and dialysis-based interventions) have uncontrolled secondary hyperparathyroidism,

Uncontrolled secondary hyperparathyroidism is defined as:

(a) Two consecutive intact parathyroid hormone (iPTH) values ≥ 31.8 and ≤53.0 pmol/L (≥ 300 and ≤ 500 pg/mL), taken a minimum of three months apart,

AND

(b) Two corresponding calculated calcium x phosphorus product values

≥4.5 $mmol^2/L^2$ (55 mg^2/dL^2), taken a minimum of three months apart

OR

(a) An iPTH value > 53.0 pmol/L (> 500 pg/mL)

NOTE:
Intact PTH must be monitored every 4 weeks (measured at least 12 hours post dose) and the dose titrated accordingly to achieve a target iPTH between 15.9 and 31.8 pmol/L. During this titration phase, approval will be limited to provide sufficient supply for 4 weeks of treatment at subsequent dosage levels of 30 mg, 60 mg, 90 mg, 120 mg and 180 mg. The duration of the titration phase should be no longer than 6 months.

Continuing treatment by a nephrologist of patients who have previously been issued an Authority prescription for this drug.

NOTE:
Approval will be limited to provide sufficient supply for up to 6 months treatment per prescription. Intact PTH should be monitored quarterly (measured at least 12 hours post dose) and the dose adjusted as necessary to maintain iPTH between 3 to 5 times the upper limit of normal.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Cinacalcet modulates the activity of the calcium-sensing receptor (CaR), the primary regulator of PTH secretion, and is used to reduce both PTH and Ca x P (serum calcium x phosphorus product).

6. Comparator

The submission nominated placebo for add-on to standard medical management involving dietary modification, vitamin D products in association with calcium-based phosphate binders and dialysate-based interventions as the appropriate comparator.

The PBAC accepted the comparator was appropriate**.**

7. Clinical Trials

The submission presented three pivotal, Phase 3 multicentre, placebo-controlled trials of cinacalcet for the treatment of secondary hyperparathyroidism in patients with end stage renal disease receiving haemodialysis or peritoneal dialysis. Additionally, 12-month safety and efficacy data are available from a Phase 3, placebo-controlled, double-blind extension study for patients completing two of these three studies.

The list of trials forming the basis of the submission is shown below:

Trial/First author	Protocol title	Publication citation
Trials 172 and 183/ Block et al.	Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis.	N Engl J Med 2004;350:1516-25.
Trial 188/ Lindberg et al.	Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary	J Am Soc Nephrol 2005;16:800-7.

Trial/First author	Protocol title	Publication citation
	hyperparathyroidism in hemodialysis and peritoneal dialysis: A randomised, double-blind, multicenter study.	
Trial 240/ Sprague et al.	Long-term treatment of secondary hyperparathyroidism (HPT) with cinacalcet HCl (Sensipar) in patients receiving dialysis.	ASN 2004, abstract F-PO964.
Trial 141/ Malluche et al	Cinacalcet HCL reduces bone turnover and bone marrow fibrosis in hemodialysis patients with secondary hyperparathyroidism (HPT).	Cinacalcet EDT-ERA XLI Congress; Abstract Blood:218b, Abstract MO16. The submission only provided information in one abstract (3) for this trial.

8. Results of Trials

The results of the key trials are summarised in the table below:

Proportion of patients attaining iPTH (intact parathyroid hormone) level of ≤26.5 pmol/L

Trial	Cinacalcet	Placebo	p-value*	ARD (95% CI)	NNT (95% CI)
Trial 172	84/205 (41%)	8/205 (4%)	<0.001	0.37 (0.30, 0.44)	3 (2.3, 3.3)
Trial 183	76/166 (46%)	11/165 (7%)	<0.001	0.39 (0.31, 0.48)	3 (2.1, 3.2)
Trial 188	104/292 (35%)	6/101 (6%)	<0.001	0.29 (0.22, 0.37)	3 (2.7, 4.5)
Lumped	264/663 (40%)	25/471 (5%)	<0.001	0.35 (0.30, 0.39)	3 (2.6, 3.3)
Pooled	-	-	<0.001	0.356 (0.311, 0.400)	3 (2.5, 3.2)

* Cochran-Mantel-Haenszel test

The submission used the term "pooled" for the combined analysis, but the presented analysis was, in fact, a "lumped" analysis. A formal meta-analysis of the data (by fixed effects) was presented in the last row of the table above ($p<0.001$), with a test for heterogeneity Q of 3.327 ($p=0.189$). The results demonstrated a statistically significant difference between cinacalcet and placebo for the primary outcome (intact parathyroid hormone levels). Differences of similar statistical significance were found for two secondary biochemical outcomes, percent change in Ca×PO4 product and proportion of patients with iPTH reduction of ≥30%.

The third secondary outcome, kidney-specific quality of life (% change in KDQOL (Kidney Disease Quality of Life) cognitive functioning score), did not show a statistically significant difference.

With respect to toxicity, compared to placebo, cinacalcet showed a greater incidence of nausea and vomiting, which could be treatment-limiting, but a lesser incidence of hypotension, and a greater incidence of hypocalcemia.

For PBAC's view on the trial results, see Recommendation and Reasons.

9. Clinical Claim

The submission described cinacalcet as having significant advantages in effectiveness over placebo and having similar toxicity.

The PBAC accepted that the results demonstrated a statistically significant difference between cinacalcet and placebo for the primary outcome of intact parathyroid hormone levels.

See Recommendations and Reasons for the PBAC's view.

10. Economic Analysis

A preliminary trial-based economic evaluation adopting a cost-effectiveness approach was presented. The economic analyses were done with the targets recommended by the (American) National Kidney Foundation (1) in 2003 and used in the requested restriction sub-groups. These targets are iPTH ≤31.8 pmol/L, Ca×PO4 <4.5 $mmol^2/L^2$, phosphorus of 1.1-1.8 mmol/L, and calcium of 2.1-2.4 mmol/L.

The resources included were drug costs, monitoring costs and hospitalisation costs. The overall comparative costs and outcomes for each alternative and the incremental costs and outcomes were summarised separately for patients in the two sub-groups requested in the restriction and for the primary and secondary outcomes.

The trial-based incremental cost/extra patient achieving iPTH ≤31.8 pmol/L and other biochemical outcomes were separated into the two patient sub-groups specified in the requested restriction:

- Subgroup 1: baseline iPTH ≥31.8, but ≤53.0 pmol/L and baseline Ca×PO4 ≥4.5 mmol/L;
- Subgroup 2: baseline iPTH >53 pmol/L.

In Subgroup 1, the base case incremental cost-effectiveness ratio (ICER) was <$15,000, and in Subgroup 2 the base case ratio was between $15,000 and $45,000.

A modelled economic evaluation was not presented. The PBAC considered a cost effectiveness approach was valid.

For PBAC's view's, see Recommendations and Reasons for the PBAC's view.

11. Estimated PBS Usage and Financial Implications

The submission claimed that the likely number of patients/year would be up to 2,000 in Year 4 of listing.

The submission estimated the financial cost/year to the PBS would be between $10 million to $25 million in Year 4 of listing.

12. Recommendation and Reasons

The PBAC accepted that the comparator, placebo for add-on to standard medical management involving dietary modification, vitamin D products in association with calcium-based phosphate binders and dialysate-based interventions, was appropriate. It was noted that surgery and more intense (double quotidian) dialysis might be attempted, but only in a minority of eligible patients.

The PBAC noted that the submission was based on three almost identical, randomised, placebo-controlled, 24-week trials comparing cinacalcet with titration targeting the lowering of intact parathyroid hormone (iPTH) in dialysis patients with secondary

hyperparathyroidism. The Committee accepted that the duration of the trials was a likely source of being under-powered to detect patient-relevant outcomes directly. It was also accepted that the results demonstrated a statistically significant difference between cinacalcet and placebo for the primary outcome of the proportion of patients attaining an iPTH level of less than or equal to 26.5 pmol/L. The PBAC noted that the Pre-Sub-Committee Response also emphasised a tertiary outcome in the form of the SF-36, which showed two of eight domains (bodily pain and general health perception) and one of the two summary scores (physical component) being statistically significantly different. However, overall, there was no convincing evidence of a quality of life improvement demonstrated by the trials.

Noting a presentation during the sponsor's hearing, the PBAC agreed that it was plausible that there was a relationship between the surrogate measures reported and benefits in outcomes which are directly meaningful to the patient, although the nature of such a relationship was not presented in quantified manner. However, further to this and more importantly, the submission gave no basis to establish a quantitative or qualitative relationship between any changes in PTH levels or other biochemical markers reported for cinacalcet or any other intervention and any changes in ANY measure of clinically manifest disease. Thus, there was uncertainty over the extent to which cinacalcet-associated changes in the reported biochemical surrogate outcomes would translate into changes in outcomes such as bone fractures, cardiovascular events, quality of life, parathyroidectomies averted and mortality. The PBAC noted that surrogate outcomes which are arguably closer to these outcomes are not inclusive. In particular, preliminary bone turnover data were not conclusive. Although an excess of PTH causes bone disease, there was no evidence presented in the submission or during the hearing that lowering PTH reduced the rate of disease progression, let alone improved bone disease. The PBAC noted the impact of cinacalcet on the risk of adynamic bone disease has not been conclusively determined and considered there was a theoretical concern about reduced mineralisation increasing the risk of fracture. There were also no data on calcium deposition in the myocardium.

The PBAC noted that the TGA-approved Product Information also contained statements about the lack of demonstrated benefits in terms of impact on bone disease and quality of life.

The uncertainty in the cost-effectiveness analysis stemmed largely from the clinical uncertainty regarding the use of biochemical rather than directly patient-relevant outcomes. In the absence of quantified improvements in patient-relevant outcomes, the PBAC considered that it was difficult to judge the value of potential improvements in order for them to judge whether the clear incremental costs were justified. The PBAC noted that an economic model would have been helpful in making such judgements.

The PBAC thus 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 are 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.

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 intends to work collaboratively with clinicians and the PBAC to find a way to move forward with reimbursement of cinacalcet.