PUBLIC SUMMARY DOCUMENT
Product: Cinacalcet hydrochloride, tablets, 30 mg, 60 mg and 90mg, Sensipar®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought listing as a Section 100 (Highly Specialised Drugs) Private hospital authority required item for use in patients with end stage renal disease receiving dialysis who have uncontrolled secondary hyperparathyroidism (SHPT).

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

Submissions seeking a PBS listing of cinacalcet for the treatment of secondary hyperparathyroidism in patients with end stage renal disease receiving dialysis were rejected at the November 2005 PBAC meeting and again at the July 2006 PBAC meeting because of uncertain extent of clinical benefit and the resultant uncertain, thus inadequately demonstrated, cost-effectiveness. *(See also Public Summary Documents for November 2005 and July 2006)*.

3. Registration Status

Cinacalcet was TGA registered on 25 January 2005 for the following indications:

- 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

1. Initial treatment for up to 6 months, by a nephrologist for patients with CKD-5D who have sustained secondary hyperparathyroidism with iPTH ≥50 pmol/L, not responding to conventional therapy.

Continuation criteria: a decrease of ≥30% in iPTH concentrations after 6 months treatment.

2. Initial treatment for up to 6 months, by a nephrologist for patients with CKD-5D who have sustained secondary hyperparathyroidism with iPTH >15 pmol/L and <50 pmol/L AND an (adjusted) serum calcium concentration ≥2.6 mmol/L, not responding to conventional treatment.

Continuation criteria: an iPTH level >15 pmol/L and an (adjusted) serum calcium concentration <2.6 mmol/L after six months treatment.

Note: Intact PTH should be monitored four weekly (measured ≥12 hours post dose) and dose titrated until an appropriate iPTH concentration is achieved. During the titration phase, approval will be limited to sufficient supply for four weeks treatment at a time, with doses between 30 and 180 mg/day according to the patient's response and tolerability.

Note: Approval will be limited to provide sufficient quantity for 4 weeks treatment and up to 5 repeats for doses between 30 and 180 mg/day according to the patient's response and tolerability. Intact PTH should be monitored quarterly (measured ≥12 hours post dose) and dose adjusted as necessary to maintain an appropriate iPTH concentration.

Sustained = at least 2 blood samples collected over a period of 2-4 months.

Grandfathering:
Continuing treatment by a nephrologist for patients with CKD-5D, with a prior diagnosis of secondary hyperparathyroidism who were receiving treatment with cinacalcet prior to [insert effective PBS listing date], who met the initial treatment criteria defined as an iPTH concentration ≥50 pmol/L OR an iPTH concentration >15 pmol/L and <50 pmol/L AND an (adjusted) serum calcium concentration ≥2.6 mmol/L AND who meet the continuation criteria.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Cinacalcet would assist with the management of uncontrolled secondary hyperparathyroidism 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 plus standard medical management as the main comparator. This was previously accepted by the PBAC.

Standard medical management includes dietary modification, vitamin D products in association with calcium based phosphate binders and dialysate-based interventions.

7. Clinical Trials

The pivotal trials included in the submission were Study 172, 188, 183, 240, (blinded extension of studies 172 and 183) and 141. The supportive evidence included were Study 187 and Study 130, which had not previously been submitted. Study 130 was an open-label, single-arm, multi-centre trial that investigated long term safety and efficacy of cinacalcet.

The object of the trials was to assess the effects of cinacalcet on biochemical parameters (i.e. intact Parathyroid hormone, calcium and phosphate levels).

The direct randomised trials published at the time of submission were as follows:

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

172	A phase 3 study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of end stage renal disease treated with hemodialysis, 08 August 2003	Kidney International 2005, 68(4):1793-1800
183	A phase 3 study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of end stage renal disease treated with hemodialysis, 15 August 2003	Kidney International 2005, 68(4):1793-1800
188	A placebo-controlled, double-blind, multicenter study to assess the efficacy and safety of an oral calcimimetic agent (AMG 073) in secondary hyperparathyroidism of chronic kidney disease (hemodialysis and peritoneal dialysis), 12 August 2003 Lindberg. Cinacalcet HCl, an Oral Calcimimetic agent for the Treatment of Secondary Hyperparathyroidism in Hemodialysis and Peritoneal Dialysis: A Randomized, Double-Blind, Multicenter Study.	Kidney International 2005, 68(4):1793-1800 J Am Soc Nephrol 2005; 16:800-807
141 Malluche H	Cinacalcet HCL reduced bone turnover and bone marrow fibrosis in hemodialysis patients with secondary hyperparathyroidism (HPT) [*abstract*]	41st Congress. European Renal Association. European Dialysis and Transplantation Association. Lisbon, Portugal, May 15-18, 2004.
Supplementary randomised trial		
OPTIMA	OPTIMA: An open-label, randomised study using cinacalcet to improve achievement of K/DOQI targets in patients with ESRD	East and North Hertfordshire NHS Trust
Meta-analyses of direct randomised trials		
Cunningham trials (Trials 172, 183, 188, 240, &141)	Danese, Olson, 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

8. Results of Trials

The results of the primary outcome analyses are reproduced in the table below.

Comparative summary of results of direct randomised trials: Proportion of patients attaining PTH level of ≤26.5pmol/L

Trial	Duration	Cinacalcet	Placebo	p-value*	ARD (95% CI)	NNT (95% CI)
Trial 172	26 wks	84/205 (41%)	8/205 (4%)	<0.001	0.37 (0.30, 0.44)	3 (2.3, 3.3)
Trial 183	26 wks	76/166 (46%)	11/165 (7%)	<0.001	0.39 (0.31, 0.48)	3 (2.1, 3.2)
Trial 188	26 wks	104/292 (35%)	6/101 (6%)	<0.001	0.29 (0.22, 0.37)	3 (2.7, 4.5)

Trial	Duration	Cinacalcet	Placebo	p-value*	ARD (95% CI)	NNT (95% CI)
Lumped analysis		264/663 (40%)	25/471 (5%)	<0.001	0.35 (0.30, 0.39)	3 (2.6, 3.3)
Pooled analysis				*<0.001*	*0.36 (0.31, 0.40)*	*3 (2.5, 3.2)*

* Cochran-Mantel-Haenszel test

The events used in the July 2006 submission and the current submission are the safety data on deaths, cardiovascular hospitalisations, fractures, and parathyroidectomy surgery from Trials 172, 183, and 188 plus the extension trial (Trial 240) and a small bone study (Trial 141).

Results of patient-relevant events, 95% confidence intervals, and heterogeneity tests (I^2) in meta-analyses of direct randomised trials are as follows:

Event	Risk difference (95% CI) Dichotomous variables Current submission Random effects model	Hazard ratio* (95% CI) Dichotomous variables Current submission Random effects model	Hazard ratio (95% CI) Time-to-event variables July 2006 submission Fixed effect model (assumes no heterogeneity)
Death	-0.01 (-0.03, 0.01) p=0.33 I^2 = 0%	0.76 (0.43, 1.34) p=0.34 I^2 = 0%	0.81 (0.45, 1.45) p=0.47
Cardiovascular hospitalization	-0.03 (-0.07, 0.00) p=0.07 I^2 = 0%	0.58 (0.37, 0.93) p=0.02 I^2 = 51.7%	0.61 (0.43, 0.86) p=0.005
Fractures	-0.02 (-0.04, 0.00) p=0.07 I^2 = 0%	0.45 (0.21, 0.96) p=0.04 I^2 = 10.9%	0.46 (0.22, 0.95) p=0.04
Parathyroidect-omy surgery	-0.02 (-0.04, -0.01) p=0.003 I^2 = 0%	0.15 (0.03, 0.62) p=0.009 I^2 = 0%	0.07 (0.01, 0.55) p=0.009

* Although the submission calls these hazard ratios, technically they are relative risks.

For PBAC's view of these results, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed that cinacalcet had advantages in effectiveness over placebo add-on to standard care and the toxicity data showed more nausea and vomiting compared to placebo.

For PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented an updated preliminary trial-based economic evaluation. The trial-based incremental cost per extra life year gained was estimated to be greater than $200,000.

The submission presented an updated modelled economic evaluation. The PBAC noted that the cost offsets in the modelled evaluation had been significantly reduced compared to the prior submission and that a price reduction attempted to address the uncertainty in the clinically relevant outcomes.

The base case modelled incremental discounted cost per extra discounted quality adjusted life year was estimated by the submission to be in the range $15,000 to $45,000 for the clinical practice based dose (ADD=62mg).

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 5,000 in Year 5. The financial cost per year to the PBS was estimated to be in the range $10 million to $30 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of cinacalcet on the PBS for the treatment for up to 6 months, by a nephrologist, for a patient with chronic kidney disease on dialysis (CKD-5D) who have sustained secondary hyperparathyroidism with iPTH ≥50 pmol/L, not responding to conventional therapy on the basis of acceptable cost-effectiveness compared with placebo.

The PBAC agreed that cinacalcet should also be listed in section 85 for maintenance treatment as suggested by the Australian and New Zealand Society of Nephrology, to enable patients in rural areas easier access to continuing treatment. The PBAC considered that the requested restriction was tight and clinically manageable.

The PBAC noted new toxicity data on case reports of hypotension and worsening heart failure including two cases with a positive re-challenge. The PBAC considered that the risk/benefit profile of cinacalcet may develop further as its exposure increases.

The PBAC expressed some concern regarding the extrapolation of significant changes in surrogate endpoints to patient relevant outcomes, but considered that the data supported changes in iPTH (with subsequent reduction in parathyroidectomies) and reductions in cardiovascular related hospitalisations and fractures. The PBAC noted that the cost offsets in the modelled evaluation had been significantly reduced compared to the prior submission and that a price reduction attempted to address the uncertainty in the clinically relevant outcomes.

The PBAC considered that there was uncertainty in all three dosing assumptions used in the modelled economic analysis but noted that this was addressed through the proposed risk sharing arrangement.

The PBAC requested the sponsor provide ongoing data from the EVOLVE trial when available as this would provide evidence of efficacy in outcomes relevant to patients. The commitment to provide the PBAC with ongoing data on the efficacy and cost-effectiveness of cinacalcet, taking into account any changes in the treatment algorithm occurring over time, should also be incorporated into the risk sharing agreement.

Recommendation

Restriction: Authority required
Maintenance therapy, following initiation and stabilisation of treatment with cinacalcet, of a patient with chronic kidney disease on dialysis who has after 6 months treatment:

(i) a decrease of at least 30% in iPTH concentrations; or
(ii) iPTH greater than 15 pmol/L and an (adjusted) serum calcium concentration of less than 2.6 mmol/L.

Note: During the titration phase, intact PTH should be monitored four weekly (measured at least 12 hours post dose) and dose titrated until an appropriate iPTH concentration is achieved. During the titration phase, approval will be limited to sufficient supply for four weeks treatment at a time, with doses between 30 and 180 mg per day according to the patient's response and tolerability.

Note: During the maintenance phase, approval will be limited to provide sufficient quantity for 4 weeks treatment up to a maximum of 6 months supply for doses between 30 and 180 mg per day according to the patient's response and tolerability. Intact PTH should be monitored quarterly (measured at least 12 hours post dose) and dose adjusted as necessary to maintain an appropriate iPTH concentration.

Maximum quantity: 28 (30mg, 60 mg and 90mg)
No of repeats: 5

Restriction: **Section 100 (Highly Specialised Drug)**
Private Hospital Authority Required
Management, including initiation and stabilisation, by a nephrologist, of a patient with chronic kidney disease on dialysis who has sustained secondary hyperparathyroidism with iPTH of at least 50 pmol/L, not responding to conventional therapy.

Note: During the titration phase, intact PTH should be monitored four weekly (measured at least 12 hours post dose) and dose titrated until an appropriate iPTH concentration is achieved. During the titration phase, approval will be limited to sufficient supply for four weeks treatment at a time, with doses between 30 and 180 mg per day according to the patient's response and tolerability.

Note: During the maintenance phase, approval will be limited to provide sufficient quantity for 4 weeks treatment up to a maximum of 6 months supply for doses between 30 and 180 mg per day according to the patient's response and tolerability. Intact PTH should be monitored quarterly (measured at least 12 hours post dose) and dose adjusted as necessary to maintain an appropriate iPTH concentration.

"Sustained" means the abnormality was detected on at least 2 blood samples collected over a period of 2 to 4 months.

Pack size: 28 (30mg, 60 mg and 90mg)

Private Hospital Authority Required

Management, including initiation and stabilisation, by a nephrologist, of a patient with chronic kidney disease on dialysis who has sustained secondary hyperparathyroidism with iPTH of at least 15 pmol/L and less than 50 pmol/L AND an (adjusted) serum calcium concentration at least 2.6 mmol/L, not responding to conventional treatment.

Note: During the titration phase, intact PTH should be monitored four weekly (measured at least 12 hours post dose) and dose titrated until an appropriate iPTH concentration is achieved. During the titration phase, approval will be limited to sufficient supply for four weeks treatment at a time, with doses between 30 and 180 mg per day according to the patient's response and tolerability.

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"Sustained" means the abnormality was detected on at least 2 blood samples collected over a period of 2to 4 months.

Pack size: 28 (30mg, 60 mg and 90mg)

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

Amgen is pleased that cinacalcet will be made available through the PBS to Australian dialysis patients with secondary hyperparathyroidism.