PUBLIC SUMMARY DOCUMENT

Product: Cinacalcet, tablets, 30 mg, 60 mg and 90 mg, Sensipar®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The purpose of the submission was to address the requirements of the risk share agreement for cinacalcet, to provide the results of the EVOLVE trial and consider the impact of the results on the cost-effectiveness of cinacalcet and to update the clinical management algorithm based on Australian clinical practice.

2. Background

At the November 2007 meeting, the PBAC recommended the listing of cinacalcet based on a meta-analysis of five biomarker randomised controlled trials (RCTs) which suggested that treatment with cinacalcet was associated with changes in intact-parathyroid hormone (iPTH) levels and subsequent reductions in parathyroidectomies, cardiovascular-related hospitalisations and fractures compared to placebo.

The patient-relevant outcomes were reported as secondary/safety outcomes from the trials and thus were considered limited by not being primary outcomes of the trials, by lack of statistical significance in the mortality estimate, and by use of random effects meta-analysis with few trials and the presence of heterogeneity in the meta-analyses of cardiovascular hospitalisations and fractures.

PBS listing occurred on 1 July 2008. The risk-sharing arrangement required that the company provide all ongoing data to the Commonwealth on the efficacy and cost-effectiveness of the drug, taking into account any changes in the cost-effectiveness ratio of the drug that formed the basis of the PBAC recommendation, including details of changes in the treatment algorithm occurring in Australian clinical practice; and that the data to be submitted by the company includes data from the EVOLVE trial.

The November 2007 Public Summary Document is available on the PBS website.

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

The submission did not request any changes to the current PBS listing or the price.

5. Clinical Place for the Proposed Therapy

Secondary hyperparathyroidism is one of the principle manifestations of chronic kidney disease. It is a metabolic condition that is characterised by the excessive secretion of parathyroid hormone by the parathyroid glands in an attempt to regulate calcium and phosphate levels as the kidney fails. Secondary hyperparathyroidism is associated with an increase in cardiovascular events, pathological fractures and overall mortality in patients with chronic kidney disease.

6. Comparator

The comparator in the submission was placebo plus standard medical management. This was consistent with the comparison upon which listing was recommended at the November 2007 meeting.

7. Clinical Trials

The EVOLVE trial was an international, randomised, double-blind trial comparing the effects of cinacalcet and placebo on mortality and cardiovascular morbidity in dialysis patients with secondary hyperparathyroidism (n=3,883). Publication details of the EVOLVE trial are presented in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
20050182 (EVOLVE)	Amgen (2013). Evaluation of cinacalcet HCl therapy to lower cardiovascular events	Internal study report
	Chertow et al (2012). Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis	New England Journal of Medicine 367: 2482-2494
	Chertow et al (2012). Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial	Nephrology, Dialysis, Transplantation 27: 2872-2879
	Chertow et al (2007). Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview	Clinical Journal of the American Society of Nephrology 2: 898-905

8. Results of Trials

With respect to comparative effectiveness, the EVOLVE trial did not demonstrate a statistically significant difference in the primary outcome (time to death or non-fatal cardiovascular event) between cinacalcet and placebo (48.2% in the cinacalcet group and 49.2% in the placebo group; HR = 0.93 (95%CI, 0.85, 1.02).

Comparison of key outcomes between November 2007 and current submissions

Outcome	Nov 2007 submission RR (95% CI)	EVOLVE ITT RR (95% CI) (n=3883)	EVOLVE multivariate HR (95% CI) [used in economic model]
Death	0.76 (0.43, 1.34)	0.97 (0.90, 1.06)	0.85 (0.75, 0.95)
CV hospitalisation[a]	0.58 (0.37, 0.93)	NR	0.85 (0.73, 0.98)
Fracture	0.45 (0.21, 0.96)	0.93 (0.79, 1.09)	0.89 (0.72, 1.09)
Parathyroidectomy	0.15 (0.03, 0.42)	0.50 (0.41, 0.61)	0.40 (0.31, 0.50)
Average daily dose	62mg	66.8mg	39.62mg (adjusted)
Quality of life data	0.033 utility gain based on one biomarker RCT comparing cinacalcet with placebo (OPTIMA trial)	EQ-5D – no difference from placebo	0.02 (0.01-0.03) gain from Briggs et al (2013) in the pre-sub-committee response
ICER per QALY gained	$15,000 - $45,000		Base case $15,000 – $45,000 Revised with Briggs et al 2013 utilities $45,000 – $75,000

CV, cardiovascular; HR, hazard ratio, NR, not reported; RR, relative risk

[a] It is unclear whether the previous November 2007 definition of CV hospitalisation include stroke. The estimates of CV hospitalisation from the EVOLVE trial specifically exclude stroke

The PBAC noted the sponsor's arguments in the submission and the Pre-submission Committee Response that study design limitations biased the estimate of treatment effect toward the null. The sponsor singled out a 1-year difference in the mean/median age between treatment groups, difference in discontinuations rates of 71% in the placebo arm compared to 67% in the cinacalcet arm, and that 23% of patients in the placebo arm commenced commercially available cinacalcet before the occurrence of a primary event compared to 11% in the cinacalcet arm.

The PBAC agreed with the advice of the Economics Sub-Committee (ESC) that attributing the negative result for a pre-specified primary composite endpoint to baseline "imbalances" is not reasonable. In particular, a one-year difference in average age across the two arms is a very small difference. The PBAC considered that the EVOLVE trial suggested that age may be a treatment-effect modifier and not a confounder.

With respect to comparative harms cinacalcet treatment was associated with a higher incidence of adverse events and treatment-related events compared to placebo. The difference in treatment arms was primarily driven by the increased incidence of nausea, vomiting, hypocalcaemia and nervous system disorders with cinacalcet treatment.

The PBAC noted that new warnings regarding seizures, QT prolongation and ventricular arrhythmia secondary to hypocalcaemia as well as neoplasms were recently added to the cinacalcet product information. The Committee also noted that the submission stated that the cinacalcet paediatric trial program had been placed on hold due to safety reasons (fatal case of hypocalcaemia).

Benefit/harms summary (cinacalcet vs. placebo)

Outcome	Number of participants (studies)	Relative effect from trials[a]	Control event rate per 100 patients	Intervention event rate per 100 patients	Increment
Benefits					
Death or non-fatal cardiovascular event[b]	3883 (1)	HR 0.93 (0.85, 1.02)	49 (5 years)	48 (5 years)	-
Bone fracture	3883 (1)	HR 0.89 (0.75, 1.07)	13 (5 years)	12 (5 years)	-
Parathyroidectomy	3883 (1)	HR 0.44 (0.36, 0.54)	14 (5 years)	7 (5 years)	-7 (5 years)
Harms					
Nausea	3861 (1)	NR	16 (5 years)	29 (5 years)	-
Vomiting	3861 (1)	NR	14 (5 years)	26 (5 years)	-
Hypocalceamia	3861 (1)	NR	2 (5 years)	12 (5 years)	-

HR, hazard ratio; NR, not reported
Note: Rounded to nearest whole patient
[a] ITT analysis
[b] primary outcome

9. Clinical Claim

The submission stated that the EVOLVE trial results were consistent with the clinical claims made in the previous November 2007 submission. The submission described cinacalcet as superior in terms of efficacy and inferior in terms of safety compared to placebo (standard medical management).

The PBAC disagreed with these claims on the grounds that the EVOLVE trial did not demonstrate a statistically significant difference over placebo in the primary outcome, and there was a higher incidence of adverse events with cinacalcet. The PBAC considered that the only benefit that was consistently observed with cinacalcet treatment was a reduction in parathyroidectomy.

10. Economic Analysis

The submission presented a modelled cost-effectiveness analysis of cinacalcet compared to placebo. The submission modelled improvements in mortality, cardiovascular hospitalisations, fractures and parathyroidectomies with cinacalcet treatment. The PBAC considered that with the exception of parathyroidectomies, these modelled effects are inadequately supported by data from the EVOLVE trial.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission did not present any analyses about the utilisation/financial implications associated with the continued listing of cinacalcet on the PBS.

12. Recommendation and Reasons

The PBAC accepted the advice of the ESC that the most reliable clinical evidence on which an economic analysis of cinacalcet should be based would incorporate a treatment benefit for parathyroidectomy only, a dose which more accurately reflects the unadjusted dose of the EVOLVE clinical trial (66.8mg) and what would be used in clinical practice, and using the revised utilities from Briggs et al.

The incremental cost-effectiveness analysis associated with the above inputs would be greater than $200,000 per quality-adjusted life-year (QALY) gained. Alternative dose regimens of 52.1mg (based on the Adelaide utilisation data) or 62.1mg (based on data from Tasmania) would result in lower ratios although still greater than $200,000 per QALY gained, in each case. All ICER figures far exceeded the original ratio of between $15,000 and $45,000 per QALY gained that enabled the PBAC to recommend the PBS listing of cinacalcet in 2007.

Although age appears to be a treatment-effect modifier, the PBAC considered the sponsor's arguments in the pre-PBAC response and agreed that a future PBS restriction for patients older than 65 years would not be feasible.

Therefore, the PBAC made a new recommendation for cinacalcet which varies its initial recommendation of November 2007 as follows: the PBAC considered that based on the new evidence from the EVOLVE trial, at the current price cinacalcet is not cost-effective. The PBAC considered that a significant price reduction would be needed to restore the cost-effectiveness of cinacalcet to the level considered to be acceptable in 2007.

In making that recommendation the PBAC also considered matters raised by the sponsor in its responses to the evaluation prior to the PBAC meeting.

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 believes that cinacalcet has a role in the management of Australian patients with chronic kidney disease and disagrees with the PBAC's view that the only benefit that was consistently observed with cinacalcet treatment in EVOLVE was a reduction in parathyroidectomy.