

PUBLIC SUMMARY DOCUMENT

Product: CINACALCET, tablets, 30 mg, 60 mg and 90 mg, Sensipar[®]

Sponsor: Amgen Australia Pty Ltd

Date of PBAC Consideration: March 2014

1. Purpose of Application

To consider the response from the sponsor in relation to the PBAC's November 2013 recommendation for cinacalcet, which varied its initial recommendation of November 2007 (see Background)

To provide advice to the Minister under s101(4AAB) of the *National Health Act 1953* (Act) in relation to the possible revocation of the declaration that cinacalcet is a drug to which Part VII of the Act applies in the event the sponsor and the Commonwealth cannot reach agreement on price.

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 agreed between the sponsor and the Commonwealth required that the sponsor 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 sponsor included data from the EVOLVE trial.

The PBAC considered the data from the EVOLVE trial at its November 2013 meeting. The PBAC considered 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 ratio (ICER) 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 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 exceed 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 that a future PBS restriction for patients older than 65 years would not be feasible.

Therefore, at its November 2013 meeting, the PBAC made a new recommendation for cinacalcet, which varied its initial recommendation of November 2007 as follows: the PBAC considers 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.

The November 2013 Public Summary Document is available on the [PBS website](#).

3. Listing Requested

The submission proposed the following change to the current initial restriction criteria marked in *italics* and strikethrough:

Section 100 Highly Specialised Drugs Program

Private Hospital Authority required

Public Hospital Authority required (STREAMLINED)

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~~ 63 pmol per L, not responding to conventional therapy.

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 per L and less than ~~50~~ 63 pmol per L AND an (unadjusted) serum calcium concentration at least 2.6mmol per L, not responding to conventional treatment.

The submission did not request a change to the continuing/maintenance restriction criteria.

4. PBAC Discussion

The PBAC considered the sponsor's submission of 4 March 2014. The submission offered a revised price for cinacalcet and proposed updating the eligibility criteria for treatment with PBS-subsidised cinacalcet, in line with the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines.

The sponsor's submission proposed a significant price reduction for patients aged less than 65 years, with the current price to be maintained for patients aged 65 years and over. The submission claimed that this reflected "...the greater benefit observed in EVOLVE patients aged 65 years and over, and the associated positive impact on cost-effectiveness..." The submission proposed that among the eligible population, the split of patients aged less than

65 years and aged 65 years and over was 50:50. The PBAC considered that the latter assumption was reasonable.

The PBAC reaffirmed that it did not consider that a PBS restriction based on a patient age above and below 65 years would be feasible in practice. The PBAC again agreed that age was apparently a treatment effect modifier. However, the PBAC did not consider it was plausible that a patient would derive such a marked variation in clinical benefit as proposed in the submission, only on the basis of being aged under or over 65 years. The PBAC reaffirmed its view of the evidence from the EVOLVE trial that the magnitude of the treatment benefit in all patients, including those patients over 65 years is less than predicted in 2007 as shown in the table below.

Comparison of clinical outcomes between November 2007 submission and the EVOLVE trial

Outcome	Nov 2007 submission RR (95% CI)	EVOLVE ITT RR (95% CI)	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)

Abbreviations: 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 that, even were it to accept that age is a treatment effect modifier to the extent proposed in the submission, the resulting ICERs were both between \$45,000 and \$75,000 per QALY gained in patients aged less than 65 years (including the proposed price reduction for that population), and for patients aged 65 years and over. The PBAC noted that these ICERs remain higher than the original ICER of between \$15,000 and \$45,000, which formed the basis for the PBAC’s listing recommendation in 2007.

The PBAC advised that it would remain open to the sponsor to make a future submission to demonstrate that cinacalcet is cost-effective, including by targeting further a listing for the patient group that is most likely to benefit from treatment with cinacalcet. However, the mere potential for such a submission to be made in the future, would not justify the government continuing to pay a higher subsidy in the meantime.

The PBAC therefore rejected the sponsor’s proposal, considering that the price reduction offered was not sufficient to restore the cost-effectiveness of cinacalcet. The PBAC reaffirmed its advice of November 2013 that, at its current price, cinacalcet is not cost effective. The PBAC recognised that the Minister may choose to delist cinacalcet from the PBS in the event the sponsor and the Commonwealth cannot reach agreement on price. The PBAC considered that there were no reasons why the Minister should not delist cinacalcet by revoking the declaration that cinacalcet is a drug to which Part VII of the Act applies.

The PBAC considered that the Minister should take into account the potential for Quality Use of Medicine and safety issues to arise from any delisting of cinacalcet from the PBS and recommended that a minimum of three, and up to six-months, notice be given, with a comprehensive communication and education plan, involving the National Prescribing Service, prescriber and consumer groups. The key message should include the reasons for the change in PBS availability. The PBAC considered that, in line with best clinical practice,

if treatment is to be withdrawn this should be under close medical supervision to mitigate against abrupt cessation of treatment and recommended that the sponsor should ensure that no patients are inappropriately withdrawn from treatment.

5. 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.

6. Sponsor's Comment

While the sponsor understands the basis for the PBAC's view, the sponsor respectfully disagrees with the PBAC's assessment of the Evaluation of Cinacalcet HCl Therapy to Lower CardioVascular Events (EVOLVE) trial on a range of issues. The trial aimed to demonstrate improved mortality and cardiovascular morbidity in dialysis patients.

The sponsor noted and acted upon the PBAC's request of November 2013, for a significant price reduction in order to restore the cost-effectiveness of cinacalcet.

While the PBAC did not accept the sponsor's proposal, it advised that a future submission for a more targeted population could demonstrate the cost-effectiveness of cinacalcet.

Cinacalcet is the only agent in its class and, because of this, it has a role in the management of Australian patients with chronic kidney disease who are on dialysis.

The sponsor is committed to working with the PBAC to demonstrate cost-effectiveness of cinacalcet in a targeted group of patients most likely to benefit from treatment. The sponsor intends to provide a submission to the PBAC's November 2014 meeting. Meanwhile, the sponsor and the Commonwealth have reached agreement on arrangements that ensure cinacalcet remains available on the PBS.