PUBLIC SUMMARY DOCUMENT
Product: Zoledronic acid, solution for I.V. infusion, 5 mg (as monohydrate) in 100 mL, Aclasta®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

To request an extension to the current authority required PBS listing for zoledronic acid to include treatment of patients with corticosteroid-induced osteoporosis (CIO).

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

On 2 July 2009 the TGA registration for zoledronic acid 5 mg in 100 mL was extended to include:

- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use;
- To prevent glucocorticoid induced bone mineral density loss.
- To increase bone mineral density in men with osteoporosis

Zoledronic acid 5 mg in 100 mL is also registered for the following indications:

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and nonvertebral fractures. Treatment should be restricted to three annual doses;
- Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures. Treatment should be restricted to three annual doses;
- Treatment of Paget's disease of bone.

4. Listing Requested and PBAC's View

Authority required

Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.

The duration and dose of corticosteroid therapy together with the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Only 1 treatment each year for 3 years per patient in a lifetime will be PBS-subsidised.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Corticosteroids are widely used in a variety of chronic non-infectious inflammatory diseases because of their immunosuppressant and anti-inflammatory properties. However, patients receiving high doses of corticosteroids are at increased risk of significant bone loss and

fractures. The two most serious adverse events reported are osteoporosis and related fractures.

Non-pharmacological treatments and management strategies include adequate nutrition (particularly calcium and vitamin D) and exercise to increase muscle strength and fall-prevention strategies. Pharmacological treatment includes the bisphosphonates which have shown to increase bone mineral density and reduce the risk of vertebral fractures.

Zoledronic acid, an intravenous formulation, would provide an alternative treatment to the current oral bisphosphonates for corticosteroid-induced osteoporosis in patients on long term corticosteroid therapy, who are at risk of fracture.

6. Comparator

The submission nominated risedronate, administered as an oral dose of 5 mg daily, as the main comparator. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented one randomised trial that compared zoledronic acid (5 mg annual infusion) with risedronate (5 mg orally daily for 12 months) in patients on corticosteroid therapy (equivalent to at least 7.5 mg of prednisone per day). The 'treatment' subpopulation of this trial consisted of patients on corticosteroid therapy for more than 3 months at randomisation. Results for patients who would be eligible under the requested listing (baseline T-score ≤ -1.5) were drawn from a *post-hoc* subgroup analysis of this treatment subpopulation.

The table below details the published trial presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Reid DM, et al. (Study 2306)	Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial.	Lancet 2009; 373(9671):1253-63

8. Results of Trials

The results for the trial's primary outcome measure, percent change in lumbar spine BMD at 12 months relative to baseline are shown in the following table, together with the result at the 6 month time-point.

Change in lumbar spine BMD relative to baseline for the treatment subpopulation

	Zoledronic acid		Risedronate		LS mean difference (95% CI) [a]	*P* Value [a]
	n	LS mean (%)	n	LS mean (%)		
Change in baseline lumbar spine BMD at 12 months						
MITT	249	4.06	245	2.71	1.36 (0.67, 2.05)	0.0001
Per protocol	235	4.03	230	2.70	1.33 (0.64, 2.03)	0.0002
Change in baseline lumbar spine BMD at 6 months						
MITT	249	3.43	245	2.39	1.04 (0.46, 1.62)	0.0005
Per protocol	235	3.42	230	2.43	0.99 (0.40, 1.59)	0.0011

[a] 95% confidence interval and P value are calculated from a three-way ANOVA with treatment, region and gender in the model
BMD=Bone mineral density, CI=Confidence interval, LS=Least squares, MITT=Modified intention-to-treat

The non-inferiority criterion was met as the lower bound of the 95% confidence interval (CI) of the mean difference between zoledronic acid and risedronate for the primary outcome of percent change in lumbar spine bone mineral density at 12 months was more than the non-inferiority margin of -0.70%. Similar changes between treatment groups were seen in the BMD at all anatomical sites at 6 and 12 months based on the modified intention-to-treat population.

The non-inferiority criterion was also met for the post-hoc analysis for the treatment subgroup with a baseline T-score of ≤ -1.5 for the primary outcome of percent change in lumbar spine bone mineral density at 12 months. It was noted that numerically, there was a smaller gain in lumbar spine bone mineral density at 12 months from baseline in the subgroup with a baseline T-score of ≤ -1.5 versus the full treatment subpopulation (0.88% vs. 1.36%, modified intention-to-treat population).

The submission presented limited fracture data and no differences were shown between zoledronic acid and risedronate. No separate data were presented for patients on corticosteroid therapy for > 3 months or for those with a baseline T-score of ≤ 1.5.

The PBAC recalled the Public Summary Document (PSD) for risedronate following the July 2008 PBAC meeting stated: "The Committee further noted that Kanis (2007) pooled and compared all available data for all bisphosphonates in CIO and post menopausal osteoporosis (PMO) and concluded that the fracture risk reductions seen in the two populations were of the same magnitude and that the lack of statistical significance observed in CIO only reflected the smaller sample size within the CIO trials. The overall conclusion from Kanis (2007) was that there was no evidence to support the hypothesis that the effects of bisphosphonates (and risedronate in particular) on fracture risks (including non-vertebral fractures) differ between CIO and PMO. Overall the PBAC agreed that the relative risk reduction in this indication should be the same if the baseline risk of fracture is equivalent."

In addition, the PBAC has previously noted that "the clinical use of the bisphosphonates in this condition (corticosteroid-induced osteoporosis) is widely accepted thus making the availability of further studies unlikely on ethical grounds."

Study 2306 showed no differences in quality of life between zoledronic acid and risedronate.

The trial results showed that adverse events suspected to be related to study drug occurring in ≥ 2% of subjects were reported statistically significantly more frequently in patients on zoledronic acid compared to patients on risedronate (38.2% vs. 18.3%, $P<0.0001$). The submission stated that this difference was due to a higher incidence of post-dose symptoms associated with zoledronic acid.

Trial reports of adverse events associated with zoledronic acid were considered to be consistent with the known risk profile for this bisphosphonate. The PBAC noted that in relation to osteonecrosis of the jaw, the submission stated that clinical trials and post-marketing observations have not shown a greater risk of this condition in osteoporosis.

9. Clinical Claim

The submission described zoledronic acid as non-inferior to risedronate in terms of efficacy, and stated that this claim is conservative because zoledronic acid was found to be superior to

risedronate for the primary outcome. Zoledronic acid was significantly more likely to result in an adverse event due to the post-dose syndrome, but was comparable in terms of serious or significant adverse events over risedronate.

The PBAC noted that the trial had been designed as a non-inferiority trial and accepted that zoledronic acid was non-inferior to risedronate.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as zoledronic acid 5 mg annually and risedronate 5 mg daily based on data from the pivotal trial.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year as between 10,000 – 50,000 in Year 5 of listing. There was some uncertainty associated with submission's estimate as:

- the requested listing of patients with a BMD T-score of ≤ -1.5 includes a proportion of patients with osteopenia whereas calculations were based on patients with osteoporosis;
- if the method used to estimate the likely number of patients excluded patients who may qualify for bisphosphonate therapy under current PBS listings; and
- uncertainty in the estimated market-share of zoledronic acid and market growth for bisphosphonates in CIO.

The estimated financial cost per year to the PBS was less than $10 million in Year 5 of listing.

12. Recommendation and Reasons

The PBAC recommended extending the listing of zoledronic acid to include treatment for corticoid-induced osteoporosis in a patient on long-term, high-dose corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less on a cost-minimisation basis with risedronate. The equi-effective doses are zoledronic acid 5 mg annually and risedronate 5 mg daily, and the dispensed price maximum quantity should take account of the administration costs associated with zoledronic acid.

The submission presented one randomised trial comparing zoledronic acid (5 mg annual infusion) with risedronate (5 mg daily orally for 12 months) in patients on corticosteroid therapy. The PBAC noted a *post-hoc* subgroup analysis of patients who would be eligible for treatment under the requested listing showed that the non-inferiority criterion for the primary outcome of percent change in lumbar spine BMD at 12 months was met.

While limited fracture data were presented in the submission, and no fracture data for this sub-group, the PBAC noted its previous comments on this matter (July 2008 Risedronate Public Summary Document) and accepted that the trial was not powered to evaluate differences in fracture rates.

Trial reports of adverse events associated with zoledronic acid were considered to be consistent with the known risk profile for this bisphosphonate. The PBAC noted that in relation to osteonecrosis of the jaw, the submission stated that clinical trials and post-marketing observations have not shown a greater risk of this condition in osteoporosis.

Recommendation:
ZOLEDRONIC ACID, solution for I.V. infusion, 5 mg (as monohydrate) in 100 mL,

Extend the current restriction to include:

Restriction: Authority required

Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.

The duration and dose of corticosteroid therapy together with the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Only 1 treatment each year for 3 years per patient in a lifetime will be PBS-subsidised.

Maximum quantity: 1
Repeats: nil

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 welcomes the PBAC's decision to make zoledronic acid 5 mg available on the PBS for this patient population.