PUBLIC SUMMARY DOCUMENT
Product: Zoledronic acid, solution for I.V infusion, 5 mg in 100 mL, Aclasta®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission requested an Authority required (streamlined) PBS listing for zoledronic acid for both the primary prevention of fractures in high risk women (aged over 70 years with a BMD T-score < -3.0), and the secondary prevention of fractures in post-menopausal women.

2. Background

At the July 2008 meeting the PBAC recommended an Authority required listing of zolendronic acid on the PBS for the treatment of established osteoporosis in patients with a hip fracture due to minimal trauma and in post-menopausal women with other minimal trauma fractures on a cost-minimisation basis with alendronate. The PBAC reaffirmed its view, according to its Guidelines, that alendronate was the appropriate main comparator as it is the treatment most likely to be replaced in clinical practice. The Committee did not accept the results of the cost-effectiveness analysis presented in the submission because the time-trade-off study commissioned by the sponsor to explore the utilities associated with zoledronic acid and alendronate had a number of biases that favoured zoledronic acid (See also Public Summary Document of July 2008).

3. Registration Status

Zoledronic acid 5 mg in 100 mL was TGA registered on 23 June 2008 for the following indications:

- Treatment of osteoporosis in patients aged 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 3 annual doses.
- Treatment of osteoporosis in post-menopausal women, to reduce the incidence of hip, vertebral and non-vertebral fractures. Treatment should be restricted to 3 annual doses.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in women aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less.
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.

Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in women with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.
A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Zoledronic acid 5 mg would provide an alternative anti-resorptive treatment option with once yearly dosing and an intravenous route of administration for the treatment of women with post-menopausal osteoporosis.

6. Comparator

The submission nominated alendronate sodium as the main comparator and risedronate sodium as an alternative main comparator. The PBAC considered that this was appropriate as alendronate was the treatment most likely to be replaced in clinical practice.

7. Clinical Trials

No changes were made to the trial data for secondary prevention of postmenopausal osteoporosis (PMO) presented in the July 2008 submission. The basis of the requested indication for primary prevention was an indirect analysis of one randomised trial of zoledronic acid (Trial 2301), one randomised trial of alendronate (FIT-CFA), one randomised trial of risedronate (HIP), one meta-analysis of risedronate (Heaney et al, 2002) and a PBAC Public Summary Document from March 2007 for risedronate (R-PSD 2007).

The trials published at the time of the submission are presented in the table below.

Trial ID	Protocol title/ Publication title	Publication citation
Zoledronic acid vs. placebo		
2301 (Clinical trial report Study ZOL446H2301)	A multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D.	
Black DM et al	Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis.	N Eng J Med. 2007; 356 (18): 1809-1822
Alendronate trials vs. placebo		
FIT-CFA Cummings SR et al,	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. (Clinical fracture arm of FIT trial)	JAMA.1998 Dec 23-30;280(24):2077-82
Risedronate vs. placebo		
HIP McClung MR, Geusens P, Miller PD et al	Hip Intervention Program Study Group. 2001 Effect of risedronate on the risk of hip fracture in elderly women.	N Engl J Med.2001 Feb 1;344(5):333-40
Meta-analysis risedronate		
Heaney et al Meta-analysis	Risedronate reduces the risk of first vertebral fracture in osteoporotic women. Meta-analysis of: • VERT-NA (primary prevention data not published separately) • HIP (McClung 2001)	Heaney, 2002 Osteoporosis International 2002; 13(6):501-505

	• BMD-MN (Fogelman 2000) BMD-NA (McClung 1997)	
Other (risedronate)		
R-PSD	PBAC 2007 Risedronate sodium Public Summary Document, July 2007	

PMO = postmenopausal

8. Results of Trials

The data for secondary prevention were the same as that presented in July 2008. In the primary prevention subpopulation of Trial 2301, zoledronic acid treatment compared with placebo showed a statistically significant difference only for the outcome of morphometric vertebral fractures. The indirect analyses between zoledronic acid and alendronate did not show any statistically significant differences, though this may reflect a lack of power and differences between the trial populations.

The PBAC considered that there was an absence of clinical trial evidence to suggest a clinical advantage of zoledronic acid relative to alendronate, and that it was uncertain whether zoledronic acid was non-inferior with alendronate in terms of comparative effectiveness and toxicity in a primary prevention post-menopausal osteoporosis population. The PBAC noted that in the subanalysis of Trial 2301, zoledronic acid treatment compared with placebo showed a statistically significant difference only for the outcome of morphometric vertebral fractures. The indirect analyses between zoledronic acid and alendronate did not show any statistically significant differences, but this may reflect a lack of power and differences between the trial populations. However, a statistically significant treatment effect was observed with alendronate for morphometric vertebral, non-vertebral and hip fractures.

No new toxicity data were presented in the submission. The most common adverse events were the acute phase reaction lasting up to 3 days with zoledronic acid, compared with gastrointestinal problems with alendronate. No data were reported for adverse events involving the injection site. As there is less than 12 months experience internationally with zoledronic acid in a postmenopausal population there is little relevant data concerning extended assessment of comparative harms.

The PBAC noted that there was a lack of long-term safety data and risk for serious unwanted events for zoledronic acid and considered that the balance of benefits to harms of an intravenous compared to an oral bisphosphonate preparation for primary prevention is not as favourable in primary prevention due to injection site reactions and acute phase reactions.

9. Clinical Claim

In July 2008 the PBAC recommended zoledronic acid on a cost-minimisation basis in comparison with alendronate for the secondary prevention indication. The current submission did not present any new clinical data for this indication. In terms of primary prevention, the submission described zoledronic acid as equivalent in terms of comparative effectiveness in a primary prevention population and equivalent in terms of comparative safety over alendronate.

10. Economic Analysis

The submission presented a modelled economic evaluation based on an indirect comparison of randomised trials for the comparison of zoledronic acid and alendronate in primary prevention. The type of economic evaluation presented was a cost-utility analysis. The

submission also presented a cost-minimisation analysis of zoledronic acid versus risedronate in primary prevention.

In general, the model had the same basic structure as that presented in July 2008, with differing placebo event rates and with the relative risk of fracture with zoledronic acid and alendronate equal.

The incremental cost per QALY gained was < $15,000. There was considerable uncertainly concerning the results of the economic evaluation, with concerns regarding the structure of the model (not Markov), the assumption of no differences between utilities of different fracture states, and the utilities assigned to zoledronic acid and alendronate treatment.

The model for primary prevention (as with secondary prevention) was most sensitive to the utilities assigned to zoledronic acid and alendronate treatment.

For PBAC's view see Recommendation and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year were estimated in the submission to be between 10,000 and 50,000 in Year 5 for each of primary and secondary prevention, while the financial cost/year to the PBS for substitution of alendronate and risedronate for primary prevention and for secondary prevention were each estimated to be < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended extending the listing of zoledronic acid to include the treatment of osteoporosis in women aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less on a cost-minimisation basis compared with alendronate and recommended the equi-effective doses are alendronate 70 mg weekly for 52 weeks versus zoledronic acid 5 mg once per year, less the cost of infusing zoledronic acid.

The PBAC noted that the sponsor had recently accepted the listing for zoledronic acid recommended at the July 2008 PBAC meeting on a cost-minimisation basis compared with alendronate for the treatment of established osteoporosis in women with facture due to minimal trauma and in men with hip fracture due to minimal trauma.

The submission nominated alendronate as the comparator and risedronate as a secondary comparator and the PBAC considered that this was appropriate as alendronate was the treatment most likely to be replaced in clinical practice.

The PBAC considered that there was an absence of clinical trial evidence to suggest a clinical advantage of zoledronic acid relative to alendronate, and that it was uncertain whether zoledronic acid was non-inferior with alendronate in terms of comparative effectiveness and toxicity in a primary prevention post-menopausal osteoporosis population. The PBAC noted that in the subanalysis of Trial 2301, zoledronic acid treatment compared with placebo showed a statistically significant difference only for the outcome of morphometric vertebral fractures. The indirect analyses between zoledronic acid and alendronate did not show any statistically significant differences, but this may reflect a lack of power and differences between the trial populations. However, a statistically significant treatment effect was observed with alendronate for morphometric vertebral, non-vertebral and hip fractures.

The PBAC also noted that there was a lack of long-term safety data and risk for serious unwanted events for zoledronic acid and considered that the balance of benefits to harms of an intravenous compared to an oral bisphosphonate preparation for primary prevention was not as favourable in primary prevention due to injection site reactions and acute phase reactions.

The PBAC noted that in terms of primary prevention, neither the guidelines cited in the submission nor any other guidelines accessed during the evaluation recommended zoledronic acid as a first-line therapy in primary prevention.

The PBAC agreed that the appropriate approach to modelling osteoporosis was to use a Markov model, noting that all recently published economic analyses, including those considered by NICE, were Markov models. However, the model presented in the submission was a non-Markov model and included the same time-trade-off (TTO) study used in the previous submission which was commissioned by the sponsor to explore the utility Australian patients assign to treatment with either annual IV or weekly oral bisphosphonate with different adverse event profiles. The PBAC had previously considered that this study had a number of biases that favoured zoledronic acid, and that the low baseline utilities for no treatment were themselves implausible. The PBAC noted that the utilities derived from the TTO study was the major driver in the derivation of cost per QALY and considered that there was considerable uncertainty about these utilities and that the use of a non-Markov model also led to economic uncertainty. Therefore, the PBAC could not recommend an extension to the listing of zoledronic acid in the primary prevention of osteoporosis on a cost-effectiveness basis due to uncertainty in the economic model.

The PBAC, however, recommended that the listing for zoledronic acid be extended to include the primary prevention of osteoporosis on a cost-minimisation basis compared with alendronate.

The PBAC noted that there was a potential Quality Use of Medicines issue regarding the administration of zoledronic acid in hospital and the subsequent use of oral bisphosphonates on discharge as it may not be known to the patient or local doctor that the yearly dose of zoledronic acid has been administered. The PBAC requested that NPS raise awareness of this issue to prescribers. The PBAC also requested that the DUSC monitor the first 12 months of usage.

Recommendation
ZOLEDRONIC ACID, solution for infusion, 5 mg in 100 mL, Aclasta®, Novartis Pharmaceuticals.

Restriction:
Authority required

Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in women aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less.
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.

Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in women with fracture due to minimal trauma.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in men with hip fracture due to minimal trauma.

In all cases, the fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated.

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

NOTE:
Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

Maximum quantity: 1
Number of repeats: 0

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 chose not to comment