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: July 2008

1. Purpose of Application

The submission sought an Authority Required (Streamlined) listing for zoledronic acid for the treatment of established osteoporosis in patients with a hip fracture due to minimal trauma.

In a separate minor submission to the PBAC, the sponsor requested that the listing also include the secondary prevention of osteoporotic fractures in postmenopausal women with a low trauma fracture.

2. Background

Zoledronic acid for the above requested indications or in this formulation had not previously been considered by the PBAC.

3. Registration Status

Zoledronic acid was TGA registered on 23 June 2008 for the following indications:

- 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 osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures. Treatment should be restricted to three annual doses.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in patients with hip 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.

Authority required (STREAMLINED)
Treatment as the sole-subsidised anti-resorptive agent for established postmenopausal 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.

5. Clinical Place for the Proposed Therapy

Zoledronic acid 5 mg will provide an alternative treatment option for post menopausal women who have established osteoporosis and patients with a hip fracture which is due to minimal trauma.

6. Comparator

The submission nominated alendronate sodium as the main comparator and risedronate sodium as an alternative main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

There were no head-to-head trials of zoledronic acid and either alendronate or risedronate. The submission presented:

One placebo-controlled trial of zoledronic acid 5 mg in patients with surgical repair of a hip fracture within the previous 90 days (Trial 2310).

One placebo-controlled trial of zoledronic acid in the treatment of osteoporosis in postmenopausal women with either:

(1) radiological evidence of at least two mild or one moderate existing vertebral fracture(s) and a femoral neck BMD T-score of ≤ -1.5, OR
(2) a femoral neck T-score of ≤ -2.5 with or without evidence of an existing vertebral fracture (Trial 2301).

Two indirect comparisons are made with placebo as the common reference:

a. one trial of alendronate 5 mg orally per day for the first 12 months, then 10 mg per day thereafter, compared with placebo, in patients with a previous vertebral fracture (Black, based on FIT-VFA)
b. a meta-analysis of two trials of risedronate 5 mg orally per day with compared with placebo in patients with a previous vertebral fracture (McClung, Reginster).

The trials and associated reports of randomised trials for the prevention of fractures in osteoporosis with zoledronic acid (with prior low-trauma hip fracture), alendronate (with prior vertebral fracture) and risedronate (with prior vertebral fracture) published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Zoledronic acid vs placebo		
2310 (Clinical trial report Study No. ZOL446H2310) Black 2007	A multicenter, double-blind, randomized, placebo controlled, parallel group study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in post-menopausal women taking calcium and vitamin D	NEJM 2007; 356:1809-22
Lyles 2007	Multinational, multicenter, double-blind, randomized, placebo controlled, parallel group study assessing the efficacy of intravenous zoledronic acid in preventing subsequent osteoporotic fractures after a hip fracture.	NEJM 2007;357;1799-809
Alendronate vs placebo: no trials in patient with hip fracture - inferred from Black (1996)		
FIT-VFA (Fracture Intervention Trial - Vertebral Fracture Arm)	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.	Lancet 1996; (348): 1535-1541.
Black 1999; Black 2000 Ensrud 1997;		
Risedronate vs placebo: no trials in patient with hip fracture - inferred from pooled VERT-MN & HIP trials		
VERT-MN (Vertebral Efficacy with Risedronate Therapy - Multinational) Reginster, 2000	Randomised trial of the effects of risedronate on vertebral fractures in women with established post-menopausal osteoporosis.	Osteoporosis International 2000; 11:83-91
HIP (Hip Intervention Program) McClung, 2001	Effect of risedronate on the risk of hip fracture in elderly women.	NEJM 2001; 344:333-40

8. Results of Trials

The results of the indirect comparison, zoledronic acid (with prior hip fracture) vs. alendronate (with prior vertebral fracture) are summarised below:

Trial ID	Zoledronic acid n/N (%)	Placebo n/N (%)	Alendronate n/N (%)	RR (95% CI)	Indirect RR (95% CI)
Any clinical fracture					
2310	92/1065 (8.6)	139/1062 (13.1)		0.66 (0.51,0.85)	
Black*		183/1005 (18.2)	139/1022 (13.6)	0.75 (0.61,0.92)	0.88 (0.64,1.22)
Clinical vertebral fracture					
2310	21/1065 (2.0)	39/1062 (3.7)		0.54 (0.32,0.91)	
Black*		50/1005(5.0)	23/1022 (2.3)	0.45 (0.28,0.74)	1.19 (0.58,2.43)
Non-vertebral fracture					
2310	79/1065(7.4)	107/1062 (10.1)		0.74 (0.56,0.97)	
Black*		148/1005 (14.7)	122/1022 (11.9)	0.81 (0.65,1.01)	0.91 (0.64,1.30)
Hip fracture					
2310	23/1065(2.2)	33/1062 (3.1)		0.70 (0.41,1.18)	
Black*		22/1005 (2.2)	11/1022 (1.1)	0.49 (0.24,1.01)	1.41 (0.58,3.45)

* Black et al 1996, a report of the Fracture Intervention Trial – Vertebral Fracture Arm

The PBAC considered that the results of the indirect comparison of Study 2310 for zoledronic acid and the Vertebral Fracture Arm of the Fracture Intervention Trial for alendronate (Black et al, 1996) demonstrated that zoledronic acid is non-inferior to alendronate in terms of its efficacy in preventing any new clinical fractures, new clinical vertebral fractures, new non-vertebral fracture or new hip fractures.

The PBAC was prepared to extrapolate the results of study 2310 to the population of post-menopausal women with minimal trauma fractures, as it has not previously made a distinction between types of prior fracture in estimating the benefits of bisphosphonate treatment in preventing future fractures. In this context, the Committee was reassured by the data from the unevaluated study 2301, which supports the conclusion that zoledronic acid is at least non-inferior to alendronate in preventing future osteoporotic fractures. Although the same extrapolation argument could be applied to the population of males with non-hip low trauma osteoporotic fractures, the current TGA indication prevents the PBS listing from including this group.

In the head to head trials comparing zoledronic acid and alendronate, influenza-like illness in the three days following zoledronic acid infusion (20.3% vs 5.1%), as well as myalgia (17.4% vs 5.1% Saag 2007) and fatigue (9.7% vs 1.8% McClung 2007), were significantly more likely to occur than with alendronate treatment, which were consistent with known effects of zoledronic acid post-infusion.

In Trial 2301 compared with placebo, there was an increased risk of spontaneous reported serious atrial fibrillation (1.3% vs 0.5%), cardiorespiratory arrest and death due to myocardial infarction, and concerns were raised regarding death due to cerebrovascular accident (though the relative risk did not reach statistical significance). In trial 2310 compared with placebo, the incidence of cardiovascular events was similar in the two groups: serious atrial fibrillation was reported in 12 patients (1.1%) in the zoledronic acid group and 14 patients (1.3%) in the placebo group.

In the extended assessment of comparative harms other AEs of interest included hypocalcaemia, osteonecrosis of the jaw (some data has suggested that osteonecrosis of the jaw may occur more frequently in patients treated with zoledronic acid than other bisphosphonates), other osteonecrosis outside the maxillofacial area, renal toxicity and ocular disorders.

9. Clinical Claim

The submission stated that, in patients who had already experienced a hip fracture, zoledronic acid starting within 90 days after surgical repair of a low-trauma hip fracture, is superior to placebo.

The submission claimed that zoledronic acid is more effective than alendronate sodium in reducing the risk of morphometric vertebral and clinical vertebral fractures.

With respect to the comparison against alendronate in the population with a prior hip fracture, the submission stated that the indirect comparison demonstrated that zoledronic acid is no worse than alendronate in terms of efficacy, but that, in light of differences between trial

2310 (men and women who immediately after post-hip fracture) and FIT-VFA (post-menopausal osteoporosis with a prevalent vertebral fracture), the results of the indirect comparison were inconclusive.

The submission further stated that zoledronic acid was superior to alendronate in terms of increased utility due to patient preference for the annual treatment, and was equivalent in terms of comparative safety.

Finally, the submission claimed that there was no meaningful difference in the safety profiles of zoledronic acid and alendronate or risedronate.

For PBAC's view, see Recommendation and Reasons.

10. Premodelling studies:

The submission presented the results of an investigator initiated time-trade-off (TTO) study funded by the sponsor to explore the utility of Australian patients assigned to treatment with either an annual I.V. bisphosphonate or a weekly oral bisphosphonate with different adverse event profiles.

For PBAC's view, see Recommendation and Reasons.

11. Economic Analysis

The economic evaluation presented in the submission was based on the secondary prevention post-menopausal osteoporosis population (ie Trial 2301 vs FIT-VFA). The events included in the model were: clinical vertebral fracture, proximal humerus fracture, wrist fracture, hip fracture and death. The incremental cost per extra quality adjusted life year gained was estimated to be less than $15,000.

For PBAC's view, see Recommendation and Reasons.

12. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be between 10,000 – 50,000 patients in Year 5, including patients switching from alendronate and risedronate.

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

13. Recommendation and Reasons

The PBAC recommended the listing of zoledronic 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 equi-effective doses for the purposes of setting the listing price for zoledronic acid for these indications are alendronate 70 mg weekly for 52 weeks versus zoledronic acid 5 mg once per year, with the price to pharmacist of zoledronic acid reduced to take into account an administration cost of $49.95.

The PBAC reaffirmed its view, as expressed in listing recommendations for other osteoporosis treatments, that, according to its Guidelines, alendronate is the appropriate main comparator as it is the treatment most likely to be replaced in clinical practice.

For PBAC's comments on the results, *see 'Results of Trials'*.

The Committee did not accept the results of the cost-effectiveness analysis presented in the submission because the time-trade-off study funded by the sponsor to explore the utilities associated with annual IV versus weekly oral bisphosphonates had a number of significant biases that favoured zoledronic acid.

The PBAC also agreed that the appropriate approach to modelling osteoporosis is to use a Markov model, noting that all recently published economic analyses, including those considered by NICE, were Markov models.

Finally, the Committee agreed that the Quality Use of Medicine (QUM) issues related to the prescribing of zoledronic acid were important and that particular attention needs to be given to establishing appropriate policies for administration of this agent in hospitals. The PBAC requested the Secretariat alert the state Health Departments to this issue.

Recommendation

ZOLEDRONIC ACID, solution for I.V infusion, 5 mg in 100 mL

Restriction:	Authority required Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in women with facture due to minimal trauma. 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. 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. Only one treatment each year for three consecutive years per patient 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
Repeats:	Nil

14. 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.

15. Sponsor's Comment

The sponsor chose not to comment.