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 2012

1. Purpose of Application

To extend the current Authority Required (Streamlined) listing for the treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older, with a Bone Mineral Density (BMD) T-score of -2.5 or less.

2. Background

At the July 2008 meeting (major submission), the PBAC recommended an Authority required listing for zoledronic acid for the treatment of established osteoporosis in men with a hip fracture due to minimal trauma and in women with fracture due to minimal trauma 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 were 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 administration costs.

At the November 2008 meeting (major submission), the PBAC recommended extending the listing of zoledronic acid on a cost-minimisation basis compared with alendronate, to include the treatment of osteoporosis for women aged 70 years of age or older in the primary prevention setting, which they had previously defined as a BMD T-score of -3.0 or less.

At the November 2009 meeting (major submission), the PBAC recommended extending the listing of zoledronic acid on a cost-minimisation basis compared with alendronate to include the treatment of established osteoporosis in men with fracture due to minimal trauma as well as the treatment of osteoporosis in men aged 70 years of age or older with a BMD T-score of -3.0 or less.

At the July 2011 meeting (minor submission), the PBAC recommended removing the 3-year treatment limit from the zoledronic acid PBS listings. The PBAC also recommended changing the PBS listing of zoledronic acid from 'Authority required' to 'Authority required (STREAMLINED)'.

3. Registration Status

Zoledronic acid is TGA-approved for the treatment of postmenopausal osteoporosis, male osteoporosis, Paget disease and the prevention/treatment of glucocorticoid-induced osteoporosis.

Zoledronic acid is PBS listed for the primary (patients aged ≥70 years with a BMD T-score ≤ -3.0) and secondary prevention of fracture associated with osteoporosis (males and females), treatment of symptomatic Paget disease and the treatment of glucocorticoid-induced osteoporosis.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)

Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years or older with a bone mineral density (BMD) T-score of -2.5 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 osteoporosis in a patient 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. 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.

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

5. Clinical Place for the Proposed Therapy

Osteoporosis is a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk (RACGP osteoporosis guidelines). Loss of bone strength occurs gradually over many years and usually shows no symptoms. Many people are not diagnosed with osteoporosis until a fracture occurs.

Zoledronic acid is an intravenous infusion given once a year. The algorithm presented in the submission positions zoledronic acid as an alternative to alendronate and denosumab (women only) in the subgroup of primary prevention patients aged ≥ 70 years with a BMD T-score between -3.0 and -2.5.

6. Comparator

The submission nominated alendronate as the comparator which was considered appropriate by the PBAC.

7. Clinical Trials

The sponsor noted that the PBAC (November 2008, November 2009) has previously accepted the claim that zoledronic acid is non-inferior to alendronate in the primary prevention of fracture associated with osteoporosis. Therefore the aim of the submission was to demonstrate that the efficacy and safety of zoledronic acid in the target population (patients with BMD T-score between -3.0 and -2.5, aged ≥ 70 years, no prevalent fracture) is similar to the broader primary prevention osteoporosis population.

The submission was based on post-hoc analyses of two zoledronic acid vs. placebo trials (HORIZON – postmenopausal women, Study 2309 - males) comparing fracture outcomes between different primary prevention subgroups:

- Patients with BMD T-score ≤-2.5, no prevalent vertebral fracture (this subgroup from the HORIZON trial was previously presented in the November 2008 submission)

- Patients with BMD T-score between -3.0 and -2.5, no prevalent vertebral fracture
- Patients with BMD T-score between -3.0 and -2.5, no prevalent vertebral fracture, aged ≥70 years (target population, HORIZON trial only)

The submission presented data on the proportion of patients with new morphometric vertebral fractures, clinical vertebral fractures, clinical non-vertebral fractures, hip fractures, wrist fractures and 'other' non-vertebral fractures.

The published trials presented in the submission are shown below.

Trial ID/First author	Publication title	Publication citation
Zoledronic acid vs. Placebo trials		
Study 2301 (HORIZON) Black et al	Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis	*New England Journal of Medicine* (2007); 356: 1809-1822
Study 2301E1 Black et al	The Effect of 3 Versus 6 Years of Zoledronic Acid Treatment of Osteoporosis: A Randomized Extension to the HORIZON-Pivotal Fracture Trial (PFT).	*Journal of Bone and Mineral Research* (2012); 27: 243-254
Alendronate vs. Placebo trials		
FIT-CFA Cummings et al	Effect of Alendronate on risk of fracture in women with low bone density but without vertebral fractures	*Journal of the American Medical Association* (1998); 280: 2077-2082
FLEX Black et al	Effects of continuing or stopping alendronate after 5 years of treatment, the Fracture Intervention Trial Long-Term Extension (FLEX: a randomized trial)	*Journal of the American Medical Association* (2006); 296: 2927–2938

8. Results of Trials

Postmenopausal women with osteoporosis

There were statistically significant reductions in morphometric vertebral fractures with zoledronic acid treatment compared to placebo in the three specified post-hoc primary prevention subgroups (target population: Relative risk (RR) 0.35 [95% Confidence Interval (CI): 0.17, 0.75]; number-needed-to-treat (NNT): 23 [95% CI: 13, 68]).

There were similar reductions in the relative risk of clinical vertebral fractures (not statistically significant in primary prevention subgroups) but event rates were low in both treatment arms with only a small difference in absolute risk (target population: RR 0.22 [95% CI 0.05, 1.05]; NNT 74 [95% CI: 33, 1032]).

There were consistently fewer fractures in zoledronic acid treated patients compared to placebo for other fracture types (clinical non-vertebral fractures, hip fractures, wrist fractures and 'other' non-vertebral fractures) but these differences were not statistically significant in the primary prevention subgroups.

There were no statistically significant interactions between morphometric vertebral fracture risk and age, history of falls or femoral neck BMD T-scores.

Males with osteoporosis

While there were fewer fractures in patients treated with zoledronic acid compared to placebo, there were no statistically significant differences in morphometric, clinical vertebral or clinical non-vertebral fracture risk between treatments in the two primary prevention subgroups analysed. No fracture data were presented for the target population (age ≥70 years, BMD T-score between -3.0 and -2.5) in Study 2309. The post-hoc subgroups only included a small number of patients with low event rates which limited any meaningful comparison of fracture rates between treatments.

Subgroup analyses of adverse event data did not identify any new safety issues in the specified primary prevention populations.

A Periodic Safety Update Report (PSUR) for zoledronic acid indicates that the sponsor is continuing to monitor the risks of hypocalcaemia, osteonecrosis of the jaw (ONJ), osteonecrosis, delayed fracture healing, renal dysfunction, ocular disorders, anaphylaxis, atrial fibrillation, cerebrovascular accidents and atypical stress fractures.

Long-term follow-up data from a randomised double-blind extension of the HORIZON trial indicated that transient increases in serum creatinine levels occurred more frequently in patients treated with zoledronic acid for 6 years compared with patients who stopped treatment at 3 years (2.9% vs. 0.7%, p = 0.002). There was also higher incidence of serious cardiovascular events with long-term zoledronic acid treatment but these differences were not statistically significant (strokes 3.1% vs. 1.5%, p = 0.06; atrial fibrillation 2.0% vs. 1.1%, p = 0.26; arrhythmia 3.3% vs. 1.8%, p = 0.11). There was also an unexplained lower incidence of hypertension in patients receiving zoledronic acid for 6 years compared to 3 years (7.8% vs. 15.1%, p = 0.0001).

The FDA has recently issued updated warnings on the risk of renal impairment associated with zoledronic acid treatment (Zoledronic acid: Drug Safety Communication, September 2011). The safety brief noted that cases of acute renal failure requiring dialysis or having a fatal outcome following zoledronic acid treatment have been reported to the FDA. Consistent with the FDA warning, the current TGA-approved product information states that zoledronic acid is contraindicated in patients with renal impairment (creatinine clearance < 35 mL/min) and notes that creatinine clearance should be calculated before each zoledronic acid dose.

9. Clinical Claim

The submission claims that the efficacy and safety of zoledronic acid in the target population (patients with BMD T-score between -3.0 and -2.5, aged ≥ 70 years, no prevalent fracture) is similar to that observed with zoledronic acid in the broader primary prevention osteoporosis population. The PBAC considered this was reasonable.

10. Economic Analysis

The submission presented a cost-minimisation analysis of zoledronic acid compared to alendronate. The analysis was based on the claim that:

- The PBAC has previously accepted zoledronic acid as non-inferior to alendronate in the primary prevention setting.
- The clinical data presented in the current submission demonstrated that the efficacy and safety of zoledronic acid in the target population (patients with BMD T-score between -3.0 and -2.5, aged $\geq$ 70 years, no prevalent fracture) is similar to that observed with zoledronic acid in the broader primary prevention population.

The equi-effective doses were zoledronic acid (5 mg once per year) and alendronate (70 mg weekly for 52 weeks), based on the established therapeutic relativity between treatments in osteoporosis (PBS Therapeutic Relativity Sheets, January 2012).

The PBAC did not accept the cost-minimisation analysis based on drug costs only. The PBAC noted that zoledronic acid is currently listed on the PBS for osteoporosis on a cost-minimisation basis with alendronate with the cost of infusion accounted for in the cost of zoledronic acid. The PBAC therefore recommended that the price of zoledronic acid should be based on an equivalent treatment cost compared with alendronate, taking into account the previously accepted cost of infusion.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended that the current Authority required (Streamlined) listing for zoledronic acid solution for IV infusion 5 mg (as monohydrate) in 100 mL for treatment of osteoporosis in the primary prevention setting be extended to include patients aged 70 years of age or older with a bone mineral density (BMD) T-score of -2.5 or less on a cost minimisation basis with alendronate. The equi-effective doses are alendronate 70 mg weekly for 52 weeks and zoledronic acid 5 mg per year, less the cost of infusing zoledronic acid, based on the established therapeutic relativity between treatments in osteoporosis. The PBAC recommended that the price of zoledronic acid should be based on an equivalent annual treatment cost compared with alendronate alone, and that this was consistent with its March 2012 recommendation for denosumab for the same extension to listing.

The nominated comparator of alendronate was considered appropriate by the PBAC.

The PBAC noted that the basis of the submission was post hoc analyses of two trials of zoledronic acid versus placebo (HORIZON (in post-menopausal women) and Study 2309 (in males)) comparing fracture outcomes between different primary prevention subgroups. The PBAC recalled that it had previously (in November 2008 and November 2009) accepted that zoledronic acid is non-inferior to alendronate in the primary prevention setting for osteoporosis, and accepted the current submission's approach to demonstrate that the efficacy and safety of zoledronic acid in the target sub-population, (patients aged 70 years and older with a BMD T-score between -3.0 and -2.5 with no prevalent fracture), is similar to the broader primary prevention population.

From the HORIZON trial, the PBAC noted that there were statistically significant reductions in morphometric vertebral fractures with zoledronic acid compared to placebo in the specified

post-hoc primary prevention subgroups. For the target sub-population, relative risk (RR) = 0.35 [95% CI: 0.17, 0.75]. For the more clinically relevant outcomes of clinical vertebral fractures and clinical non-vertebral fractures, the PBAC noted that there were no statistically significant reductions in fracture in any of the primary prevention subgroups.

From Study 2309, the PBAC noted that there were no statistically significant differences in fracture risk for any fracture subgroup (morphometric, clinical vertebral or clinical non-vertebral) in the primary prevention subgroups analysed.

In relation to comparative harms, the PBAC considered that the toxicity of bisphosphonates is well recognised and understood and noted the ongoing safety monitoring of zoledronic acid being undertaken by the sponsor. The PBAC also noted that no new safety concerns had been identified in the specified primary prevention populations in the key trials.

The PBAC did not accept the cost-minimisation analysis based on drug costs only. The PBAC noted that zoledronic acid is currently listed on the PBS for osteoporosis on a cost-minimisation basis with alendronate with the cost of infusion accounted for in the cost of zoledronic acid. The PBAC therefore recommended that the price of zoledronic acid should be based on an equivalent treatment cost compared with alendronate, taking into account the previously accepted cost of infusion.

The PBAC noted that the uptake of alendronate and denosumab in this extended primary prevention population has been lower than expected. The PBAC requested that the DUSC review zoledronic acid around 18 months after the extension to listing has taken effect.

The PBAC noted that the Safety Net 20 Day Rule does not currently apply to zoledronic acid. Nor is zoledronic acid currently included in the list of PBS medicines for prescribing by nurse practitioners.

Recommendation:
Amend the BMD-T score requirement from -3.0 to -2.5 in the current restriction for the primary prevention indication. There are no changes to the restrictions for other indications.

Restriction:

Authority required (STREAMLINED)
Osteoporosis

- Patient must be aged 70 years or older;
- Patient must have a bone mineral density (BMD) T-score of ~~-3.0~~ *-2.5* or less;
- Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition; and
- Patient must not receive more than one PBS-subsidised treatment per year

Prescriber Instructions:

- 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.

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 has no further comment.