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

The submission sought to extend the current general (section 85) listing such that zoledronic acid would be available for men for the same conditions as it is now available for women, that is:

- for established osteoporosis with fractures other than hip fractures due to minimal trauma; and
- for men aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3 or less.

2. Background

At the July 2008 meeting, the PBAC recommended an Authority Required listing for zoledronic acid 5 mg for the treatment of established osteoporosis in patients with a hip fracture due to minimal trauma and in 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 less the cost of infusion.

At the November 2008 meeting, the PBAC recommended extending the listing of zoledronic acid 5 mg 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 infusion.

3. Registration Status

The TGA approved indications at 2 July 2009 for zoledronic acid are:

- 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;
- 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;
- To increase bone mineral density in men with osteoporosis;
- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use;
- To prevent glucocorticoid induced bone mineral density loss;
- Treatment of Paget's disease of bone.

4. Listing Requested and PBAC's View

The listing requested was the same as the current osteoporosis listings for zoledronic acid with the exception that "women" would be replaced by "patient". As a consequence, the listing for established osteoporosis in men with hip fracture was requested to be deleted from the current listing as it would be encompassed by the changed wording.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The extension to listing would provide men with the same access to zoledronic acid as women.

6. Comparator

The submission nominated alendronate sodium and risedronate sodium, which are not restricted to use in women, as the main comparators.

7. Clinical Trials

The submission presented a non-inferiority study (study 2308) as the key clinical trial to extend the current PBS listing for the primary and secondary prevention of osteoporosis to cover male patients. Study 2308 examined the effect of IV zoledronic acid 5 mg annually on lumbar spine bone mineral density using oral alendronate 70 mg weekly as active control. Analyses were conducted on the intention-to-treat (ITT) and per protocol populations and the total study duration was approximately 25 months. The subjects were men specified to be aged 25 to 85 years inclusive who had been diagnosed with osteoporosis either secondary to hypogonadism or without specific cause. There was prior history of fracture in 67% of patients with slightly more patients in the alendronate group compared to the zoledronic acid group (70% vs 64%) and the mean baseline bone mineral density (BMD) scores at lumbar spine and femoral neck were – 2.1 and – 2.3 , with minimal differences between alendronate and zoledronic acid (respectively, -2.1 vs - 2.2 for lumbar spine and – 2.3 vs - 2.3 for femoral neck).

8. Results of Trials

The primary efficacy variable was the percent change in lumbar spine BMD relative to baseline after 24 months treatment. The PBAC considered the criterion for non-inferiority of zoledronic acid relative to alendronate was met, as the lower bound of the 95 % confidence interval (- 1.12 for ITT population, - 1.27 per protocol) exceeded the pre-specified non-inferiority margin of – 1.5%.

The submission also presented comparative analyses, which were carried out for a number of secondary parameters including change in spine BMD at intermediate time points and of the various measurements of hip BMD (total hip, femoral neck, trochanter) and total body BMD. The PBAC noted that biomarkers of bone resorption showed similar reductions relative to baseline between treatment groups at month 24, although the nadir for IV zoledronic acid was at 9-11 days post infusion.

Overall, the percentage of patients who reported adverse events was similar in both treatment groups (zoledronic acid 93.5%, alendronate 93.2%). Adverse events consistent with post-dose symptoms occurred more frequently with zoledronic acid (within 3 days of IV infusion) than with alendronate. The PBAC noted that a number of adverse effects common to the bisphosphonate class occurred with zoledronic acid administration but no increase in the rate of occurrence of these effects was observed in the submitted studies, nor were any new or unexpected safety concerns evident.

9. Clinical Claim

Using a change to its registered indications and a non-inferiority study against alendronate, the submission claimed that zoledronic acid is no worse than alendronate sodium in treating all patients for its current PBS restricted indications.

10. Economic Analysis

No economic evaluation was presented in the submission.

11. Estimated PBS Usage and Financial Implications

No estimated PBS usage and financial implications were presented in the submission.

12. Recommendation and Reasons

The PBAC recommended amending the listing of zoledronic acid 5 mg infusion to include men with established osteoporosis with fractures other than hip fracture due to minimal trauma, and men aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3 or less on the basis of non-inferiority to alendronate sodium in these patient groups.

The PBAC noted the TGA approved indications for zoledronic acid had recently been extended to include these two patient groups.

The PBAC noted the results of the study presented (study 2308) in the primary efficacy variable of percent change in lumbar spine BMD relative to baseline after 24 months treatment demonstrated the criterion for non-inferiority of zoledronic acid relative to alendronate had been met. The PBAC noted the subjects were men specified to be aged 25 to 85 years inclusive who had been diagnosed with osteoporosis either secondary to hypogonadism or without specific cause, but did not consider this a matter of concern.

Recommendation:

ZOLEDRONIC ACID, solution for IV infusion, 5 mg (as monohydrate) in 100 mL

Replace the current restrictions for osteoporosis with the following:

Restriction:

Authority Required

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 -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.

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

Authority required

Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis 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.

Only 1 treatment each year for 3 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
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'decision to extend the PBS restriction for zoledronic acid 5 mg.