PUBLIC SUMMARY DOCUMENT

Product: Ibandronic Acid, tablet, 150 mg, Bonviva® Once Monthly

Sponsor: Roche Products Pty Limited

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought an authority required listing for the treatment of established postmenopausal osteoporosis in patients with fracture due to minimal trauma.

2. Background

The PBAC had not previously considered a submission for ibandronic acid film-coated tablet for osteoporosis.

3. Registration Status

Bonviva Once Monthly is registered by the TGA on 4 July 2006 for treatment of postmenopausal osteoporosis. Osteoporosis may be confirmed by the finding of low bone mass (at least 2.0 SD below the normal mean) or by the presence or history of osteoporotic fracture.

4. Listing requested and PBAC's View

The submission requested an authority required listing for:
Initial treatment as the sole anti-resorptive agent for established postmenopausal osteoporosis in patients 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 included in the authority application.
A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of the 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;
Continuing treatment as the sole anti-resorptive agent for established postmenopausal osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.

For PBAC's view, see Recommendation and Reasons.

5. Clinical place for the proposed therapy

Postmenopausal osteoporosis is a common disorder affecting a large number of women above the age of 50 years. In the treatment of postmenopausal osteoporosis, ibandronic acid provides an alternative treatment to the bisphosphonates and raloxifene.

6. Comparator

The submission nominated alendronate 70 mg once weekly as the main comparator. The PBAC considered the comparator appropriate.

7. Clinical Trials

The scientific basis of comparison involved six RCTs comparing ibandronate, alendronate and placebo. A two-step indirect comparison was conducted comparing 150mg/month ibandronate with 70 mg/week alendronate over 1 to 3 years as follows:

1. The equivalence of ibandronate 150 mg/month to ibandronate 2.5 mg/day was directly demonstrated (MOBILE study [1-year and 2-year data]) - BMD data.
2. The equivalence of alendronate 70 mg/week to alendronate 10 mg/day was directly demonstrated (Schnitzer et al. 2000 [1-year data] and Rizzoli et al. 2002 [2-year data]) - BMD data.
3. The equivalence of ibandronate 2.5 mg/day and alendronate 10 mg/day was indirectly demonstrated using placebo as a common reference (BONE study for ibandronate; Black et al. 1996 [FIT study] and Liberman et al. 1995 for alendronate [3-year data]) - Fracture data.

The trials published at the time of the submission were as follows:

Trial/First author	Protocol/Publication title	Publication citation
Protocol BM 16549/ Miller PD	Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year result from the MOBILE study.	Journal of Bone and Mineral Research, 2005; 20(8): 1315-1322
Schnitzer T	Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis.	Aging - Clinical and Experimental Research, 2000; 12(1): 1-12
Rizzoli R	Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis.	Journal of Bone and Mineral Research, 2002; 17(11): 1988-1996
Protocol MF 4411/Chestnut III CH	Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis.	Journal of Bone and Mineral Research, 2004; 19(8): 1241-1249
Delmas PD	Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study.	Osteoporosis International, 2004; 15(10): 792-798
Black DM	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures (FIT)	Lancet, 1996; 348(9041): 1535-1541
Liberman UA	Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis.	New England Journal of Medicine, 1995; 333(22): 1437-1443

8. Results of Trials

Both ibandronate 2.5 mg/day and alendronate 10 mg/day were statistically significantly superior to placebo and resulted in similar reductions in the risk of new or worsening vertebral fracture and new clinical vertebral fractures.

The indirect estimate of effect (ratio of relative risks) for new or worsening vertebral fractures was 0.83 (95% CI: 0.55, 1.24). The indirect estimate of effect (ratio of relative risks) for new clinical vertebral fractures was 1.24 (95% CI: 0.63, 2.44). These estimates

suggest no statistically significant difference between ibandronate and alendronate, as the 95% CIs include one.

Ibandronate and alendronate had similar adverse event profiles. The acute phase reaction like events were only reported for ibandronate in the MOBILE study. The approved Product Information notes concerns about the potential for osteonecrosis of the jaw and adynamic bone disease with long term bisphosphonate therapy (including ibandronate). However, there was no evidence presented in this submission on the development of these adverse events and no evidence provided to suggest that patients receiving ibandronate are at more or less risk of osteonecrosis or adynamic bone disease compared to other bisphosphonates.

9. Clinical Claim

The submission described ibandronic acid 150 mg/month as being no worse than alendronate 70 mg/week in terms of effectiveness and overall toxicity. The PBAC considered there were doubts about the acceptability of the claim of fracture efficacy for ibandronic acid 150 mg based on a two-step indirect comparison.

10. Economic Analysis

A preliminary economic evaluation was presented adopting a cost-minimisation approach. The resources included were drug costs.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year accounting for market share was in the range 100,000 – 200,000 patients in year 5, while the financial cost per year to the PBS (excluding co-payments) was > $100 million in year 5 for all bisphosphonates. The net cost of ibandronic acid to the PBS after subtracting patient co-payments was estimated to be < $1 million in Year 5. The overall market was not expected to grow or to grow more rapidly as a result of listing of ibandronic acid as ibandronic acid will substitute for existing PBS subsidised therapies.

12. Recommendation and Reasons

The PBAC noted that both ibandronic acid 2.5 mg/day and alendronate 10 mg/day were statistically significantly superior to placebo. The PBAC agreed with the ESC advice that the comparison for new clinical vertebral fracture may be more robust because the results in the placebo arms for this outcome appear to be more comparable. There are marked differences across the placebo groups for the new or worsening vertebral fractures outcome which raises concerns about the appropriateness of pooling the results of the three trials.

In the BONE study there were only a small number of hip fractures reported and no statistically significant differences between ibandronic acid 2.5 mg daily and placebo for hip fractures at 3 years. The BONE trial also showed that ibandronic acid reduces vertebral fractures but does not reduce all clinical fractures.

The PBAC considered there were doubts about the acceptability of the claim of fracture efficacy for ibandronic acid 150 mg based on a two-step indirect comparison. The absolute indirect nature of the evidence presented where multiple assumptions are added in a statistical analysis which produced large 95% confidence intervals and a point

estimate that is suggestive of a worse clinical effect of ibandronic acid in comparison with alendronate, does not support an equivalence argument. This concern is even more marked for new clinical vertebral fractures, which the PBAC had concluded was the more robust clinical outcome. In addition, the data from the MOBILE and BONE trials suggest that for a number of outcomes ibandronic acid is no different from placebo.

The PBAC noted that the total weekly dose of alendronate is 7 times the daily dose, but for ibandronic acid the monthly dose is higher than 30 times the daily dose and that this may have an effect on the safety profile of ibandronic acid in terms of the relative excess of the daily dose.

The PBAC thus rejected the submission because of the inadequate evidence of demonstrating no difference between ibandronic acid and alendronate.

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 comment.