PUBLIC SUMMARY DOCUMENT

Product: ALENDRONATE SODIUM, tablet equivalent to 70 mg alendronic acid, Fosamax® Once Weekly; ALENDRONATE SODIUM with COLECALCIFEROL, tablet equivalent to 70 mg alendronic acid with 70 micrograms colecalciferol, Fosamax Plus™; ALENDRONATE SODIUM with COLECALCIFEROL tablet equivalent to 70 mg alendronic acid with 140 micrograms colecalciferol, Fosamax Plus™ 70 mg/140 mcg; ALENDRONATE SODIUM with COLECALCIFEROL and CALCIUM CARBONATE, pack containing 4 tablets containing the equivalent of 70 mg alendronic acid with 140 micrograms colecalciferol and 48 tablets calcium carbonate 1.25 g (equivalent to 500 mg elemental calcium), Fosamax Plus D-Cal®

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

Date of PBAC Consideration: July 2011

1. Purpose of Application

The re-submission sought a change to the listing of these items from patients aged 70 years of age or older with a BMD T-score of -3.0 or less to patients aged 70 years of age or older with a BMD T-score of -2.5 or less.

2. Background

At its March 2008 meeting, the PBAC rejected an application to change the listing of Fosamax Once Weekly and Fosamax Plus (70 mg/70 mcg), from patients aged 70 years of age or older with a bone mineral density (BMD) T-score of -3.0 or less to patients aged 70 years of age or older with a BMD T-score of -2.5 or less, because of concerns of a less favourable ratio of harms to benefits in this wider population and an unacceptable cost-effectiveness ratio.

3. Registration Status

Fosamax Once Weekly (alendronic acid 70 mg) was TGA registered on 9 February 2001 for the treatment of osteoporosis.

Fosamax Plus (70/70 and 70/140) were TGA registered on 8 March 2006 and 14 May 2008 respectively, for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended.

Fosamax Plus D-Cal was TGA registered on 25 March 2010 for treatment of osteoporosis in select patients where vitamin D and calcium supplementation is recommended.

Prior to treatment with all presentations, osteoporosis must be confirmed by the finding of low bone mass of at least 2 standard deviations below the gender specific mean for young adults or by the presence of osteoporotic fracture.

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 of age 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.

The PBAC agreed that the wording of the requested restriction was appropriate.

5. Clinical Place for the Proposed Therapy

The submission stated that a change to a BMD T-score of -2.5 or less will bring the PBS listing closer to meeting the clinical needs of Australians with osteoporosis and align with the treatment guidelines recommended by various professional organisations, such as the Royal Australian College of General Practitioners and Osteoporosis Australia.

6. Comparator

As previously, the submission nominated watchful waiting (patient monitoring and standard management with calcium and vitamin D) as the primary comparator.

The PBAC considered at its March 2008 meeting that the nominated comparator was appropriate.

7. Clinical Trials

As previously, the resubmission presented data from all patients in the Clinical Fracture Arm of the Fracture Intervention Trial (FIT-CFA) and a post hoc analysis of results for those with BMD T-score ≤ -2.5.

Publication details of the FIT-CFA trial have been previously reported in the March 2008 PSD.

8. Results of Trials

Results from the FIT-CFA trial have been previously reported in the March 2008 PSD.

The PBAC acknowledged that the results presented in the submission indicated that there were clinical benefits associated with alendronate treatment in the patients with BMD T-score ≤-2.5, but remained concerned that the incremental benefit associated with the requested change to alendronate's PBS listing (i.e. any benefit in patients with BMD T-score between -2.5 and -3.0) remained unknown.

A post-hoc subgroup analysis for those patients with T-scores between -3.0 and -2.5 from the pivotal FIT-CFA study was provided by the sponsor in its pre-PBAC response. Statistically significant reductions in outcomes for any clinical fracture and for hip fracture were found for this sub-group that were similar to those with T-score ≤-2.5. The test for interaction for the relative risk (age at randomisation; T-score at femoral neck; fall history in past 12 months) did not suggest treatment effect variation.

The submission presented new safety data from the FIT-CFA trial (all patients) on gastrointestinal events, as well as more detailed analyses of events of interest in the published literature i.e., osteonecrosis of the jaw (ONJ), atypical subtrochanteric or diaphyseal fractures of the femur and oesophageal cancer, focussing on adverse events in adults taking alendronate for the management of osteoporosis.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The re-submission described alendronate as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.

For PBAC's view, see Recommendation and Reasons

10. Economic Analysis

An updated modelled economic evaluation from the previous submission was presented with a base case population which included the additional group for which listing was sought, i.e. patients (aged ≥70 years) with a BMD T-score between -3.0 and -2.5. The PBAC had previously considered this was the most appropriate comparison. The submission used the Garvan Institute's fracture risk calculator to estimate baseline fracture risks. The base case incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) was between $15,000 and $45,000 for the alendronate combination products and lower but within the same range for the alendronate only product.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be between 10,000 and 50,000 in Year 5, at an estimated net cost to the PBS of less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended listing of alendronate for patients aged 70 years and above with a BMD of -2.5 or less on the basis of acceptable cost effectiveness and safety compared to placebo.

The PBAC agreed that the wording of the requested restriction was appropriate. The comparator, watchful waiting (patient monitoring and standard management with calcium and vitamin D) was also considered appropriate.

As previously, the resubmission presented data from all patients in the Clinical Fracture Arm of the Fracture Intervention Trial (FIT-CFA) and a post hoc analysis of results for those with BMD T-score ≤ -2.5. The PBAC agreed with the ESC that, although there were clinical benefits associated with alendronate treatment in the patients with BMD T-score ≤ -2.5, the relevant patients were those aged 70 years or older with a BMD T-score between -3.0 and -2.5. The PBAC considered that the key issue for the current submission was to determine the cost effectiveness of alendronate treatment specifically in patients who meet these criteria, rather than the broader population who would be eligible under the proposed new PBS restriction.

The PBAC noted that, in its Pre-PBAC Response following the ESC Advice, the sponsor provided the requested post-hoc subgroup analysis for those patients with T-scores between -3.0 and -2.5 from the pivotal FIT-CFA study. Statistically significant reductions in outcomes for any clinical fracture and for hip fracture were found for this sub-group that were similar to those with T-score ≤-2.5. The test for interaction for the relative risk (age at randomisation; T-score at femoral neck; fall history in past 12 months) did not suggest treatment effect variation.

Additionally, it was noted that the re-submission presented more detailed analyses of the rare safety events of concern with alendronate treatment (ONJ, atypical subtrochanteric or diaphyseal fractures of the femur, and oesophageal cancer). The risk-benefit assessment was an issue for PBAC consideration, given that the additional patients who would be treated under the submission's proposed PBS listing would have a lower risk of fracture but were likely to be at a similar risk of adverse events as patients currently eligible. The extended safety assessment from the sponsor covered changes to the approved Australian product information for alendronate products since 2007, additional observational studies and systematic reviews, together with the most recently available Periodic Safety Update Reports. Although the PBAC found these analyses reduced the uncertainty about these adverse events, the argument of comparable safety and tolerability of alendronate and placebo was not accepted by the PBAC, as in previous submissions.

An updated modelled economic evaluation from the previous submission was presented with a base case population which included the additional group for which listing was sought, i.e. patients (aged ≥70 years) with a BMD T-score between -3.0 and -2.5. The PBAC had previously considered this was the most appropriate comparison. The base case incremental cost effectiveness ratio (ICER) per QALY was between $15,000 and $45,000 for the alendronate combination products and lower but within the same range for the alendronate only product.

The PBAC considered that there was uncertainty associated with the baseline risk of fractures from the Garvan Institute's fracture risk calculator, as these were based on small numbers of patients in the relevant populations from the Dubbo Osteoporosis Epidemiology Study. In its Pre-PBAC Response, the sponsor stated that these provided the best estimates of fracture risks in Australia and were consistent with those that had guided previous PBAC decisions. The PBAC considered that, as per the original recommendation for primary prevention, the benefit of alendronate depends on the baseline risk of the patients and that there will likely be a smaller benefit in this new subgroup, based on the clinical evidence presented. However, the comparable ICERs in this submission to those which formed the basis of the previous recommendations, particularly with the lower priced alendronate monotherapy, alleviate some of the uncertainty in the model.

In response to previous PBAC concerns as to the likely extent to which adverse events would offset gains in terms of fracture rate reduction, sensitivity analyses were conducted to include the impact of hypothetical ONJ and atypical subtrochanteric or diaphyseal fractures. The PBAC noted that sensitivity analyses also showed that the ICER was relatively stable with respect to fracture risks and excess mortality.

The PBAC was advised that uptake in preventative population (70 years and over with a BMD of -3 or less) had not been as high as had been anticipated and although a high proportion of the population over 70 years would have a BMD of -2.5 or less, the uptake may be less than predicted in the submission.

Recommendation:
ALENDRONATE SODIUM, tablet equivalent to 70 mg alendronic acid;
ALENDRONATE SODIUM with COLECALCIFEROL, tablet equivalent to 70 mg alendronic acid with 70 micrograms colecalciferol;

ALENDRONATE SODIUM with COLECALCIFEROL tablet equivalent to 70 mg alendronic acid with 140 micrograms colecalciferol;
ALENDRONATE SODIUM with COLECALCIFEROL and CALCIUM CARBONATE, pack containing 4 tablets containing the equivalent of 70 mg alendronic acid with 140 micrograms colecalciferol and 48 tablets calcium carbonate 1.25 g (equivalent to 500 mg elemental calcium).

Restriction:	Authority required (STREAMLINED) 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. 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.
Maximum quantity:	4 (alendronate sodium, alendronate sodium with colecalciferol) ‡1 (alendronate sodium with colecalciferol and calcium carbonate)
Repeats:	5 (all presentations)

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

Merck Sharp and Dohme Australia welcomes the PBAC's decision and is pleased that alendronate will now be available for more patients over the age of 70 who have osteoporosis without a fracture.