Public Summary Document

Product:	Alendronate Sodium with Colecalciferol (vitamin D_3), tablet, 70 mg-70 micrograms (2800 i.u.), Fosamax® Plus
Sponsor:	Merck Sharp & Dohme (Australia) Pty Limited
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission sought an Authority Required listing for initial treatment of established osteoporosis in patients with fracture due to minimal trauma, in patients who require a supplemental intake of vitamin D.

2. Background

Alendronate sodium with colecalciferol (Vitamin D_3) has not previously been considered by the PBAC, however, the PBAC recommended listing alendronate 10 mg as a pharmaceutical benefit for established post-menopausal osteoporosis in patients with fracture due to minimal trauma at the September 1996 meeting. Listing was implemented on 1 February 1997.

At the December 2001 meeting the PBAC recommended the listing of alendronate 70 mg (Fosamax Once Weekly) tablet with the same restriction as the alendronate 10 mg tablet, on a cost minimisation basis with a 70 mg tablet taken weekly accepted as providing similar safety and efficacy to a 10 mg tablet taken daily. Listing was implemented on 1 April 2001.

3. Registration Status

At the time of consideration by the PBAC, alendronate sodium with colecalciferol (Vitamin D_3) was not registered by the TGA. However, at its meeting of 6-7 October 2005, the ADEC had no objection to the product being registered by the TGA for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended.

4. Listing Requested and PBAC's View

The submission requested the following listing based upon the current PBS listing for alendronate tablet 70 mg. Bolded text denotes the proposed changes.

<u>Authority required</u>

Initial treatment for established osteoporosis in patients with fracture due to minimal trauma, **in patients who require a supplemental intake of vitamin D.** 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 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;

Continuing treatment for established osteoporosis in patients with fracture due to minimal trauma, **in patients who require a supplemental intake of vitamin D**, where the patient has previously been issued with an authority prescription for this drug.

NOTE: Fosamax Plus provides a supplemental intake of vitamin D. The quantity of colecalciferol present in Fosamax Plus is not sufficient to use as the sole treatment for correction of vitamin D deficiency.

The PBAC considered that 400 iu colecalciferol per day would not be adequate for patients who are genuinely vitamin D deficient, but may assist in maintaining normalised levels in patients requiring supplementation of vitamin D. However, it was not considered necessary to include the words 'in patients who require a supplemental intake of vitamin D', in the restriction, in view of the NOTE.

5. Clinical Place for the Proposed Therapy

Fosamax Plus is a combination tablet, comprising a 70 mg dose of alendronate sodium and 2800 IU of colecalciferol. The tablet is designed to provide a bioequivalent dose to the once-weekly alendronate 70 mg tablet, and a standardised dose of colecalciferol, which may aid in providing the recommended daily patient intake of vitamin D.

6. Comparator

The submission nominated alendronate 70 mg once weekly as the comparator. The PBAC agreed this was appropriate.

7. Clinical Trials

The submission presented three trials to demonstrate the bioequivalence and bioavailability of the active components of Fosamax Plus and one pivotal efficacy study (Protocol 227), a 15-week, double-blind, randomised active controlled multi-centre study.

None of the studies had been published at the time of submission.

8. Results of Trials

In the efficacy study there were statistically significantly fewer patients with vitamin D levels in the insufficiency range in the alendronate plus colecalciferol group (11%) compared to the alendronate alone group (32%).

Statistically there were significantly fewer patients with 25OHD (25 hydroxy vitamin D) levels in the deficiency range in the alendronate plus colecalciferol group (1%) compared with the alendronate alone group (13%).

9. Clinical Claim

The submission claimed that Fosamax Plus 70 mg/2800IU once weekly is no worse than Fosamax 70 mg Once Weekly in terms of either safety or efficacy, and confers the advantage of better management of vitamin D levels in osteoporotic individuals. Whilst the PBAC accepted the claim that the combination product may assist those patients who required vitamin D supplementation, members were concerned that the dose would not be adequate to treat patients with vitamin D insufficiency, and furthermore that prescribers may not be aware of this.

10. Economic Analysis

The submission did not present an economic evaluation as the submission requested the same price as alendronate 70 mg without a premium component for the addition of vitamin D.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of patients by year 4 of listing would be >200,000. The PBAC did not find this estimate to be adequately justified given it was based on the projected market share for alendronate alone rather than allowing for the uncertainty of increased use due to the vitamin D component.

The submission estimated that the financial cost/year to the PBS would be zero as Fosamax Plus would only gain patients from alendronate 70 mg and risedronate 35 mg which were priced the same as Fosamax Plus. The PBAC considered this to be a reasonable claim.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis with the alendronate sodium 70 mg formulation, on a mg per mg basis of the alendronate component. Although the PBAC noted that alendronate plus vitamin D provides access to a combination product for patients with established osteoporosis who may require vitamin D supplementation, the Committee expressed concern over the dose of vitamin D included in this combination product. The PBAC considered that 400 iu colecalciferol per day, would not be adequate for those patients who are genuinely vitamin D deficient, but may assist in maintaining normalised levels in patients requiring supplementation of vitamin D.

The Committee noted that the submission had not requested a price premium based on a reduced fracture risk of alendronate plus vitamin D, as compared to alendronate alone. The PBAC also noted the findings of the Women's Health Initiative study - *Calcium plus Vitamin D Supplementation and the Risk of Fractures* as reported in the *New England Journal of Medicine,* February 16 2006. This study presented some supportive evidence of reduced hip fracture risk in patients receiving supplemental vitamin D at a dose of 400 iu per day, in the sub-group of patients who adhered to treatment. The overall conclusions of the study however, were that among healthy post menopausal women, calcium with vitamin D supplementation, at a dose of 1000 mg and 400 iu per day respectively, did not significantly reduce hip fracture. Baseline vitamin D levels of patients who entered the study were not assessed, therefore it was not possible to draw definite conclusions from the results.

The PBAC remained concerned that prescribers may not be aware that the dose of vitamin D included in this combination product is not sufficient to adequately treat vitamin D deficiency. Given the quality use of medicines issues likely to arise from the PBS listing of this product, the Committee requested that the National Prescribing Service develop educational activities to bring this issue to attention of potential prescribers and patients.

Recommendation

ALENDRONATE SODIUM with COLECALCIFEROL (vitamin D3), tablet,
70 mg-70 micrograms (2800 i.u.)

Restriction:	<u>Authority required</u> Initial treatment, as the sole PBS-subsidised anti-resorptive agent, for established 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 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;

Continuing treatment, as the sole PBS-subsidised anti-resorptive agent, for established osteoporosis in patients with fracture due to minimal trauma, where the patient has previously been issued with an authority prescription for this drug.

NOTE
Fosamax Plus provides a supplemental intake of vitamin D. The amount of colecalciferol present in Fosamax Plus is not sufficient to use as the sole treatment for correction of vitamin D deficiency.

Maximum Quantity: 4
Repeats: 5

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

No comment.