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®.
Sponsor: Merck Sharp & Dohme (Australia) Pty Limited.
Date of PBAC Consideration: March 2008.

1. Purpose of Application

To seek a change to the listing of these items 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.

2. Background

At its meeting in July 2006 the PBAC made a recommendation to list alendronate as the sole PBS-subsidised anti-resorptive agent for the treatment of osteoporosis in patients aged 70 years of age or older and with a BMD T-score of -3.0 or less on a cost effectiveness basis over placebo.

The current submission seeks to determine the cost-effectiveness of alendronate at the new prices in a population of patients aged 70 years of age or older and with a BMD T-score of -2.5 or less. The submission argues that due to the 12.5% price reduction (effective September 2007) and the mandated decrease by 2% each year for the next three years, the cost-effectiveness of alendronate has improved and thus use in a broader patient population is now warranted.

3. Registration Status

Fosamax Plus Once Weekly was registered by the TGA on 8 March 2006 and is indicated for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended.

Fosamax Once Weekly was registered by the TGA on 9 February 2001 and is indicated for the treatment of osteoporosis. Osteoporosis must be confirmed by the finding of low bone mass of at least two 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 considered the wording of the requested restriction appropriate.

5. Clinical Place for the Proposed Therapy

If alendronate PBS-eligibility were expanded to include patients with a BMD T-score of -2.5 or less it would extend treatment for the prevention of fracture to osteoporotic patients whose absolute risk of fracture is less than for those covered under the current listing.

6. Comparator

The submission nominates watchful waiting (patient monitoring and standard management with calcium and vitamin D, i.e. placebo) as the primary comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission made no changes to the trial data presented in the previous submission of July 2006, i.e. Fraction Intervention Trial (FIT) data. New supplementary data were presented from the FIT Long-Term Extension trial (FLEX) in women who had completed three years of alendronate treatment in the treatment groups of the FIT trial, both with and without vertebral fracture at FIT baseline (i.e. both vertebral fracture arm (VFA) and clinical fracture arm(CFA)). The FLEX trial was a randomised controlled trial, which investigated the effect of continuation of alendronate on fracture rates for a further five years post-FIT trial.

These trials have been published as detailed below.

Trial/First author	Publication title	Publication citation
Cummings et al. (FIT)	Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures.	JAMA 1998; 280:2077-82.
Black DM et al. (FLEX)	Effects of continuing or stopping alendronate after 5 years of treatment, the Fracture Intervention Trial Long-Term Extension (FLEX: a randomized trial.	JAMA 2006; 296: 2927–2938.

8. Results of Trials

The key results are summarised in the table below.

Proportion of patients in the FIT CFA T ≤-2.5 subgroup who experienced fractures during the 4.2 years of follow-up

Fracture type	Alendronate N=819	Placebo N=812	RR (95% CI)	RD (95% CI)	NNT
Primary outcome					
Any clinical	107 (13.1%)	159(19.6%)	0.67 (0.53, 0.83)	-6.5% (-10.1, -2.9)	15
Secondary outcomes					
Clinical vertebral	12 (1.5%)	14 (1.7%)	0.85 (0.40, 1.79)	-0.3% (-1.6, 1.0)	386
Hip	8 (1.0%)	18 (2.2%)	0.44 (0.20, 0.98)	-1.2% (-2.6, 0.0)	81
Wrist	34 (4.2%)	38 (4.7%)	0.89 (0.57, 1.39)	-0.5% (-2.6, 1.5)	189
Non-hip, -spine, or -wrist	71 (8.7%)	111 (13.7%)	0.63 (0.48, 0.84)	-5.0% (-8.1, -2.0)	20
Non-vertebral (combined)	101 (12.3%)	150 (18.5%)	0.67 (0.53, 0.84)	-6.1% (-9.7, -2.7)	16
	N=757	**N=763**			
Morphometric Vertebral	22 (2.9%)	44 (5.8%)	0.50 (0.31, 0.83)	-2.9% (-5.0, -0.8)	35
Multiple vertebral	2 (0.3%)	6 (0.8%)	0.34 (0.08, 1.45)	-0.5% (-1.2, 0.2)	192

Abbreviations: N = number of patients with an incident fracture, CI = confidence interval, NNT = number-needed-to-treat, RR = relative risk, RD = risk difference.

The PBAC noted these are the same data presented in the previous submission. All clinical fractures combined, i.e. all fractures causing symptoms, showed a statistically significant rate reduction, as did morphometric (non-symptomatic) vertebral fracture, and non-hip, non-

spine, non-wrist fracture. Of the three major clinical fracture types (hip, vertebral, and wrist), hip fractures are the only type that show a significant fracture rate reduction with alendronate treatment (though the upper limit of the 95% CI is 0.98).

In the FLEX extension trial a *post hoc* analysis of women with BMD T scores ≤-2.5 (who had completed at least three years of alendronate treatment in FIT) did not show any statistically significant differences in fracture rates between women who continued alendronate treatment for a further five years compared with women who ceased treatment.

The trial data did not show a marked increase in adverse effects.

The PBAC noted that an extended assessment of harms shows that gastrointestinal problems remain an issue of concern.

The assessment noted recent reports (2006-2007) which suggest that the suppression of bone turnover by alendronate and other bisphosphonates may lead to increased risk of fracture, particularly of the subtrochanteric region of the femur, which has not been considered in previous submissions.

With respect to osteonecrosis of the jaw (ONJ), the assessment advised of a recent Australian study that identified cases of ONJ by a postal survey of Australian oral and maxillofacial surgeons and other dental specialists and Adverse Drug Reactions Advisory Committee (ADRAC) data, correlated with prescription and dental extraction data (Mavrokokki et al, 2007). The findings were:

- the frequency of ONJ in osteoporotic patients treated with bisphosphonates was 1 in 8,470 (0.01%)
- the overall frequency of extraction-related ONJ associated with alendronate is 1 in 1,130 (0.09%)
- the mean total dose of oral alendronate at the onset of ONJ was 9,060 (± 7,269) mg, which corresponds to an average time to onset from initiation of therapy (with 100% compliance) of 2.5 years
- osteoporosis patients accounted for nearly one third of patients with ONJ associated with a bisphosphonate (36/114, 31.6%)

The sponsor considered these events, although serious, to be extremely rare, and would have negligible impact on the risk/benefit ratio when viewed in the context of the number of fractures which will occur in an untreated population.

9. Clinical Claim

The submission claimed that alendronate is associated with superior efficacy and similar toxicity compared with placebo.

Based on the information available to the PBAC at the meeting it was unable to accept that alendronate has superior efficacy and similar toxicity compared with placebo.

10. Economic Analysis

The PBAC noted the current submission failed to identify how to incorporate the adverse events associated with alendronate treatment into the model. This was considered relevant to the current request, which sought to extend alendronate's listing to a broader, primary

prevention population where the benefits-to-harms ratio is particularly important. This was addressed by the sponsor with the impact shown to be very small.

The type of economic evaluation presented was a cost-utility analysis. The model has three health states: well (free from fracture), post-fracture, and death, with a time horizon of 10 years, and uses a Monte Carlo simulation.

The submission presented the base case results of the modelled economic evaluation using results for the entire population with BMD ≤ -2.5. The PBAC considered that the more appropriate base case was the population who are currently not eligible for alendronate treatment, but would be eligible if the proposed restriction was recommended, i.e. patients with a BMD T-score between -3.0 and -2.5, rather than the entire population with a BMD T-score ≤ -2.5.

A sensitivity analysis with the population with BMD T-scores of -3.0 to -2.5 was conducted with a time horizon of 10 years. Incremental costs per Quality-Adjusted Life-Year (QALY) were calculated to be:

Population	ICER range
Males 70-74 years	$75,000 to $105,000
Males 75-79 years	$15,000 to $45,000
Males 80-84 years	$15,000 to $45,000
Females 70-74 years	$45,000 to $75,000
Females 74-79 years	$15,000 to $45,000
Females 80-84 years	$15,000 to $45,000

The model was very sensitive to the baseline and relative risk estimates of vertebral and hip fractures, as well as the time horizon used. The PBAC noted the optimal duration of alendronate treatment has not been established, but limited data suggest that it may be appropriate for non-high risk patients to stop treatment after five years. The data suggest that discontinuing therapy after five years does not reverse the benefits of prior alendronate treatment.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of packs dispensed per year to be in the range of 50,000 to 100,000 in Year 5.

The financial cost per year to the PBS was estimated to be less than $10 million in Year 5. This estimation is only for the increase in usage in patients with no prevalent fracture and BMD T-scores ≤-2.5 and >-3.0, which is additional to those already funded under the existing restriction i.e. with a prevalent fracture or BMD T-score ≤-3.0.

12. Recommendation and Reasons

The PBAC considered the wording of the requested restriction and the nominated comparator were appropriate.

The PBAC noted that of the three major types of osteoporotic clinical fractures, alendronate only showed a statistically significant reduction in hip fractures in women with a BMD T score <-2.5 in the FIT CFA trial, compared with placebo. There was no statistically significant effect in this subgroup on the rate of the other two major fractures types, clinical

(symptomatic) vertebral fracture and wrist fractures. There was a statistically significant reduction in morphometric (non-symptomatic) vertebral fractures and non-hip, non-spine, non-wrist fractures.

The comparative toxicity of alendronate was of concern to the PBAC given that the request for a further extension for use in the primary prevention setting would make alendronate available to more than twice as many patients as under the current restriction. The PBAC considered there was a change in risk benefit ratio in making alendronate available to a population at lower risk of fracture and at the same risk of adverse events.

The PBAC noted that although the trial data do not show a marked increase in adverse effects, the extended assessment of harms shows that gastrointestinal problems remain an issue of concern.

The PBAC also noted recent reports (2006-2007) suggest that suppression of bone turnover by alendronate and other bisphosphonates may lead to increased risk of fracture, particularly of the subtrochanteric region of the femur, which has not been considered in previous submissions. These emerging concerns of increased risk of insufficiency fracture have not been addressed in the submission, although they were later addressed by the sponsor.

With respect to increasing reports of osteonecrosis of the jaw, which is a serious adverse effect and difficult to treat, given this is a rare condition, somewhat lesser weight was placed on the impact of this adverse event compared to those mentioned above.

The PBAC was therefore unable to accept the clinical claim that alendronate is associated with superior efficacy and similar toxicity compared to placebo.

The PBAC further considered the most appropriate comparisons in the modelled economic evaluation were those relating only to the additional group for which listing was sought. In this group the weighted average incremental cost effectiveness ratio (ICER) per QALY was between $45,000 and $75,000 for men and between $15,000 and $45,000 for women, higher than those accepted when alendronate was recommended for listing for patients with a BMD T-score <-3. The PBAC noted that inclusion of the adverse events in the modelled evaluation would, to some extent, offset gains in terms of reduction of fracture rates and further increase the ICERs, and that not only is the ICER higher for the incremental group than the average cost-effectiveness across the whole population, but it is more uncertain, because of the altered risk-benefit ratio.

The PBAC rejected the application because of concerns of a less favourable ratio of harms to benefits in this wider population and an unacceptable cost-effectiveness ratio.

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 disagrees with the PBAC's decision. The harms to benefits ratio in the requested population has been accepted by the TGA and has recently been reviewed and accepted by the TGA in respect of FOSAMAX PLUS. The incidence of the adverse events particularly noted by the PBAC is very rare and causality of insufficiency fractures has not been demonstrated. For more information, the sponsor refers you to www.msd-australia.com.au.