

PUBLIC SUMMARY DOCUMENT

Product: Alendronate sodium, tablet, 70 mg Fosamax[®] Once Weekly,
Alendronate sodium with Colecalciferol, tablet, 70 mg – 70 micrograms, Fosamax Plus[®]

Sponsor: Merck Sharp and Dohme (Australia) Pty Ltd

Date of PBAC Consideration: July 2006

1. Purpose of Application

The submission sought an extension to the PBS-listing of alendronate tablet 70 mg (Fosamax Once Weekly) and alendronate tablet 70 mg with colecalciferol 70 mcg (Fosamax Plus) to include patients with low bone mineral density (BMD) and without prevalent fracture.

2. Background

Alendronate 10 mg tablet was recommended for listing at the February 1997 PBAC meeting, the 70 mg tablet was listed on 1 May 2001 and the 70 mg tablet with colecalciferol 70 mcg was listed on 1 August 2006.

The PBAC has considered and rejected a number of applications to extend the listing of alendronate (and risedronate and raloxifene) to include patients without prevalent fracture for alendronate (and risedronate and raloxifene).

The most recent consideration was a joint submission to the March 2005 meeting.

The PBAC rejected the application because of uncertain but over-estimated extent of long-term clinical benefit and resulting uncertain cost-effectiveness which does not provide a sufficiently confident basis to conclude that the cost-effectiveness is acceptable.

3. Registration Status

Alendronate 70 mg tablets were first approved by TGA on 7 February 2001 for the treatment of osteoporosis in postmenopausal women.

With amendment, the current TGA registered indication for Fosamax for the treatment of osteoporosis is:

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. Requested Listing and PBAC's view:

An authority required listing was sought for:

Initial treatment of osteoporosis for patients at high risk of fracture.

A high risk of fracture is defined as:

- A) The presence of an existing 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 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; OR

- B) A bone mineral density (BMD) T-score of -3.0 or less in a patient aged 70 years or older. The initial authority application must state the date, site (femoral neck OR lumbar spine) and score of the qualifying BMD measurement.

The radiological and/or laboratory reports supporting eligibility under (b) must be available for audit by the HIC.

Continuing treatment for osteoporosis in patients with either a fracture due to minimal trauma and/or a bone mineral density T score of -3.0 or less, where the patient has previously been issued with an authority prescription for this drug.

The revised eligibility criteria as detailed above were proposed by the sponsor in its pre-sub-Committee response.

The PBAC's view was that BMD scanning of the patients who will potentially become eligible for PBS-subsidised treatment under the expanded listing is not currently funded through Medicare and that the logistics and funding of this BMD scanning would require resolution prior to any PBS listing. *See also the Recommendations and Reasons.*

5. Clinical Place for the Proposed Therapy

If alendronate were listed on the PBS for prevention of fracture, it would provide a treatment for the prevention of fracture in osteoporotic patients considered to have a similar risk of fracture as patients who have had a prior fracture due to minimal trauma.

6. Comparator

The comparator was placebo or 'watchful waiting' (patient monitoring and standard management with calcium and vitamin D).

7. Clinical Trials

The key trial in the current re-submission was the same as that presented in previous alendronate submissions, the Fracture Intervention Trial (FIT). The re-submission was based on an *a priori* defined subgroup analysis of patients with a BMD T-score ≤ -2.5 in the Clinical Fracture Arm of FIT. This trial was published as:

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.

8. Results of Trials

The submission provided the key results of the Fracture Intervention Trial (FIT) Clinical Fracture Arm (CFA) for the entire population (CFA) and the subgroup of patients with a

baseline BMD T-score ≤ -2.5 (CFA T ≤ -2.5) to show comparative effectiveness (table below).

Fracture/ population	Alendronate	Placebo	RD (95% CI)	RR (95% CI)
Any clinical				
- CFA	272/2214 (12.3%)	312/2218 (14.1%)	-1.8% (-3.8, 0.2)	0.87 (0.75, 1.02)
- CFA T ≤ -2.5	107/819 (13.1%)	159/812 (19.6%)	-6.5% (-10.1, -2.9)	0.67 (0.53, 0.83)
Morphometric Vertebral				
- CFA	43/2057 (2.1%)	78/2077 (3.8%)	-1.7% (-2.7, -0.6)	0.56 (0.39, 0.80)
- CFA T ≤ -2.5	22/757 (2.9%)	44/763 (5.8%)	-2.9% (-5.0, -0.8)	0.50 (0.31, 0.83)
Clinical vertebral				
- CFA	18/2214 (0.8%)	27/2218 (1.2%)	-0.4% (-1.0, 0.2)	0.67 (0.37, 1.20)
- CFA T ≤ -2.5	12/819 (1.5%)	14/812 (1.7%)	-0.3% (-1.6, 1.0)	0.85 (0.40, 1.79)
Non-vertebral				
- CFA	261/2214 (11.8%)	294/2218 (13.3%)	-1.5% (-3.4, 0.5)	0.89 (0.76, 1.04)
- CFA T ≤ -2.5	101/819 (12.3%)	150/812 (18.5%)	-6.1% (-9.7, -2.7)	0.67 (0.53, 0.84)
Hip				
- CFA	19/2214 (0.9%)	24/2218 (1.1%)	-0.2% (-0.8, 0.4)	0.79 (0.44, 1.43)
- CFA T ≤ -2.5	8/819 (1.0%)	18/812 (2.2%)	-1.2% (-2.6, 0.0)	0.44 (0.20, 0.98)
Wrist				
- CFA	83/2214 (3.7%)	70/2218 (3.2%)	0.6% (-0.5, 1.7)	1.19 (0.87, 1.62)
- CFA T ≤ -2.5	34/819 (4.2%)	38/812 (4.7%)	-0.5% (-2.6, 1.5)	0.89 (0.57, 1.39)
Other*				
- CFA	182/2214 (8.2%)	227/2218 (10.2%)	-2.0% (-3.7, -0.3)	0.80 (0.67, 0.97)
- CFA T ≤ -2.5	71/819 (8.7%)	111/812 (13.7%)	-5.0% (-8.1, -2.0)	0.63 (0.48, 0.84)

CFA: Clinical Fracture Arm of the FIT; CFA T ≤ -2.5 : subgroup analysis of patients with a BMD T-score ≤ -2.5 in the Clinical Fracture Arm of the FIT; *Non-hip, -spine, -wrist

The results of the FIT trial for any clinical fractures show that overall in the CFA arm, that is, patients who had no prevalent vertebral fracture at the time of enrolment in the trial, the overall risk of a clinical fracture was no different between alendronate and placebo. There was a relative risk of 0.87 with confidence intervals that overlap 1, during an average follow-up period of 4 years. With respect to the sub-group, the fracture risk is higher, as shown by the placebo event rate of 14% in the overall population as opposed to 19.6% in the sub-group. In addition, the relative risk reduction is statistically significant for any clinical fracture, morphometric vertebral, non-vertebral fractures, hip and other vertebral fractures. The test for effect modification conducted during the evaluation also confirmed that that this subgroup is an effect modifier for these outcomes. Therefore, although the overall results are not significant there is a qualitative interaction in one subgroup that is significantly different than the overall group.

No new toxicity data were presented in the re-submission. The toxicity data from the previous re-submission indicated similar rates of adverse events, including upper gastrointestinal adverse events in alendronate- and placebo-treated patients.

9. Clinical Claim

The submission claimed that alendronate has significant advantages in effectiveness over placebo and has similar or less toxicity.

For the PBAC's views see the Recommendation and Reasons

10. Economic Analysis

A preliminary economic evaluation was presented. The trial-based incremental discounted cost per extra discounted patient avoiding clinical fracture or vertebral fracture over four years compared to placebo was estimated to be between \$15,000 and \$45,000.

An updated modelled economic evaluation was presented. The structure of the model was the same as that presented in the March 2005 re-submission. There were, however, concerns regarding the appropriateness of the baseline fracture risks and fracture multipliers used in the model, which may significantly overestimate the effectiveness and cost-effectiveness of alendronate.

The ESC requested that additional calibration exercises be undertaken in order to establish the most reliable estimate for baseline fracture rates for the Australian population and take into account all fracture types not only hip fractures.

The final set of baseline fracture rates is presented below.

Population based case	Hip fracture		Clinical vertebral fracture		All vertebral	
	T-score<-3.0		T-score<-3.0		T-score<-3.0	
	Male	Female	Male	Female	Male	Female
70-74	1.9%	1.2%	1.4%	0.6%	4.7%	2.1%
75-79	0.5%	1.7%	1.3%	0.3%	4.4%	1.0%
80+	2.2%	3.0%	1.6%	2.7%	5.3%	9.1%

The incremental costs per QALY gained decreased as age increased. The incremental cost-effectiveness ratios based on the re-calibration of baseline fracture rates ranged from less than \$15,000 to between \$30,000 and \$68,000 in females in the 80-84 and 70-74 years age brackets respectively, and from \$16,000 to \$32,000 in males in 80-84 and 70-79 years age brackets respectively.

11. Estimated PBS Usage and Financial Implications

The likely number of patients on therapy in the fourth year of listing was estimated to be between 50,000 to 100,000, while the financial cost to the PBS was estimated to be between \$15-\$30 million in the fourth year of listing.

12. Recommendation and Reasons

The PBAC recommended the listing of 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

revised eligibility criteria were proposed by the sponsor in its pre-sub-Committee response.

The PBAC agreed that the data presented from the clinical fracture arm (CFA) of the Fracture Intervention Trial (FIT) supported the conclusion that alendronate reduces morphometric vertebral, hip, non-vertebral and other fractures, but not clinical vertebral fractures, in the patients with a T score ≤ -2.5 . A T score < -2.5 was a treatment effect modifier. There remained some residual areas of uncertainty namely that the primary outcome (analysis of all clinical fractures in the entire population in the CFA arm) of CFA-FIT was negative, whether the subgroup from the CFA-FIT was representative of the proposed PBS population, and the likely post-hoc specification of the sub-group in CFA-FIT. However the Committee agreed that overall, there was reasonably good, but not conclusive evidence that alendronate is effective in the high risk group of the CFA arm which approximates the proposed patient population in the Australian context. There was trial evidence in both absolute terms as well as relative terms, supporting the hypothesis that the benefit of alendronate depends on the baseline risk of the patients and that there will be a higher benefit in the subgroup.

The PBAC did not accept the submission's claim that the toxicity of alendronate is equivalent to placebo. The Committee considered this claim to be untrue for gastrointestinal events and for osteonecrosis of the jaw, which although rare, is very difficult to treat.

The Committee noted that the same economic model was presented as in the March 2005 submission but with updated unit costs, re-analysed baseline fracture risks, revised health state utilities and BMD screening costs included. Although the economic model in the submission was initially for the 60+ age group with a T score ≤ -2.5 which resulted in cost effectiveness ratios that were uncertain and high, the data from the narrower indication (age ≥ 70 , T-score < -3.0) resulted in acceptable cost effectiveness, with the cost per QALY ranging from less than \$15,000 to between \$45,000 and \$75,000 in females in the 80 – 84 and 70 – 74 age brackets respectively, and from \$15,000 to \$45,000 in males in the 80 – 84 and 70 – 74 age brackets respectively.

An area of major concern to the PBAC was that of case finding through BMD scanning. The Committee noted that BMD scanning of the patients who will potentially become eligible for PBS-subsidised treatment under the expanded listing is not currently funded through Medicare. This issue was not addressed at the time of the PBAC consideration. The PBAC considered that the logistics and funding of BMD scanning requires resolution prior to any PBS listing.

The PBAC recommended the current restriction for use in secondary prevention not be changed at the present time.

Recommendation

Alendronate, tablet, 70 mg; Alendronate sodium with colecalciferol (vitamin D3), tablet, 70 mg-70 micrograms (2800 i.u.)

Amend restriction to read:

Authority required

Initial treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in patients aged 70 years of age or older and with a BMD T-score of -3.0 or less. The initial authority application must state the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.

Continuing treatment as the sole anti-resorptive agent for osteoporosis in patients aged 70 years of age or older and with a BMD T-score of -3.0 or less where the patient has previously been issued with an authority prescription for this drug.

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 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;

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

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 & Dohme welcomes the PBAC's decision to make alendronate available on the PBS for use in primary prevention of osteoporosis. The sponsor notes the PBAC's concerns with respect to the reimbursement of BMD testing and is working with the Department of Health to put a solution in place.