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 calcium), Fosamax Plus D-Cal®
Sponsor: Merck Sharp & Dohme (Australia) Pty Limited
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission requested an extension to the current Authority Required (STREAMLINED) listing to include the treatment of corticosteroid-induced osteoporosis (CIO) in patients on long term (≥ 3 months) high dose (≥ 7.5 mg per day prednisolone or equivalent) corticosteroid therapy and a bone mineral density (BMD) T-score ≤ -1.5.

2. Background

This drug had not previously been considered by the PBAC for this indication.

3. Registration Status

Alendronate 70 mg tablets were TGA registered as of 9 February 2001, for the treatment of osteoporosis. 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.

Alendronate sodium 70 mg with colecalciferol 70 micrograms and alendronate sodium 70 mg with colecalciferol 140 micrograms were TGA registered as of 8 March 2006 and 14 May 2008 respectively, for the treatment of osteoporosis in select patients where vitamin D supplementation is recommended.

Alendronate sodium 70 mg with colecalciferol 140 micrograms and calcium carbonate 1.5 g (equivalent to 500 mg elemental calcium) composite pack was TGA registered on 25 March 2010 for the treatment of osteoporosis in select patients where vitamin D and calcium supplementation is recommended. Prior to treatment, 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 corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.
The duration and dose of corticosteroid therapy together with 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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Corticosteroids are widely used in a variety of chronic non-infectious inflammatory diseases because of their immunosuppressant and anti-inflammatory properties. However, patients receiving high doses of corticosteroids are at increased risk of significant bone loss and fractures. The two most serious adverse events reported are osteoporosis and related fractures.

Alendronate would provide an alternative oral bisphosphonate treatment for corticosteroid-induced osteoporosis in patients on long-term corticosteroid therapy, who are at risk of fracture.

6. Comparator

The submission nominated risedronate as the comparator. The PBAC considered this was appropriate.

7. Clinical Trials

The submission presented an indirect analysis comparing alendronate with risedronate using placebo as the common comparator. For this comparison, the submission presented four randomised controlled trials comparing alendronate with placebo and two direct randomised comparative trials and meta-analysis comparing risedronate and placebo in patients with glucocorticoid-induced osteoporosis.

The trials published at the time of submission are listed below:

Trial ID/First author	Protocol title/Publication title	Publication citation
Alendronate Studies		
Saag et al	Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis.	N Engl J Med 1998; 339:292-9
Adachi et al	Two-Year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids.	Arthritis and Rheumatism 2001; 44(1): 202-211
De Nijs et al	Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis.	N Engl J Med 2006; 355: 675-84
Stoch et al	Once-Weekly oral alendronate 70mg in patients with glucocorticoid-induced bone loss: a 12-month randomised, placebo-controlled clinical trial.	J Rheumatol 2009; 36: 1705 -14.
Risedronate Studies		
RCT 009893 Reid D.M.	Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: A randomized trial	Journal of Bone and Mineral Research 2000; 15(6): 1006-1013
RCP 009993 Cohen S	Risedronate therapy prevents corticosteroid-induced bone loss: A twelve-month, multicentre, randomized, double-blind, placebo-controlled, parallel-group study.	Arthritis & Rheumatism 1999; 42(11): 2309-2318
Wallach 2000 (meta-analyses of direct randomised trials)	Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy.	Calcified Tissue International 2000; 67: 277-285

Kanis 2007 (systematic review)	Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. (Includes all trials listed above).	Health Technol Assess 2007: 11(7)

8. Results of Trials

The efficacy of alendronate and risedronate were indirectly compared and presented as a bone mineral density analysis and fracture risk analysis.

Bone Mineral Density (BMD) Analysis

The indirect comparison of baseline percentage changes in BMD at the femoral neck showed that risedronate was associated with a slightly better increase in BMD compared with alendronate although this was not statistically significant. The submission stated that this difference was reduced if the Adachi paper, the extension study to Saag (1998), was included which may indicate that the duration of alendronate therapy is important. The difference may also be due to the large placebo effect seen in the Stoch paper.

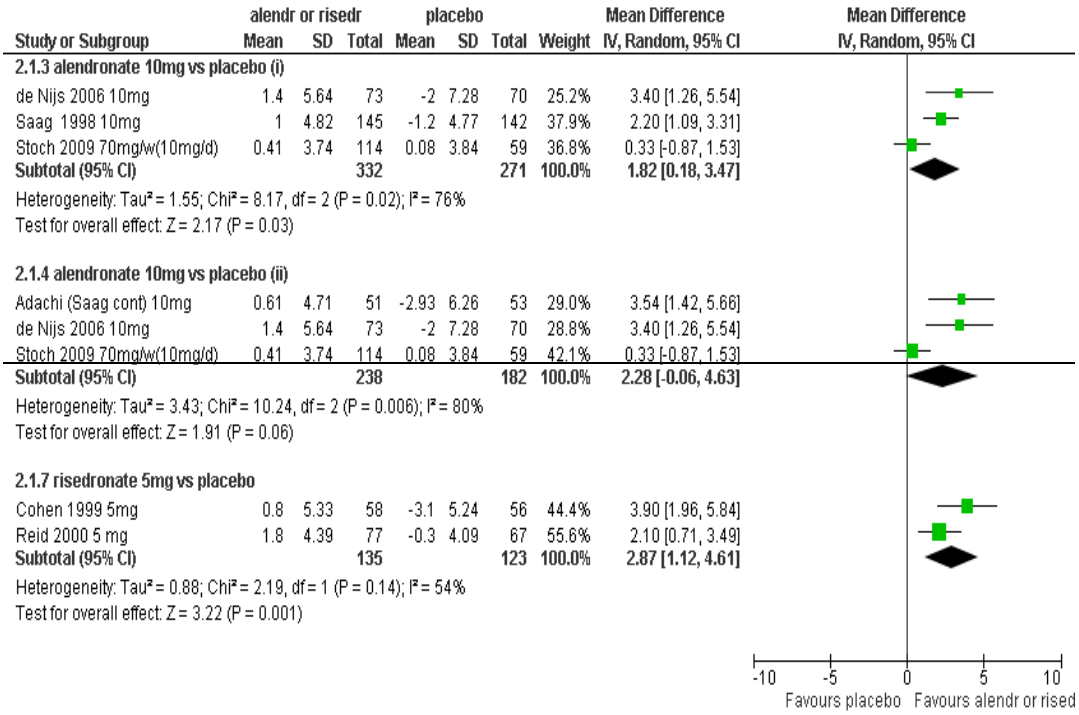
Indirect comparison of alendronate vs. risedronate via placebo as common comparator: WMD in percentage change in BMD at the femoral neck

Study ID and active dose group(s) of placebo controlled trials included in the indirect comparison of alendronate vs. risedronate				**Indirect estimate of effect:**		
alendronate vs. placebo	**alendronate dose group**	**risedronate vs. placebo**	**risedronate dose group**	**indirect WMD**	**(indirect 95% CI)**	**p-value**
Population: All						
Saag 1998	10mg	Cohen 1999	5 mg	-1.04	(-3.44,1.35)	0.393
de Nijs 2006	10mg	Reid 2000	5mg			
Stoch 2009	70mg weekly					
Adachi 2001 (Saag cont.)	10mg	Cohen 1999	5 mg	-0.58	-3.51, 2.34	0.697
de Nijs 2006	10mg	Reid 2000	5mg			
Stoch 2009	70mg weekly					

WMD, weighted mean difference
A negative WMD indicates difference in favour of risedronate

There is large statistical heterogeneity in changes in femoral neck BMD for both the pooled analysis of the alendronate studies (I^2=76%) and the risedronate studies (I^2=54%), as shown in the following figure.

Forest plots showing difference in percentage change in BMD at the femoral neck (direct comparison of active therapy relative to placebo) for pooling of studies used in the indirect meta-analyses of alendronate versus risedronate via placebo – analysis for total patient population



The indirect comparison of baseline percentage changes in BMD at the lumbar spine also showed no significant difference between alendronate and risedronate.

Indirect comparison of alendronate vs. risedronate via placebo as common comparator: WMD in percentage change in BMD at the lumbar spine

Study ID and active dose group(s) of placebo controlled trials included in the indirect comparison of alendronate vs. risedronate				**Indirect estimate of effect:**		
alendronate vs. placebo	**alendronate dose group**	**risedronate vs. placebo**	**risedronate dose group**	**indirect WMD**	**(indirect 95% CI)**	**p-value**
Population: All						
Saag 1998	10mg	Cohen 1999	5 mg	0.42	(-0.70, 1.53)	0.464
de Nijs 2006	10mg	Reid 2000				
Stoch 2009	70mg weekly					
Adachi 2001 (Saag cont.)	10mg	Cohen 1999	5 mg	0.75	(-0.56, 2.07)	0.262
de Nijs 2006	10mg	Reid 2000	5mg			

WMD, weighted mean difference
A positive WMD indicates difference in favour of alendronate

Fracture Risk Analysis

The submission stated that only the overall non-vertebral and morphometric vertebral fractures were compared as the incidence of fractures in all studies was low which made it impossible to perform sub-group analyses.

Of the two risedronate studies, only Cohen (1999) reported non-vertebral fracture data. The data from Cohen included all non-vertebral fractures in the 2.5 mg and 5.0 mg treatment groups. In non-vertebral fractures, the indirect comparison showed there was a non-

significant reduction in fractures in favour of risedronate when only the Saag and de Nijs studies are included, although when the Adachi study was included there was a non-significant reduction in non-vertebral fractures in favour of alendronate.

Indirect comparison of alendronate vs. risedronate via placebo as common comparator: Risk ratio of non vertebral fracture

Study ID and active dose group(s) of placebo controlled trials included in the indirect comparison of alendronate vs. risedronate				Indirect estimate of effect:		
alendronate vs. placebo	**alendronate dose group**	**risedronate vs. placebo**	**risedronate dose group**	**indirect risk ratio**	**(indirect 95% CI)**	**p-value**
Population: All						
Saag 1998 de Nijs 2006	5/10 mg or 10 mg	Cohen 1999	2.5/5 mg	1.21	(0.28, 5.25)	0.799
Adachi 2001 (Saag cont.) de Nijs 2006	5/10 mg or 10 mg	Cohen 1999	2.5/5 mg	0.76	(0.17,3.47)	0.725

Indirect risk ratio less than 1 indicates result in favour of alendronate

In morphometric vertebral fractures, the indirect comparison showed no significant difference between alendronate and risedronate. However, with the inclusion of the Adachi study, there was an overall reduction in morphometric vertebral fractures for alendronate that reached statistical significance. When both the Cohen and Reid studies were combined, the reduction in morphometric vertebral fractures also reached statistical significance vs. placebo.

Indirect comparison of alendronate vs. risedronate via placebo as common comparator: Risk ratio of (morphometric) vertebral fracture

Study ID and active dose group(s) of placebo controlled trials included in the indirect comparison of alendronate vs. risedronate				Indirect estimate of effect:		
alendronate vs. placebo	**alendronate dose group**	**risedronate vs. placebo**	**risedronate dose group**	**indirect risk ratio**	**(indirect 95% CI)**	**p-value**
Population: All						
Saag 1998 de Nijs 2006	5/10 mg or 10mg	Cohen 1999 Reid 2000	2.5/5 mg	1.29	(0.43, 3.93)	0.649
Adachi 2001 (Saag cont.) de Nijs 2006	5/10 mg or 10mg	Cohen 1999 Reid 2000	2.5/5 mg	0.70	(0.19, 2.68)	0.607

Indirect risk ratio less than 1 indicates result in favour of alendronate

9. Clinical Claim

The submission claimed that alendronate is non-inferior to risedronate in the treatment or prevention of glucocorticoid-induced osteoporosis as there is no significant difference between alendronate and risedronate in BMD in the lumbar spine and femoral neck and for non-vertebral and morphometric vertebral fractures. The PBAC accepted this claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

As this was a minor submission, no economic analysis was presented.

11. Estimated PBS Usage and Financial Implications

The submission stated that this listing was not expected to grow the market and that alendronate uptake would be mainly from patients switching from risedronate. The sponsor stated that it would be unlikely for patients to switch from zoledronic acid once yearly IV therapy to alendronate once weekly oral therapy, therefore zoledronic acid had not been included in modelling uptake estimates.

The submission estimated financial savings per year to the Government of less than $10 million in Year 5 of listing due to the lower dispensed price for maximum quantity (DPMQ) of alendronate compared to risedronate.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended extending the listing of alendronate and its combinations with calcium and/ or colecalciferol to include an Authority Required (Streamlined) listing for the treatment of corticosteroid-induced osteoporosis in patients currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less on a cost minimisation basis with risedronate sodium at the price proposed in the submission. The equi-effective doses are 70 mg alendronic acid weekly and 35 mg risedronate sodium weekly.

The PBAC considered, based on the totality of the evidence presented, that alendronate is of non-inferior efficacy and safety to risedronate in the treatment of corticosteroid-induced osteoporosis. The PBAC noted that the submission presented an indirect analysis comparing alendronate with risedronate using placebo as the common comparator. For this comparison, the submission presented four randomised controlled trials comparing alendronate with placebo, and two direct randomised comparative trials and a meta-analysis comparing risedronate and placebo in patients with glucocorticoid-induced osteoporosis. The PBAC noted that although some of the alendronate studies used 5 mg or 10 mg once daily doses, Stoch 2009 used the 70 mg once weekly dose. The PBAC also noted that it had previously recommended the listing of alendronate 70 mg tablets taken once weekly on a cost minimisation basis with the 10 mg tablet once daily for the treatment of osteoporosis and accepted that the two dosage regimens provided similar safety and efficacy.

The PBAC agreed that the listing of alendronate would not be expected to grow the market for corticosteroid-induced osteoporosis and considered that alendronate uptake is likely to be mainly from patients switching from PBS subsidised risedronate, and hence that the listing of alendronate for corticosteroid-induced osteoporosis would not be expected to result in any increased financial cost to the Government. The PBAC also considered the submission's claim that it is unlikely that patients would switch from treatment with zoledronic acid once yearly I.V. to alendronate once weekly orally, as reasonable.

Recommendation:

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 calcium), Fosamax Plus D-Cal®

Extend the current restriction to include:

Restriction:	Authority required (STREAMLINED) Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less. The duration and dose of corticosteroid therapy together with 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 (70 mg, 70 mg/70 mcg and 70 mg/140 mcg) ‡1 (70 mg/140 mcg with 1.25 g calcium)
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

The sponsor welcomes the PBAC's decision to make alendronate available to patients with corticosteroid-induced osteoporosis.