PUBLIC SUMMARY DOCUMENT
Product: Denosumab, injection 60 mg in 1 mL pre-filled syringe, Prolia®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission requested an extension of the current PBS listing for denosumab for the treatment of post-menopausal osteoporosis to include women aged 70 years of age or older with a bone mineral density (BMD) T-score of -2.5 or less.

2. Background

At its July 2010 meeting, the PBAC recommended listing of denosumab pre-filled syringe 60 mg in 1 mL for treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman aged 70 years of age or older with a BMD T-score of -3.0 or less on a cost-minimisation basis compared with zoledronic acid. Listing was effective from 1 December 2010.

A copy of the Public Summary Document (PSD) from the July 2010 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Denosumab-july10

At its November 2011 meeting, the PBAC recommended that the current Authority Required listing for denosumab pre-filled syringe 60 mg in 1 mL for the treatment of osteoporosis be changed to a Streamlined Authority listing. This change was effective from 1 March 2012.

3. Registration Status

Denosumab injection, 60 mg in 1 mL was TGA registered on 22 June 2010 for the treatment of osteoporosis in postmenopausal women.

4. Listing Requested and PBAC's View

The submission sought to extend the current listing to read as follows (change is highlighted in bold).

Authority Required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman 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;

Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in a woman 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 documented in the patient's medical records when treatment is initiated.

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.

Note
Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

Note
Continuing Therapy Only:
For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Osteoporosis is a disease in which the density and quality of bone are reduced, leading to weakness of the skeleton and increased risk of fracture.

Denosumab is a subcutaneous injection given every six months. The submission proposed the place in therapy for denosumab is as an alternative therapy to oral alendronate for the primary prevention population of women aged 70 years or older with a BMD T-score greater than -3.0 and less than or equal to -2.5.

6. Comparator

The submission nominated alendronate as the main comparator. This comparator was considered appropriate by the PBAC.

7. Clinical Trials

The basis of the submission was an indirect comparison of fracture outcomes between denosumab (FREEDOM trial) and alendronate (FIT-VFA (vertebral fractures at baseline) and FIT-CFA (no vertebral fractures at baseline) trials) using firstly a mixed primary/secondary prevention population and secondly a primary prevention sub-group population (BMD T-score < -2.5 without prevalent vertebral fractures).

A direct comparison of BMD outcomes, patient satisfaction and treatment adherence with denosumab and alendronate was presented as supportive evidence (DECIDE, STAND and Study 232). These studies were presented to support the comparison of denosumab with alendronate in the submission for the original listing.

Details of the trials published at the time of submission are shown below. Publication details of DECIDE and STAND have been previously reported in the July 2010 Public Summary Document.

Randomised trials presented in the submission

Trial ID/First author	Protocol title/ Publication title	Publication citation
Denosumab vs. Placebo trials		
Study 216 (FREEDOM) Cummings et al (2009).	Denosumab for prevention of fractures in postmenopausal women with osteoporosis.	NEJM 361: 756-765
Alendronate vs. Placebo trials		
FIT Black et al (1996).	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.	Lancet 348:1535-41
Cummings et al (1998).	Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures.	JAMA 280:2077-2082
Black et al (2000).	Fracture Risk Reduction with Alendronate in Women with Osteoporosis: The Fracture Intervention Trial	Journal of Clinical Endocrinology & Metabolism 85:4118-4124

For PBAC's view, see Recommendations and Reasons.

8. Results of Trials

The results of the indirect comparison of fracture outcomes between FREEDOM and FIT trials for the mixed primary/secondary prevention population are presented in the table below.

Results of the indirect comparison of fracture outcomes between the FREEDOM and FIT trials (mixed primary/secondary prevention population)

Trial	Denosumab	Placebo	Alendronate	Treatment effect HR (95% CI)
Proportion of patients with new morphometric vertebral fractures (paired radiograph population) [n/N (%)]				
FREEDOM	86/3702 (2.3)	264/3691 (7.2)	-	0.32 (0.25, 0.40)[a]
FIT-VFA	-	145/965 (15.0)	78/981 (8.0)	0.51 (0.39, 0.67)[a]
FIT-CFA	-	78/2077 (3.8)	43/2057 (2.1)	0.55 (0.38, 0.80)[a]
			Meta-analysis of FIT trials [RR (95% CI)]	0.52 (0.42, 0.65)
			Indirect estimate of effect [RR (95% CI)]	**0.62 (0.45, 0.85)**
Proportion of patients with any clinical vertebral fracture (ITT population) [n/N (%)]				
FREEDOM	29/3902 (0.7)	92/3906 (2.4)	-	0.31 (0.21, 0.48)
FIT-VFA	-	52/1005 (5.2)	24/1022 (2.3)	0.45 (0.27, 0.73)
FIT-CFA	-	27/2218 (1.2)	18/2214 (0.8)	0.67 (0.37, 1.21)
			Meta-analysis of FIT trials [HR (95% CI)]	0.53 (0.36, 0.77)
			Indirect estimate of effect [HR (95% CI)]	0.58 (0.33, 1.03)
Proportion of patients with any non-vertebral fracture (ITT population) [n/N (%)]				
FREEDOM	238/3902 (6.1)	293/3906 (7.5)	-	0.81 (0.68, 0.96)
FIT-VFA	-	148/1005 (14.7)	122/1022 (11.9)	0.80 (0.63, 1.01)
FIT-CFA	-	294/2218 (13.3)	261/2214 (11.8)	0.88 (0.75, 1.04)
			Meta-analysis of FIT trials [HR (95% CI)]	0.85 (0.74, 0.98)
			Indirect estimate of effect [HR (95% CI)]	0.95 (0.76, 1.19)

Proportion of patients with any hip fracture (ITT population) [n/N (%)]				
FREEDOM	26/3902 (0.7)	43/3906 (1.1)	-	0.60 (0.37, 0.98)
FIT-VFA	-	22/1005 (2.2)	11/1022 (1.1)	0.49 (0.24, 1.01)
FIT-CFA	-	24/2218 (1.1)	19/2214 (0.9)	0.79 (0.43, 1.45)
			Meta-analysis of FIT trials [HR (95% CI)]	0.65 (0.41, 1.04)
			Indirect estimate of effect [HR (95% CI)]	0.92 (0.47, 1.81)

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk
[a] Relative risk

The indirect analysis showed a statistically significant difference between denosumab and alendronate in new morphometric vertebral fractures only in the mixed primary/secondary prevention population (RR 0.62; 95% CI 0.45, 0.85). There were no statistically significant differences between denosumab and alendronate in risk of clinical vertebral fractures, non-vertebral fractures and hip fractures.

The results of the indirect comparison of fracture outcomes between FREEDOM and FIT trials for the primary prevention sub-population (BMD T-score less than -2.5 without prevalent vertebral fractures) are presented in the table below.

Results of the indirect subgroup comparison of fracture outcomes between the FREEDOM and FIT-CFA trial (BMD T-score < -2.5 without prevalent vertebral fractures)

Trial	Denosumab	Placebo	Alendronate	Treatment effect HR (95% CI)
Proportion of patients with new morphometric vertebral fractures [n/N (%)]				
FREEDOM	45/2727 (1.7)	143/2727 (5.2)	-	0.31 (0.22, 0.43)[a]
FIT-CFA	-	44/763 (5.8)	22/757 (2.9)	0.50 (0.30, 0.83)[a]
			Indirect estimate of effect [RR (95% CI)]	0.62 (0.34, 1.15)
Proportion of patients with any clinical vertebral fracture [n/N (%)]				
FREEDOM	16/2864 (0.6)	50/2840 (1.8)	-	0.32 (0.18, 0.56)
FIT-CFA	-	14/812 (1.7)	12/819 (1.5)	0.85 (0.39, 1.84)
			Indirect estimate of effect [HR (95% CI)]	**0.37 (0.14, 0.97)**
Proportion of patients with any non-vertebral fracture [n/N (%)]				
FREEDOM	151/2864 (5.3)	209/2854 (7.3)	-	0.71 (0.58, 0.88)
FIT-CFA	-	150/812 (18.5)	101/819 (12.3)	0.64 (0.50, 0.83)
			Indirect estimate of effect [HR (95% CI)]	1.11 (0.80, 1.53)
Proportion of patients with any hip fracture [n/N (%)]				
FREEDOM	13/2864 (0.5)	29/2854 (1.0)	-	0.45 (0.23, 0.86)
FIT-CFA	-	18/812 (2.2)	8/819 (1.0)	0.44 (0.19, 1.01)
			Indirect estimate of effect [HR (95% CI)]	1.02 (0.35, 2.93)

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk
[a] Relative risk

There was no statistically significant difference in the risk of new morphometric vertebral fractures between denosumab and alendronate in the primary prevention subgroup (RR 0.62; 95% 0.34, 1.15). The difference was statistically significant in favour of denosumab for clinical vertebral fractures (HR 0.37; 95% CI 0.14, 0.97). The low event rates for clinical vertebral fractures contributed in part to the wide confidence interval around the estimate. There were no statistically significant differences between denosumab and alendronate in risk of non-vertebral fractures and hip fractures.

The PBAC noted that the supportive head-to-head trials suggested that denosumab and alendronate have similar short-term (1-2 years) safety profiles. There were no direct,

long-term data on the comparative safety of denosumab and alendronate.

The Periodic Safety Update Report for denosumab indicated that the sponsor was continuing to monitor the safety of denosumab treatment by monitoring the following adverse events as events of heightened surveillance: hypocalcaemia, osteonecrosis of the jaw, serious skin infections, infections, hypersensitivity reactions, cardiovascular events, malignancy, immunogenicity, cataracts, avascular necrosis, fracture healing complications, atypical fractures, dermatologic events and pancreatitis.

9. Clinical Claim

The submission described denosumab as superior in terms of comparative efficacy and similar in terms of comparative safety over alendronate.

The PBAC considered that the indirect analyses did not adequately support the submission's claim of superior efficacy over alendronate.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis based on the recommended doses of denosumab (60 mg injection every 6 months) and alendronate (70 mg tablet weekly).

The submission proposed a weighted overall price for denosumab based on the predicted split in use between the new target population (priced against alendronate/alendronate combinations) and the existing eligible populations (current DPMQ).

For PBAC's view, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated in the submission to be less than 10,000 packs in Year 5 at an estimated net cost to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended that the current Authority Required (STREAMLINED) listing for denosumab 60 mg in 1 mL injection for the treatment of post-menopausal osteoporosis be extended to include women aged 70 years of age or older with a bone mineral density (BMD) T-score of -2.5 or less on a cost-minimisation basis compared with alendronate 70 mg once weekly tablets. The equi-effective doses are based on the recommended doses, denosumab 60 mg once every 6 months and alendronate 70 mg once weekly. The PBAC considered that the price of denosumab should be based on an equivalent annual treatment cost compared with alendronate alone as a single treatment agent.

The nominated comparator of alendronate was considered appropriate by the PBAC.

The PBAC noted that the basis of the submission was two indirect comparisons of fracture outcomes between denosumab (FREEDOM trial) and alendronate (FIT-VFA, FIT-CFA trials) using firstly a mixed primary/secondary prevention population and

secondly a primary prevention sub-group population (BMD T-score < -2.5 without prevalent vertebral fractures). The PBAC noted that no data were presented specifically for the extended population of women aged 70 years of age or older with a BMD T-score between -3.0 and -2.5.

The indirect analyses showed statistically significant differences between denosumab and alendronate in new morphometric vertebral fractures only in the mixed primary/secondary prevention population and borderline statistical significance in favour of denosumab for clinical vertebral fractures in the primary prevention subgroup. There were no statistically significant differences in non-vertebral fractures (including hip) between the treatments.

Due to the limitations of the indirect comparison (applicability, comparability and uncertainty about the robustness of results), the PBAC considered that the indirect analyses did not adequately support the submission's claim of superior efficacy over alendronate. Based on the data presented, the PBAC agreed that denosumab appears similar to alendronate with respect to comparative efficacy and short-term safety profile, however there are insufficient data to compare the long-term safety of denosumab and alendronate.

The PBAC considered that the price of denosumab should be based on an equivalent annual treatment cost compared to alendronate as a single treatment agent alone, not based on a weighted alendronate price that includes alendronate combinations, and irrespective of any expected splits between the extended population and existing indications as there is uncertainty around the uptake of denosumab in the extended population, given that the uptake of alendronate in this recently extended population has been lower than expected.

The PBAC also recommended that the DUSC review denosumab in 12 months time.

In making this recommendation the PBAC noted the consumer comments on this item.

The PBAC recommended that denosumab 60 mg in 1 mL injection is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

Recommendation:
DENOSUMAB, injection 60 mg in 1 mL pre-filled syringe

Amend the current listing to read as follows (change is highlighted in bold).

Restriction:	Authority Required (STREAMLINED) Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman 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;

Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in a woman 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 documented in the patient's medical records when treatment is initiated.

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.

Note
Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, denosumab, disodium etidronate, raloxifene hydrochloride, strontium ranelate and zoledronic acid.

Note
Continuing Therapy Only:
For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

Max quantity: 1
Repeats: 0

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

Amgen is pleased that denosumab will be made available through the PBS for this new group of women with postmenopausal osteoporosis.