PUBLIC SUMMARY DOCUMENT
Product: DENOSUMAB, injection, 60 mg in 1 mL, single use pre-filled syringe, Prolia®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for:

1. the treatment of osteoporosis in women aged 70 years of age or older with a bone mineral density (BMD) T-score of -3.0 or less, and
2. the treatment of established post-menopausal osteoporosis in patients with fracture due to minimal trauma.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Denosumab was TGA registered on 22 June 2010 for the treatment of osteoporosis in postmenopausal women. Denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

4. Listing Requested and PBAC's View

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 -3.0 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.

Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal 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 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, disodium etidronate, raloxifene hydrochloride, strontium ranelate, zoledronic acid and denosumab.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Osteoporosis affects the skeleton and is characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and susceptibility to fracture.

Denosumab is a subcutaneous injection given every 6 months and has a different mechanism of action to other PBS-listed drugs for osteoporosis treatment. It would provide an alternative treatment option for women with post-menopausal osteoporosis.

6. Comparator

The submission nominated a mixed comparator comprising of alendronate, risedronate, strontium and zoledronic acid based on post-menopausal women initiating therapy.

The submission nominated alendronate as the main clinical comparator as it is the efficacy benchmark against which the other treatments in the nominated mixed comparator were assessed for PBS listing.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The basis of the submission was a direct comparison of BMD outcomes, patient satisfaction and treatment adherence, using four head-to-head trials of denosumab and alendronate in post-menopausal osteoporosis (DECIDE, STAND, Study 179 and Study 232) as well as an indirect comparison of fracture outcomes with denosumab (FREEDOM), alendronate (FIT-VFA, FIT-CFA), risedronate (VERT-MN, VERT-NA, HIP), zoledronic acid (HORIZON-PFT, HORIZON-RFT) and strontium ranelate (TROPOS, SOTI).

Fracture outcomes from two additional risedronate trials (BMD-MN and BMD-NA) were presented in a secondary pooled analysis of risedronate trials.

The key trials published at the time of submission are shown in the tables below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Denosumab vs. Alendronate trials		
Study 141 (DECIDE) Brown JP et al. (2009)	Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomised, blinded, phase 3 trial.	J Bone Miner Res (JBMR) 2009; 24:153–161.
Study 234 (STAND) Kendler et al.	Effects of Denosumab on Bone Mineral Density and Bone Turnover in Postmenopausal Women Transitioning from Alendronate Therapy.	JBMR 2010;25(1):72-81
Study 179 Seeman E et al Seeman E et al.	Baseline Remodelling Intensity and Greater Suppression by Denosumab Than Alendronate: Effects on HR-pQCT Parameters at the Radius. Microarchitectural deterioration of cortical and trabecular bone: Differing effects of denosumab and alendronate.	ASBMR 31st Annual meeting 2009, Abstract A09001600. JBMR 2010; 25(8);1886-94

Placebo-controlled trials included in the submission

Trial ID / First author	Protocol title / Publication title	Publication citation
Denosumab vs. Placebo trials		
Study 216 (FREEDOM) Cummings S et al.	Denosumab for prevention of fractures in postmenopausal women with osteoporosis.	NEJM 2009; 361:756-765
Alendronate vs. Placebo trials		
FIT-VFA Black et al.	Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.	Lancet 1996; 348:1535-41.
FIT-CFA Cummings et al.	Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures.	JAMA 1998; 280:2077-2082.
Risedronate vs. Placebo trials		
BMD-MN Fogelman I et al.	Risedronate Reverses Bone Loss in Postmenopausal Women with Low Bone Mass: Results From a Multinational, Double-Blind, Placebo-Controlled Trial.	Journal of Clinical Endocrinology & Metabolism 2000; 85: 1895-1900
BMD-NA McClung MR et al.	Risedronate increases BMD at the hip, spine and radius in postmenopausal women with low bone mass [abstract].	Journal of Bone and Mineral Research 1997; 12(Suppl 1):S169
HIP McClung MR et al.	Effect of risedronate on the risk of hip fracture in elderly women.	NEJM 2001; 344:333-40
Zoledronic acid vs. Placebo trials		
HORIZON-PFT Black DM et al.	Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis.	NEJM 2007; 356:1809-22.
HORIZON-RFT Lyles KW et al.	Zoledronic acid and clinical fractures and mortality after hip fracture 1049.	NEJM 2007; 357:1799-809
Strontium ranelate vs. Placebo trials		
TROPOS Reginster JY et al.	Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study.	Journal of Clinical Endocrinology & Metabolism 2005; 90:2816-22.
SOTI Meunier PJ et al.	The Effects of Strontium Ranelate on the Risk of Vertebral Fracture in Women with Postmenopausal Osteoporosis.	NEJM 2004; 350:459-68

8. Results of Trials

The head-to-head trials of denosumab and alendronate [DECIDE and STAND] showed that denosumab treatment was associated with a small but statistically significant increase in BMD compared to alendronate (approximately 1% in absolute terms at all measured locations) after 12 months of treatment. Differences between treatments in Study 179 were not formally assessed.

Patient surveys administered during these trials suggested that most patients preferred a 6-monthly injection to receiving a weekly oral tablet.

The primary analysis of fracture outcomes presented in the submission was based on the total population which included results from trials in primary and/or secondary prevention. Supportive analyses were also presented separately for patients without prior vertebral

fracture (approximating a primary prevention population) and for patients with a prevalent vertebral fracture (approximating a secondary prevention population). There was doubt about whether the included trials were sufficiently comparable to enable an indirect comparison.

The results of the indirect meta-analysis for morphometric vertebral fractures suggested that denosumab treatment may reduce morphometric vertebral fractures compared to alendronate in a mixed population of osteoporosis patients (relative risk (RR) 0.60, 95% CI 0.44, 0.83). There were statistically significant reductions in morphometric vertebral fractures in denosumab treated patients compared to risedronate and strontium ranelate.

The results of the indirect meta-analysis for clinical vertebral fractures identified no statistically significant difference between denosumab and alendronate. However, the submission noted that denosumab was associated with a numerically greater reduction in clinical vertebral fractures in the total population analysis (RR 0.60, 95% CI 0.34, 1.04) and this result is similar to that observed for morphometric vertebral fractures. The reduction in clinical vertebral fracture risks was numerically greater in patients without prior fracture (RR 0.48, 95% CI 0.21, 1.07) compared to patients with a prevalent fracture (RR 0.69, 95% CI 0.31, 1.51).

The results of the indirect meta-analyses for hip fractures or other non-vertebral, non-hip fractures indicated there were no statistically significant differences between denosumab and the comparator drugs in the total osteoporosis population or the subgroups with and without fracture at baseline. The confidence intervals around the estimates in the indirect analyses of hip fracture were wide, reflecting the small numbers of events in these trials.

The PBAC noted that the indirect analyses did not demonstrate statistically significant differences between denosumab and zolendronic acid for any of the above outcomes.

For PBAC's comments on these results, see Recommendation and Reasons.

Denosumab and alendronate appeared to have similar short-term (1-2 years) safety profiles in the direct clinical trials. There are limited data on the long-term adverse event profile of denosumab treatment.

A review by the U.S Food and Drug Administration (FDA) also noted that denosumab treatment appeared to be associated with a slightly increased risk of breast cancer, pancreatic cancer, gastrointestinal cancer and reproductive cancers compared to placebo. However, there were more new cases of malignant respiratory neoplasm among patients receiving placebo than denosumab. Denosumab was also associated with a slightly increased risk of serious infection (skin, ear, abdominal system and urinary tract) compared to placebo. The review noted that denosumab markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters were also suppressed. The FDA review suggested that long-term denosumab treatment may lead to delayed fracture healing, ONJ or atypical fracture.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that denosumab treatment is associated with a reduction in the incidence of vertebral fractures and an improvement in persistence relative to a mixed comparator comprised of alendronate, risedronate, zoledronic acid and strontium ranelate. The PBAC did not accept this claim.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation with the modelled results of the primary and secondary populations presented separately. However, the efficacy estimates used in the economic model were based on the total population (mixed primary and secondary) indirect analysis.

Based on the structure and assumptions used in the submission's model, denosumab treatment was associated with an incremental cost of between $15,000 and $45,000 per QALY gained in the primary prevention setting and less than $15,000 per QALY gained in the secondary prevention setting compared to the mixed comparator.

The PBAC considered a cost effectiveness approach was not valid. *See Recommendation and Reasons, for PBAC's view.*

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated by the submission to be between 50,000 and 100,000 in Year 5. The submission estimated that 56% of eligible patients receive treatment for primary prevention while the remaining 44% receive treatment for secondary prevention. The estimate was considered highly uncertain and it was more likely that the majority of patients received treatment for secondary prevention.

The financial cost per year to the PBS was estimated by the submission to be between $10 and $30 million in Year 5. The submission did not provide a break down of net costs in the primary and secondary prevention settings. However, the PBAC considered that the net cost could potentially be between $10 and $30 million in the secondary prevention setting alone.

12. Recommendation and Reasons

The PBAC recommended listing on a cost minimisation basis compared with zoledronic acid. The equi-effective doses are denosumab 60 mg administered every six months and zoledronic acid 5 mg administered once per year. Pricing should also take account of the two doctor's visits required for the administration of denosumab, as well as the administration costs for zoledronic acid.

Although there were concerns about possible signals for long-term toxicity with denosumab, in particular of an increased risk of certain types of cancer and serious infections, the PBAC noted that there was no difference in the overall rate of neoplasms between denosumab and placebo. The PBAC also noted from the hearing that any skin infections resulting from denosumab treatment are readily treated with a single course of antibiotics. The clinician at the hearing also indicated that experts in the field, including the Australian Bone and Mineral Society and the Medical and Scientific Committee of Osteoporosis Australia, believe that denosumab should provide a further first line treatment option to the currently listed agents,

given its novel mechanism of action. The PBAC therefore agreed that denosumab should not be listed as second line to current therapies. However, a streamlined authority listing was not considered appropriate for a member of this new class of agents, which has limited clinical and safety data and that will be subject to on-going surveillance with Risk Management Plans.

The PBAC considered that the comparator should be zoledronic acid, as an alternative injectable agent, noting that the comparison of denosumab with zoledronic acid showed no differences between the two drugs. The information provided by the clinician during the hearing was also consistent with zoledronic acid being the key comparator.

The PBAC considered that alendronate was a relevant but secondary comparator and noted that denosumab treatment was associated with a small but statistically significant increase in BMD compared to alendronate (approximately 1% in absolute terms at all measured locations) after 12 months of treatment in the DECIDE and STAND trials. Differences between treatments in Study 179 were not formally assessed however BMD results at the lumbar spine and distal 1/3 radius favoured denosumab while BMD results at the total hip, femoral neck and trochanter favoured alendronate. The PBAC agreed that the clinical importance of differences in BMD outcomes between denosumab and alendronate is unclear and that there is uncertainty regarding how changes in BMD translate into differences in clinical fractures.

The PBAC noted there was no head-to-head trial evidence comparing fracture outcomes for denosumab with any of the nominated comparators. Further there was doubt about whether the included trials were sufficiently comparable to enable an indirect comparison, given the differences in patient populations (e.g. fracture history including type of previous fracture, age, BMD), treatment characteristics (e.g. use of non-approved doses, calcium and vitamin D, concomitant therapy) and study design (e.g. trial duration). The PBAC also noted that the results of an indirect analysis showed a statistically significant reduction in morphometric vertebral fractures (clinical importance unknown) with denosumab treatment compared to alendronate, risedronate and strontium ranelate as well as a trend towards a greater clinical vertebral fracture reduction with denosumab. Denosumab did not significantly reduce the risk of hip fractures compared to other treatments. The PBAC noted that the indirect analyses did not demonstrate statistically significant differences between denosumab and zolendronic acid for any outcomes.

The PBAC thus did not accept the claim of superiority against oral bisphosphonates and considered denosumab had been demonstrated to be similar in effectiveness to zoledronic acid.

The PBAC noted the 12 month results of Study 232 (unpublished) suggest that patients treated with denosumab are likely to be more adherent, compliant and persistent with therapy compared to alendronate patients. The PBAC considered that the results of this study may not to be representative of adherence and persistence in a PBS population. Furthermore, given that the PBAC considered zoledronic acid to be the appropriate comparator, the issue of compliance with oral agents was irrelevant.

Given the uncertainty about improvements in either efficacy or compliance, a cost effectiveness approach was not considered to be valid and the results of the modelled

economic evaluation were therefore not relevant. The PBAC did note however that there were a number of issues of concern raised about the model by the ESC, including the issue of double counting with the effect of persistence, overestimate of fracture mortality and utility estimates.

The PBAC was concerned about the long-term toxicity of denosumab. In addition to concerns about risks of cancer and serious infection, the PBAC noted that denosumab markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters were also suppressed. Further, the FDA review suggests that long-term denosumab treatment may lead to delayed fracture healing, ONJ or atypical fracture. The PBAC also noted that the Advisory Committee on Prescription Medicines had recommended a risk management plan as a pre-requisite for registration, including the establishment of a patient registry. The PBAC requested that it be kept informed about any toxicity signals that may arise from this post-marketing surveillance.

The PBAC requested that NPS produce a RADAR for denosumab in view of the potential for long-term toxicity.

Recommendation:
DENOSUMAB, injection, 60 mg in 1 mL, single use pre-filled syringe, Prolia®

Restriction:

Authority required
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 -3.0 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.

Authority required
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, disodium etidronate, raloxifene hydrochloride, strontium ranelate, zoledronic acid and denosumab.

Maximum 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 Australian women with postmenopausal osteoporosis