Public Summary Document

Product: Denosumab, injection, 60 mg/mL, Prolia®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested extension of the current Authority required (Streamlined) listing as the sole PBS-subsidised anti-resorptive agent for osteoporosis to include both male and female patients (currently females only).

The submission was lodged under the TGA/PBAC parallel process. At the time of PBAC consideration both the Clinical Evaluation Report and the TGA Delegate's Summary were available.

2. Background

Denosumab has not been previously considered by PBAC for this indication.

Denosumab is currently PBS listed for osteoporosis and established post-menopausal osteoporosis.

At its July 2010 meeting, the PBAC recommended listing of denosumab pre-filled syringe 60 mg in 1 mL on a cost-minimisation compared with zoledronic acid. A copy of the Public Summary Document (PSD) from the July 2010 meeting is available at Public Summary Document for Denosumab – July 2010

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.

At the March 2012 PBAC meeting, the PBAC recommended that the Authority required 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. Listing was effective from 1 August 2012.

For male osteoporosis, the PBAC recommended listing of alendronate in December 1998 and risedronate in September 2002. Zoledronic acid was recommended for male osteoporosis in November 2009 on the basis of one randomised non-inferiority trial comparing BMD outcomes between zoledronic acid and alendronate.

3. Registration Status

Denosumab is TGA registered for treatment of osteoporosis in post menopausal women and treatment to increase bone mass in men with osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer.

Denosumab was TGA registered on 12 September 2013 for the extended indication: Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.

4. Listing Requested and PBAC's View

The submission sought to extend the current listing to read as follows:

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.
(Change is from specifying 'female patient' to 'patient')

Authority required (STREAMLINED)
Treatment as the sole PBS-subsidised anti-resorptive agent for established osteoporosis in a patient 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.
(Change is from specifying 'established post menopausal osteoporosis' to 'established osteoporosis')

Listing was requested on a cost-minimisation basis versus zoledronic acid.

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. The most common fractures occur at the hip, spine and wrist and can lead to increased mortality, long-lasting pain, reduced mobility and disability.

Denosumab is a subcutaneous injection given every six months. The submission proposed denosumab as an alternative therapy to existing osteoporosis therapies listed for men with osteoporosis (alendronate, risedronate, etidronate, strontium ranelate, zoledronic acid), and most closely aligned with once yearly intravenous zoledronic acid.

6. Comparator

The submission nominated zoledronic acid as the main comparator.

The PBAC considered the comparator appropriate and consistent with the comparator accepted previously for denosumab in women.

The submission also presented a comparison of denosumab versus alendronate as part of the indirect comparison with zoledronic acid.

7. Clinical Trials

The submission presented two indirect comparisons based on four randomised controlled trials (RCT) that compare denosumab to zoledronic acid:

- A two-step indirect comparison, with placebo and alendronate as the common references:
  - one RCT comparing denosumab with placebo in 242 men with osteoporosis (ADAMO)
  - one RCT comparing zoledronic acid with alendronate in 302 men with osteoporosis (Study 2308)
  - one RCT comparing alendronate with placebo in 241 men with osteoporosis (Orwoll 2000)
- A one-step indirect comparison, with placebo as the common reference:
  - one RCT comparing denosumab with placebo in 242 men with osteoporosis (ADAMO)
  - one RCT comparing zoledronic acid with placebo in 1199 men with osteoporosis (Boonen 2012)

The submission nominated changes (increase) in BMD scores from baseline at lumbar spine, hip/total hip, femoral neck and trochanter as primary outcomes. However, the PBAC considered that reduction in fracture rate is a more patient relevant outcome. The PBAC considered that while BMD may be used as a surrogate outcome measure for fractures, there were studies indicating limited evidence supporting BMD increase with anti-resorptive agents as a reliable substitute for fracture risk[1]. The PBAC noted that there appeared to be a non-linear relationship between BMD changes and fracture risk and a threshold above which BMD increases no longer translate into fracture benefits (Li et al 2003). The PBAC also noted that the BMD-fracture risk relationship may differ between different treatments.

The PBAC considered that as defined by the proposed treatment algorithm, all trials included primary prevention (BMD T-score of -2.5 or less, no prevalent vertebral fracture), and secondary prevention populations (fracture following minimal trauma). The PBAC further noted that the mean age of the patients in each study is lower than the age specified in the PBS restriction.

The PBAC also noted that only the ADAMO trial inclusion criteria had a lower cut-off for the T-scores (LS or FN -2.0 or less and -3.5 or more). This may indicate that the ADAMO trial recruited patients with less severe osteoporosis, compared with the other trials that did not specify a lower limit in the inclusion criteria. Only Boonen 2012 recruited patients with baseline T-scores that match the proposed PBS restriction (less than -2.5).

The published trials and associated reports presented in the submission are shown in the following table:

Trial ID/ First	Protocol title/ Publication title	Publication citation

[1] Li.Z, Chines A.A., Meredith M.P. *Statistical validation of surrogate endpoints: Is bone mineral density a valid surrogate for fracture?*

author		
Denosumab and zoledronic acid trials		
Denosumab vs placebo		
ADAMO Orwoll et al.	A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density.	*Journal of Clinical Endocrinology and Metabolism* (2012); 97:3161-9.
Zoledronic acid vs alendronate		
Study 2308 Orwoll et al.	Efficacy and safety of a once-yearly i.v. infusion of zoledronic acid 5mg versus a once-weekly 70-mg oral alendronate in the treatmen tof male osteoporosis: A randomised, multicenter, double-blind, active-controlled study.	*Journal of Bone and Mineral Research* (2010); 25:2239-50.
Zoledronic acid vs placebo		
Boonen et al.	Fracture risk and zoledronic acid therapy in men with osteoporosis.	*New England Journal of Medicine* (2012);367:1714-23.
Boonen et al.	Efficacy of once-yearly zoledronic acid 5 mg in men with osteoporosis with different levels of serum total testosterone.	*Osteoporosis International* (2012); 23 S79-S80
Boonen et al.	Antifracture efficacy and safety of once-yearly zoledronic acid 5 mg in men with osteoporosis: A prospective, randomized, controlled trial.	*Osteoporosis International* (2011); 22 S112.
HORIZON-RFT Lyles et al.	Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture	*New England Journal of Medicine* (2007); 357:1799-809.
HORIZON-RFT Boonen et al.	Once-yearly zoledronic acid in older men compared with women with recent hip fracture.	*Journal of American Geriatics Society* (2011); 59 2084-90.
HORIZON-RFT Boonen et al.	Effect of once-yearly zoledronic acid in men after recent hip fracture: Results from horizon recurrent fracture trial.	*Osteoporosis International* (2011); 22 S180.
HORIZON-RFT Colón et al.	Association between timing of zoledronic acid infusion and hip fracture healing.	*Osteoporosis International* (2011); 22 2329-36.
HORIZON-RFT Boonen et al.	Effect of once-yearly i.v. zoledronic acid in men after hip fracture: Results from the horizon-recurrent fracture trial.	*Osteoporosis International* (2009); 20 S271-S272.
HORIZON-RFT Eriksen et al.	Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture.	*Journal of Bone and Mineral Research* (2009); 24 1308-13.
Additional trial to facilitate indirect comparison		
Alendronate vs placebo		
Orwoll et al.	Alendronate for the treatment of osteoporosis in men.	*New England Journal of Medicine* (2000); 343:604-10.

8. Results of Trials

The two-step indirect comparison used the placebo reference groups from the ADAMO and Orwoll 2000 studies and the alendronate reference groups from the Orwoll 2000 and Study 2308 studies. Relative to zoledronic acid, denosumab was associated with a statistically significant increase in BMD of the lumbar spine (indirect mean change (IMC): 2.3 [95% CI: 0.7, 3.8]). There were no statistically significant differences between BMD at the other

skeletal sites: femoral neck (IMC: -0.8 [95% CI: -3.1, 1.6]), hip/total hip (IMC: 0.3 [95% CI: -1.0, 1.6]) and trochanter (IMC: 0.3 [95% CI: -1.4, 2.0]).

The one-step indirect comparison of denosumab and zoledronic acid used placebo as the common reference which was based on ADAMO and Boonen 2012. No statistically significant differences in BMD change from baseline were demonstrated between denosumab and zoledronic acid at any of the 3 sites: lumbar spine (IMC: 0.1 [95% CI: -1.4, 1.6]), hip/total hip (IMC: 0.7 [95% CI: -0.3, 1.7]) and femoral neck (IMC: 0.6 [95% CI: -1.0, 2.2]).

The PBAC considered the results of both indirect comparisons suggested non-inferiority however, the Committee noted that the confidence intervals were wide and that individual trials were not powered for non-inferiority. The PBAC agreed that there were some concerns regarding exchangeability of the trials due to differences in fracture history and in inclusion criteria by BMD T-score cut-offs.

Although fracture reduction is the most patient relevant outcome, the PBAC considered that change in BMD scores has previously been presented as a surrogate outcome for submissions seeking to list zoledronic acid, the oral bisphosphonates and strontium ranelate for osteoporosis in men. The PBAC also noted the minimum regulatory requirements for registering a product for osteoporosis, as outlined in the TGA Clinical Evaluation Report.

Based on the considerations above, PBAC accepted changes (increase) in BMD score as primary outcome.

With regard to comparative harms, the PBAC noted that in general, the most frequent adverse events reported in ADAMO trial (5% or more incidence) were back pain, arthralgia, nasopharyngitis, and constipation. Compared to placebo, denosumab was not associated with significantly higher adverse events. No formal analysis was provided comparing the relative safety of denosumab relative to zoledronic acid.

The PBAC noted that the adverse events currently monitored as events of heightened surveillance include: hypocalcaemia, osteonecrosis of the jaw, skin infections leading to hospitalisation, infection, hypersensitivity reaction, osteonecrosis outside the jaw (avascular necrosis), fracture healing complications or delayed fracture healing, cardiovascular events, malignancy, immunogenicity, cataracts in all indications, atypical femoral fracture, pancreatitis, and dermatological events.

The PBAC considered that no new safety issues were evident in the male osteoporosis population or the existing female population from the data presented but existing safety concerns were not fundamentally different to those in females.

9. Clinical Claim

The submission described denosumab as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over zoledronic acid.

The PBAC accepted the claim of non-inferior comparative effectiveness based on BMD outcomes, although there were some concerns in relation to the applicability of the trials to the PBS population. The PBAC noted that the association between BMD and future fracture risk was not consistent across treatments, indicating that BMD outcomes may not be

reflective of comparative fracture outcomes between treatments. However, PBAC had previously accepted BMD as a surrogate outcome measure for osteoporosis treatments and did not consider there was sufficient basis to change its view at the present time.

The PBAC did not accept the submission's claim of superior comparative safety over zoledronic acid but instead, the Committee accepted a non-inferiority claim for denosumab for comparative safety. The PBAC agreed that the claim that denosumab offered potential advantages in terms of safety to zoledronic acid was not adequately supported by the evidence as no formal statistical analysis was provided comparing denosumab and zoledronic acid.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on annual costs of denosumab and zoledronic acid. On the basis of an indirect comparison, denosumab was demonstrated as non-inferior to zoledronic acid in terms of clinical efficacy.

The equi-effective doses estimated were denosumab 60 mg once every 6 months and zoledronic acid 5 mg once every 12 months. The denosumab regimen was the same as that in ADAMO trial and the regimen for zoledronic acid was the same as that used in Study 2039. The PBAC agreed that this was appropriate, and consistent with the equi-effective doses recommended by the PBAC in July 2010 when recommending denosumab for osteoporosis in women.

The sponsor advised in the Pre-Sub-Committee Response (PSCR) that the pricing used in the submission was a result of weighted pricing for the various indications of zoledronic acid. The PBAC agreed that accounting for the exclusion of the corticosteroid-induced osteoporosis and Paget's disease indications from the cost of zoledronic acid, and, the additional cost associated with one zoledronic acid infusion, was reasonable.

The PBAC considered that the pricing of denosumab did not appear to have taken into account the two doctor's visits required for obtaining two denosumab prescriptions compared to one doctor's visit to obtain zoledronic acid. The PBAC recalled that in July 2010, the PBAC recommended that "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" (Denosumab July 2010 Public Summary Document). The PBAC considered that accounting for any cost difference between two doctor visits for denosumab as opposed to one doctor visit for zoledronic acid would therefore be consistent with the previous July 2010 PBAC recommendation for denosumab.

The PBAC noted the cost of monitoring calcium levels after receiving denosumab (due to the risk of hypocalcaemia) and the additional costs for treating denosumab adverse events were not considered. The PBAC also noted that in the PSCR the sponsor pointed out that both denosumab and zoledronic acid would require calcium monitoring and that zoledronic acid additionally requires renal function monitoring. The PBAC agreed that it was reasonable not to account for calcium monitoring in the cost-minimisation analysis.

11. Estimated PBS Usage and Financial Implications

The PBAC noted the estimated total net cost to the PBS/RPBS was less than $10 million over the first 5 years of PBS listing. After applying the current DPMQs, the estimated total net cost to the PBS/RPBS becomes cost-savings of less than $10 million over the first 5 years.

The financial implications are to be further verified.

The PBAC noted that the submission did not calculate the cost to the Medical Benefits Schedule (MBS). Furthermore, the submission only estimated the cost offset from the avoided IV infusion that was required for the administration of zoledronic acid but did not take into consideration the additional cost of two doctor's visits required for the administration of denosumab. The PBAC therefore requested the Pharmaceutical Benefits Pricing Authority to determine the appropriate price for denosumab, taking account of the cost of two doctor's visits.

12. Recommendation and Reasons

The PBAC recommended listing of denosumab as an Authority required (Streamlined) benefit as the sole PBS-subsidised anti-resorptive agent for osteoporosis to include both male and female patients.

The PBAC accepted the claim of non-inferior comparative effectiveness based on BMD outcomes, although there were some concerns in relation to the applicability of the trials to the PBS population and whether the trials were sufficiently comparable for the indirect comparison. The PBAC noted that the association between BMD and future fracture risk was not consistent across treatments, indicating that BMD outcomes may not be reflective of comparative fracture outcomes between treatments however, PBAC previously accepted BMD as a surrogate outcome measure for osteoporosis treatments in males.

The PBAC did not accept the submission's claim of superior comparative safety over zoledronic acid but instead, the Committee accepted a non-inferiority claim for denosumab as the claim of superior safety was not adequately supported by the evidence as no formal statistical analysis was provided comparing denosumab and zoledronic acid.

The PBAC considered the submission's estimates of usage and cost to the PBS and noted that financial implications were difficult to verify during the evaluation, however the Committee considered that if the corrected price is applied to the financial estimates it appeared that there would be potential cost-savings based on the estimated substitution rates for zoledronic acid.

The PBAC noted the consumer comments received in relation to the submission.

Outcome:
Recommended

Recommended listing

The PBAC recommended that the existing denosumab listing be amended as follows (changes shown in strikethrough):

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
DENOSUMAB			
60 mg/mL injection, 1 mL pre-filled syringe	1	0	Prolia AN

Condition/Indication:	Osteoporosis
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have a Bone Mineral Density (BMD) T-score of -2.5 or less, AND Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.
Population criteria:	~~Patient must be female~~ ~~AND~~ Patient must be aged 70 years or older
Prescriber Instructions	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.

Condition/Indication:	Established ~~post-menopausal~~ osteoporosis
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have fracture due to minimal trauma, AND the Clinical criteria is: Patient must not receive concomitant treatment with any other PBS-subsidised anti-resorptive agent for this condition.
Prescriber Instructions	The fracture must have been demonstrated radiologically and the year of plain x-ray or computed tomography (CT) scan or magnetic resonance imaging (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.

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 men with osteoporosis.