PUBLIC SUMMARY DOCUMENT
Product: DENOSUMAB, solution for subcutaneous injection, 120 mg in 1.7 mL, Xgeva®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for the treatment of bone metastases from breast and hormone-resistant prostate cancer.

2. Background

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

3. Registration Status

Denosumab (Xgeva®) was TGA registered on 8 September 2011 for the prevention of skeletal related events in patients with bone metastases from solid tumours.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Bone metastases from breast cancer.
Bone metastases from hormone-resistant prostate cancer, with demonstration of biochemical progression despite maximal therapy with hormone treatments.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Among patients with advanced breast or prostate cancer, 65 to 75% develop bone metastases. Complications of bone metastases include severe pain, pathologic fractures and spinal cord compression which all have the potential to significantly impact a patient's quality of life and functional independence.

The submission proposed that the place in therapy of denosumab is as an alternative therapy for the treatment of bone metastases. Denosumab is not renally cleared and therefore it is able to be used in patients with severe renal insufficiency or by those patients receiving dialysis.

6. Comparator

The submission nominated intravenous (IV) zoledronic acid as the main comparator. This was accepted by the PBAC.

7. Clinical Trials

The basis of the submission was two head-to-head trials of denosumab compared to zoledronic acid for the prevention of skeletal related events (SREs) associated with bone metastases from breast cancer (Study 136) or hormone-resistant prostate cancer (Study 103). Both pivotal studies presented in the submission excluded patient with renal insufficiency (defined as creatinine clearance < 30 mL/min).

Publication details of the trials and associated reports presented in the submission are in the table below.

Randomised trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Breast cancer		
Study 136 Stopeck A, et al	Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomised double-blind study	Journal of Clinical Oncology 2010; 28(35): 5132-5139
Hormone-resistant prostate cancer		
Study 103 Fizazi K, et al	Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised double-blind study	Lancet 2011; 377 (9768): 813-822

8. Results of Trials

The main outcome measures of both trials were associated with the prevention of SREs.

SREs were defined as radiation therapy (for debilitating pain and the treatment or prevention of pathologic fractures/spinal cord compression); pathologic fractures; surgery to bone and spinal cord compressions. Events could be asymptomatic or symptomatic.

The SRE outcomes reported in Study 136 are presented in the table below.

SRE outcomes reported in Study 136 (breast cancer)

Outcome	Denosumab (N = 1026)	Zoledronic acid (N = 1020)
Time to first on-study SRE (both asymptomatic and symptomatic)		
Number of patients with an SRE (%)	315 (30.7)	372 (36.5)
Median time to event, days (95% CI) Median time to event, months	NE NE	806 (666, NE) 26.5
Hazard ratio (95% CI)	0.82 (0.71, 0.95)	
p-value (unadjusted)	**Non-inferiority <0.0001; Superiority 0.0101**	
First on-study SRE by subtype		
Pathological fracture (%)	212 (20.7)	238 (23.3)
Radiation to the bone (%)	82 (8.0)	119 (11.7)
Surgery to the bone (%)	12 (1.2)	8 (0.8)
Spinal cord compression (%)	9 (0.9)	7 (0.7)
Time to first-and-subsequent on-study SRE		
Number of events	474	608
Mean number of events per subject	0.46	0.60
Rate Ratio (95% CI)	0.77 (0.66, 0.89)	
p-value (unadjusted)	**0.0006**	
Time to first symptomatic SRE		
Number patients with a symptomatic SRE (%)	156 (15.2)	198 (19.4)
Median time to event, days (95% CI)	NE	NE
Hazard ratio (95% CI)	0.76 (0.61, 0.93)	
p-value	**0.0092**	

Abbreviations: CI, confidence interval; NE, not estimable; SRE, skeletal related event

The results of Study 136 indicate that denosumab treatment was associated with a statistically significant reduction in the risk of developing a first on-study SRE compared to zoledronic acid in breast cancer patients (Hazard ratio 0.82 [95% CI: 0.71, 0.95]). Denosumab

significantly reduced the risk of developing first-and-subsequent SREs by 23 % compared with zoledronic acid (Rate ratio 0.77 [95% CI: 0.66, 0.89]).

The SRE outcomes reported in Study 103 are presented in the table below.

SRE outcomes reported in Study 103 (prostate cancer)

Outcome	Denosumab (N = 950)	Zoledronic acid (N = 951)
Time to first on-study SRE (both asymptomatic and symptomatic)		
Number of patients with an SRE (%)	341 (35.9)	386 (40.6)
Median time to event, days (95% CI) Median time to event, months	629 (573, 757) 20.7	521 (456, 592) 17.1
Hazard ratio (95% CI)	0.82 (0.71, 0.95)	
p-value (unadjusted)	**Non-inferiority 0.0002; Superiority 0.0085**	
First on-study SRE by subtype		
Pathological fracture (%)	137 (14.4)	143 (15.0)
Radiation to the bone (%)	177 (18.6)	203 (21.3)
Surgery to the bone (%)	1 (0.1)	4 (0.4)
Spinal cord compression (%)	26 (2.7)	36 (3.8)
Time to first-and-subsequent on-study SRE		
Number of events	494	584
Mean number of events per subject	0.52	0.61
Rate Ratio (95% CI)	0.82 (0.71, 0.94)	
p-value (unadjusted)	**0.0044**	
Time to first symptomatic SRE		
Number patients with a symptomatic SRE (%)	241 (25.4)	289 (30.4)
Median time to event, days (95% CI)	NE	736 (630, 918)
Hazard ratio (95% CI)	0.78 (0.66, 0.93)	
p-value	**0.0051**	

Abbreviations: CI, confidence interval; NE, not estimable; SRE, skeletal related event

The results of Study 103 indicate that the risk of developing a first on-study SRE was statistically significantly reduced with denosumab treatment compared to zoledronic acid in prostate cancer patients (Hazard ratio 0.82 [95% CI: 0.71, 0.95]). Denosumab significantly reduced the risk of developing first-and-subsequent SREs by 18% compared with zoledronic acid (Rate ratio 0.82 [95% CI 0.71, 0.94]).

Outcomes reported in Study 136 showed that quality of life outcomes favoured denosumab, however, the difference between treatments was small and did not reach statistical significance. Pain outcomes also favoured denosumab but only reached statistical significance for time to moderate to severe pain (Hazard ratio 0.87 [95% CI: 0.79, 0.97]).

In both trials, overall survival and progression-free survival were similar between denosumab and zoledronic acid.

Similar proportions of patients in the denosumab and zoledronic acid treatment arms experienced adverse events during the trials, however the adverse event profiles of the two products differed. Zoledronic acid was more commonly associated with renal adverse events (including renal failure) and acute phase reactions (flu-like syndrome including pyrexia, chills, flushing, pain, arthralgia and myalgia) while denosumab was more commonly associated with hypocalcaemia, hypersensitivity reactions (a causal relationship to drug exposure has not been established) and osteonecrosis of the jaw (ONJ). However, the incidence of ONJ was low and not statistically different between treatment groups.

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

9. Clinical Claim

The submission described denosumab as superior to zoledronic acid in terms of comparative efficacy. This was accepted by the PBAC.

The submission made no specific claim in terms of comparative safety but stated that the benefit-risk profile of denosumab compared with zoledronic acid is positive.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented two separate economic analyses, one for the breast cancer population and one for the hormone-resistant prostate cancer population. Both analyses were based on single cohort Markov models with three health states (alive without an SRE whilst receiving treatment, alive with an SRE whilst receiving treatment and dead). The cohort transits through the Markov model in monthly cycles (28 days) until death. The models used a 10-year time horizon.

The results of the economic analyses showed denosumab treatment to be dominant (i.e., more effective and less costly).

During the evaluation, a series of sensitivity analyses were conducted to evaluate the impact of lowering IV zoledronic acid administration costs.

Denosumab treatment remained dominant at 50% of base case IV administration costs, however as the assumed administration costs were lowered the incremental cost-effectiveness ratio (ICER) increased. Using the lowest cost tested in sensitivity analysis, the ICER for denosumab was between $100,000 and $200,000 per quality adjusted life year (QALY) for both breast cancer and prostate cancer treatment.

The results of the multivariate sensitivity analyses conducted during the evaluation indicated that in addition to IV drug administration costs the model was also sensitive to time horizon, the disutility associated with SREs, the risk of first and subsequent SREs and the cost of managing SREs.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year was estimated in the submission to be between 50,000 and 100,000 in Year 5, at a net cost to the PBS/RPBS of between $10-30 million in Year 5. The net cost to Government health budgets (taking into account infusion cost-offsets) was estimated in the submission to be less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of denosumab on the PBS as an Authority Required benefit for treatment of bone metastases from breast cancer and hormone-resistant prostate cancer on the basis of acceptable cost-effectiveness compared with zoledronic acid 4 mg in 5 mL injection concentrate for I.V. infusion.

The PBAC recommended removal of the wording "with demonstration of biochemical progression despite maximal therapy with hormone treatments" as this was the definition of hormone-resistance and was consistent with the recommendation from the Restrictions Working Group (RWG).

The PBAC noted that denosumab treatment was associated with a statistically significant reduction in the risk of developing a first on-study skeletal related event (SRE), both asymptomatic and symptomatic, compared to zoledronic acid in breast cancer patients (HR 0.82; 95% CI 0.71, 0.95) and in prostate cancer patients (HR 0.82; 95% CI 0.71, 0.95). Denosumab treatment also significantly reduced the risk of developing first-and-subsequent SREs) in both breast and prostate cancer patients. The PBAC noted that denosumab treatment was not associated with any improvement in survival or disease progression compared to zoledronic acid and although pain and quality of life outcomes generally favoured denosumab the differences between treatments was small and did not reach statistical significance for most outcomes.

The PBAC accepted that the appropriate comparator was zoledronic acid and the submission's claim that denosumab is superior to zoledronic acid in terms of comparative efficacy. The PBAC noted that the submission did not make a specific claim regarding comparative safety. However, the overall incidence of adverse events is similar between denosumab and zoledronic acid. Denosumab was more commonly associated with hypocalcaemia, hypersensitivity reactions and osteonecrosis of the jaw while zoledronic acid was more commonly associated with renal adverse events (including renal failure) and acute phase reactions.

The PBAC was concerned that the results presented in the economic model showing dominance of denosumab treatment were primarily driven by the high drug administration cost estimate attributed to infusion of zoledronic acid. The Committee considered that there was considerable uncertainty around this estimate as there is a large disparity in drug administration costs for zoledronic acid infusions between treatment settings and between the States and Territories.

Even with the uncertainty surrounding the drug administration cost of zoledronic acid infusions, the PBAC considered that the revised base case ICERs, presented in the Pre-PBAC Response calculated with a revised price offer and with various scenarios of infusion costs for zoledronic acid were acceptable.

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

Recommendation:
DENOSUMAB, injection, 120 mg in 1.7 mL

Restriction: Authority Required
Bone metastases from breast cancer.
Bone metastases from hormone-resistant prostate cancer.

Note

Continuing Therapy Only:
For prescribing by nurse practitioner 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.

Maximum Quantity	1
No. of 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

Amgen is pleased that denosumab (Xgeva®) has been recommended for PBS listing for Australian patients with bone metastases from breast cancer and hormone-resistant prostate cancer.