

7.03 DENOSUMAB Injection 120 mg in 1.7 mL Xgeva[®], Amgen Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor re-submission sought an Authority Required (Streamlined) listing of denosumab for the treatment of bisphosphonate-refractory hypercalcaemia of malignancy (HCM) on a cost-minimisation basis with zoledronic acid.

2 Requested listing

- 2.1 The minor re-submission requested the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
DENOSUMAB 120mg/1.7mL injection, 1 x 1.7mL Vial	1	5	\$ [REDACTED]	XGEVA [®]	Amgen Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Hypercalcaemia of malignancy
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have a malignancy refractory to anti-neoplastic therapy. AND Condition must be refractory to treatment with an intravenous bisphosphonate.
Administrative Advice	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 more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 Denosumab was TGA registered on 8 September 2011, and is currently indicated for the following indications:

- Prevention of skeletal related events in patients with bone metastases from solid tumours;
- Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity; and
- Treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate.

3.2 Denosumab for hypercalcaemia of malignancy was previously considered by the PBAC in March 2016.

3.3 The PBAC rejected the submission for denosumab in March 2016 on the basis of low quality clinical data that did not support the claim of superior efficacy over zoledronic acid, and the lack of a clear clinical place for denosumab. The PBAC considered that the clinical place of denosumab had not been clearly defined, particularly in the context of refractory and relapsed patients, and that there was a high likelihood of ongoing denosumab use in patients while they are still responsive to bisphosphonates or where hypercalcaemia would be well controlled by treatment of the underlying condition. The PBAC also noted differences in the treatment algorithm between denosumab and zoledronic acid, where one was for ongoing therapy whereas the comparator was for episodic treatment.

3.4 The PBAC considered in March 2016 that a future re-submission for this indication should be a major submission, and should include a further cost-minimisation analysis between denosumab and bisphosphonates, and further identify the patient group for which PBS listing is sought.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

4.1 This submission and the March 2016 submission positioned denosumab as an alternative therapy in patients who are refractory to initial intravenous bisphosphonate treatment. The proposed current therapy for retreatment was an intravenous bisphosphonate such as pamidronate or zoledronic acid.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 The minor re-submission nominated zoledronic acid as the comparator. This was unchanged from the March 2016 submission.

- 5.2 The re-submission disagreed with the March 2016 PBAC advice that pamidronate was also a relevant comparator, on the basis that it had substantially lower utilisation than zoledronic acid, and had been accepted as being less effective than zoledronic acid for this indication. The PBS Therapeutic Relativity sheets state that “Zoledronic acid injection 4 mg (Zometa®) was listed on the basis of acceptable cost-effectiveness compared to disodium pamidronate injection 90 mg in the treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy’.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual health care professional via the Consumer Comments facility on the PBS website. The comment described a range of benefits of treatment with denosumab including the ability to improve quality of life in patients from successful treatment of bisphosphonate refractory hypercalcaemia of malignancy.

Clinical trials

- 6.3 As a minor re-submission, no new clinical trials were presented.

Comparative effectiveness

- 6.4 The trial results remained unchanged from the previous major submission considered in March 2016. The results from the March 2016 submission are repeated below.
- 6.5 The submission was based on a naïve indirect comparison between a single-arm denosumab observational study and a pooled subgroup analysis of zoledronic acid 8mg retreatment from two randomised controlled trials.
- 6.6 The submission also presented a supportive comparison of denosumab and zoledronic acid for the prevention of hypercalcaemia of malignancy based on a retrospective, pooled analysis of two randomised controlled trials.
- 6.7 No data were available to support a comparison of zoledronic acid 4 mg with denosumab for retreatment of hypercalcaemia of malignancy.
- 6.8 The PBAC concluded at the March 2016 meeting (PBAC public summary document paragraphs 6.22 and 6.23) that claims of superior comparative effectiveness and non-inferior comparative safety to zoledronic acid were not adequately supported by the data.

Economic analysis

6.9 The submission proposed listing on a cost minimisation basis with zoledronic acid. The cost minimisation analysis estimated the proportion of denosumab use that would be attributed to HCM and calculated a cost minimised price to the comparator. The submission then offset the proportion of patients receiving denosumab at the lower price against the current price of denosumab and proposed a new weighted price for denosumab as shown in the table below.

Table 1: Cost-minimisation of denosumab vs zoledronic acid dose

1. Zoledronic acid DPMQ	\$ [REDACTED]
2. Extra cost for IV administration	\$ [REDACTED]
3. Total cost of 4mg zoledronic acid dose	\$ [REDACTED]
Denosumab 120mg DPMQ	\$ [REDACTED]
Proposed % of use at lower price	[REDACTED] (%)
Proposed weighted price	\$ [REDACTED]

Source: Submission Excel worksheet Pricing, Sheet 1.

The redacted table shows the proposed weighted price as less than \$10 million.

6.10 The Secretariat noted that the submission’s financial estimates assumed patients being treated with denosumab will receive on average 5 doses of that drug, whereas patients receiving treatment with zoledronic acid were assumed to receive two doses. The cost-minimisation calculation in the submission did not account for this difference.

6.11 The weighted price was based on overall utilisation of denosumab being comprised of [REDACTED]% (conservatively rounding upwards) from HCM and [REDACTED]% from existing listings. This distribution of use is based on forecast utilisation outlined in Table 2 of the submission (replicated below). Shaded cells in Table 2 represent actual utilisation for the existing denosumab listings.¹ Forecast utilisation for the existing listings is based on annual growth rates which are assumed to diminish over time, consistent with uptake eventually plateauing. HCM forecast utilisation is based on estimates presented in the March 2016 submission with HCM patient numbers modified to reflect the more accurate numbers provided by the DUSC during the evaluation of that submission.

Estimated PBS usage & financial implications

6.12 The submission proposed a new weighted DPMQ of \$ [REDACTED] based on overall utilisation estimates of approximately [REDACTED]% use for HCM. This weighted DPMQ for all denosumab listings is based on [REDACTED]% use at \$ [REDACTED] (the price of zoledronic acid plus the cost of I.V. administration), and [REDACTED]% use at the current price of \$501.00. The submission calculated the weighted price using the formula:

$$([REDACTED] \times [REDACTED]) + ([REDACTED] \times 501.00) = \$ [REDACTED]$$

¹ Sourced online at http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp.

- 6.13 The re-submission used utilisation estimates provided by the Drug Utilisation Subcommittee (DUSC). The revised utilisation estimates are provided below.

Table 2: Utilisation estimates for denosumab

Year	Services for existing listings	Annual growth for existing listings	Services for HCM	% total denosumab use that is HCM
2011				
2012				
2013		%		
2014		%		
2015		%		
2016		%		
2017		%		%
2018		%		%
2019		%		%
2020		%		%
2021		%		%

Source: Denosumab submission, p. 3

The redacted table shows the estimated utilisation of services for existing listings in 2021 is between 50,000 – 100,000 per year and the estimated utilisation of services for HCM in 2021 is less than 10,000 per year.

- 6.14 The sponsor provided new financial estimates based on updated utilisation estimates, the revised lower price, cost offsets for substitution of zoledronic acid 4 mg and updated patient co-payments. The submission’s revised financial estimates resulted in a net cost to the PBS of less than \$10 million in year 5, and less than \$10 million over five years. The Secretariat noted that although as a minor submission the financial estimates have not been evaluated, the cost to Government appeared to largely result from the assumption that patients treated with denosumab would receive an average of 5 doses of that drug whereas patients treated with zoledronic acid would receive two doses (refer submission financial estimates spreadsheet-background and assumptions).
- 6.15 The PBAC noted that the financial estimates in the submission were no longer applicable based on the recommendation for the cost-minimisation of denosumab to pamidronate.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (Streamlined) listing of denosumab, on a cost minimisation basis to pamidronate (as the least costly bisphosphonate, given that no evidence of superiority of denosumab was provided). As with the comparison with zoledronic acid, the equi-effective doses of denosumab and pamidronate are difficult to estimate because of their different treatment regimens, with the former an ongoing therapy whereas the latter is an episodic treatment. The PBAC considered the equi-effective dose to be 5 individual SC injections of 120 mg denosumab to one 90 mg infusion of pamidronate.

- 7.2 The PBAC noted the Pre-PBAC response that asserted that the cost of an IV administration was conservative at \$60 and was more likely to be over \$300/ IV. The PBAC considered that \$60/ IV was reasonable as the majority of patients receiving pamidronate or zoledronic acid would have an IV port *in situ*.
- 7.3 The PBAC considered that the clinical place for denosumab in the treatment of HCM was in malignancy refractory to anti neoplastic therapy and as second-line to bisphosphonates. In this setting, although defining a group of patients as refractory to bisphosphonates (hence a second-line listing) was a pragmatic way forward, the PBAC recognised that identifying a truly bisphosphonate-resistant group was problematic, and that in clinical practice these patients were likely to continue to receive bisphosphonates (and other therapies).
- 7.4 The PBAC did not agree with the sponsor's claim that pamidronate was not an appropriate comparator on the basis of the continued use of bisphosphonates including pamidronate, for the treatment of HCM and the likelihood that denosumab would substitute for pamidronate in this indication. The PBAC noted the submission had not provided any data to demonstrate the superiority of denosumab over pamidronate, and as noted by the PBAC in March 2016, the comparison of denosumab and zoledronic acid was based on very poor quality data. In the absence of better quality clinical data, the PBAC considered pamidronate to be the most reasonable comparator on which to base a listing recommendation.
- 7.5 The PBAC considered that the utilisation estimates were an underestimation as there was a high likelihood of usage in patients while they are still responsive to bisphosphonates or where hypercalcaemia would be well controlled by treatment of the underlying condition.
- 7.6 The PBAC advised that denosumab is not suitable for prescribing by nurse practitioners in this indication in alignment with zoledronic acid and pamidronate.
- 7.7 The PBAC recommended that the Early Supply Rule should apply.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
DENOSUMAB 120mg/1.7mL injection, 1 x 1.7mL Vial	1	5	XGEVA®	Amgen Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
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Clinical criteria:	Patient must have a malignancy refractory to anti-neoplastic therapy. AND Condition must be refractory to treatment with an intravenous bisphosphonate.

9 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.

10 Sponsor's Comment

The sponsor had no comment.