7.07 DENOSUMAB
Injection 120 mg in 1.7 mL, Xgeva®, Amgen Australia Pty Limited

1 Purpose of Application

1.1 The minor resubmission proposed a revised price for denosumab for an Authority Required (STREAMLINED) listing for the treatment of multiple myeloma.

2 Requested listing

2.1 The proposed PBS listing is the same as requested in the July 2018 major submission.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DENOSUMAB 120 mg/1.7 mL injection, 1.7 mL vial	1	1	5	TBC*	Xgeva® Amgen

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Multiple Myeloma
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
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.

*see economic analysis section

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

3 Background

Registration status

3.1 Denosumab 120 mg was registered for use in multiple myeloma on 20 July 2018. The registered indication is:

- Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.

Previous PBAC consideration

3.2 Denosumab 120 mg is currently listed on the PBS for treatment of giant cell tumour of bone and bone metastases from breast or castrate-resistant prostate cancer.

3.3 In July 2018, the PBAC considered a major submission seeking an extension of the current Section 85 Streamlined Authority Required listing for denosumab to include treatment of patients with multiple myeloma. The PBAC decided not to recommend extending the listing as there was an inadequate basis for accepting the claim of superior effectiveness compared to zoledronic acid and the incremental cost-effectiveness based on superior progression-free survival (PFS) was implausible. The clinical evidence indicated non-inferiority to zoledronic acid for the outcome of skeletal-related events (SREs) (PBAC Public Summary Document (PSD) July 2018, paragraph 7.1).

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

4 Clinical place for the proposed therapy

4.1 The proposed clinical place remains unchanged from the July 2018 major submission, which positioned denosumab as an alternative to IV bisphosphonates for patients with multiple myeloma.

5 Comparator

5.1 In July 2018, the PBAC agreed that zoledronic acid was a relevant comparator, being the most commonly used bisphosphonate in multiple myeloma patients. However, the population in which the clinical need for denosumab may be greatest is for patients with severe renal impairment (eGFR <30 ml/min), where currently pamidronate and clodronate may be used; a recent review from Myeloma and Related Disease Registry (MRDR) suggested these patients accounted for 12% of newly diagnosed patients[1] (PBAC PSD July 2018, paragraph 7.4).

5.2 As listing of denosumab is sought for the overall multiple myeloma population and zoledronic acid remained the nominated comparator for this minor resubmission. The resubmission noted the limited use of clodronate reported in the Myeloma and Related Diseases Registry[2] (2% of patients) with zoledronic acid the most commonly used treatment (68% of patients), and pamidronate the next most commonly used treatment (27% of patients).

5.3 Although generally reserved for patients with renal impairment, pamidronate and clodronate may be relevant comparators given the eligible populations as defined by

[1] P.J. Ho et al, Haematologica 2017;102(s1):268. Abstract n. P674 [Presentation at the European Hematology Association (22nd Congress), 2017]

[2] Myeloma and Related Diseases Registry (MDRD) report 16 July 2018, Table 12.

the listings overlap with the requested listing for denosumab. Therefore, in the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. The minor resubmission sought to achieve pricing parity by increasing the expected cost of infusion for the cheaper drug therapy (see Economic analysis section).

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 that no consumer comments were received for this item.

Clinical claim

6.3 No new clinical evidence was presented in the resubmission. The relative efficacy and safety of denosumab compared with zoledronic acid in the July 2018 major submission was based on one direct trial, Study 482. In this minor resubmission the clinical claim based on this trial was:

- Denosumab is non-inferior to zoledronic acid on SRE endpoints and is associated with improved PFS.
- Denosumab is similar to zoledronic acid in terms of comparative overall safety but associated with a lower incidence of renal adverse events.

6.4 In July 2018 the PBAC considered that the claim of superior comparative effectiveness based on PFS was not adequately supported by the data. The PBAC considered that the claim of non-inferior effectiveness based on SREs was adequately supported by the data. The PBAC also considered that the claim of similar comparative safety was reasonable (July 2018 PBAC PSD, paragraphs 6.24-6.25).

6.5 The resubmission acknowledged the uncertainty in the superiority claim and has provided a mechanism for PBAC to reconsider a recommendation for denosumab based on cost minimisation with zoledronic acid (or pamidronate) at a price the sponsor is able to accept.

6.6 The minor resubmission maintained that it is reasonable to conclude that denosumab offers a benefit over zoledronic acid in terms of reduced renal toxicity.

6.7 The PBAC reiterated its consideration from July 2018 (July 2018 PBAC PSD, paragraphs 6.24-6.25) that the claim of non-inferior comparative effectiveness based on SREs and similar comparative safety to zoledronic acid was reasonably supported by the data.

Economic analysis

Price proposal

6.8 The minor resubmission proposed a staged price reduction across all denosumab 120 mg indications that, from the second year of the multiple myeloma listing, would represent a reduction of [redacted]% from the current price. The ex-manufacturer price per 120 mg vial as at 1 October 2018 was $446.50. The proposed ex-manufacturer prices under the staged reductions were:

- $[redacted] for the first year of the multiple myeloma listing.
- $[redacted] from the start of the second year of the multiple myeloma listing.

Following the above reductions, denosumab is scheduled for a 10% statutory price reduction in April 2021.

Multiple myeloma price

6.9 Multiple myeloma patients were assumed to represent [redacted]% of the patients using bone agents for either breast cancer, prostate cancer or myeloma — this was derived from the 10% Medicare Australia sample for twelve months to March 2015 used in the July 2018 major submission. The minor resubmission has thus assumed that an overall ex-manufacturer price of $[redacted] for denosumab would represent an ex-manufacturer price for use in multiple myeloma of $[redacted], based on this weighting across indications:

Current price x proportion of use in current indications + MM price x proportion of use in MM = $[redacted]

$[redacted] x 0.[redacted] + MM price x 0.[redacted]^= $[redacted]

MM price = ($[redacted] – $[redacted] x 0.[redacted]) / 0.[redacted]

MM price (ex-manufacturer) = $[redacted]

MM price (DPMQ) = $[redacted]

^ MM (multiple myeloma) patients represent [redacted]% of patients receiving bone agents (July 2018 PBAC Commentary, Table 4.1 and July 2018 pre-PBAC response).

Cost-minimisation analysis

6.10 To equate the denosumab price in multiple myeloma to the current prices of zoledronic acid or pamidronate, the minor resubmission has attributed greater infusion costs for both comparator drugs than used to establish their prices for PBS listing.

6.11 Current dispensed drug costs per dose are $183.58 (zoledronic acid) and $90.57 (pamidronate).[3] With an infusion cost assumption of $[redacted] (for zoledronic acid) or $[redacted] (for pamidronate), the total cost per dose of an IV bisphosphonate would be the same as the above cost per denosumab dose in multiple myeloma, i.e.:

- Zoledronic acid drug cost of $183.58 + infusion cost of $[redacted] = $[redacted]
- Pamidronate drug cost of $90.57 + infusion cost of $[redacted] = $[redacted].

6.12 The minor resubmission noted that bisphosphonate infusions take longer and are more complex in the multiple myeloma setting where a majority of patients have some level of renal impairment. The time to deliver pamidronate (administered over 4 hours) is much longer than for zoledronic acid (no less than 15 minutes).

6.13 The minor resubmission argued that the original denosumab submission (for bone metastases due to breast cancer), using methodology recommended in the 2008 PBAC guidelines, determined the cost of administration of an IV infusion to be $[redacted] at 2011 prices (Section C of July 2011 PBAC submission). This cost reflected that the majority (70%) of bisphosphonate infusions are given in the inpatient setting and the cost components of funding actually claimed by hospitals.

6.14 In July 2011, the PBAC recommended denosumab for PBS listing on the basis of acceptable cost-effectiveness over zoledronic acid. However it was noted that:

> *"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 the revised price offer and with various scenarios of infusion costs between $[redacted] and $[redacted] for zoledronic acid were acceptable.*
>
> *However, the PBAC considered that the issue of determining an appropriate infusion cost for zoledronic acid should be investigated and the listing for denosumab be reviewed, should the cost of infusion be below $[redacted], when this information becomes available." (paragraphs 5.6.30 & 5.6.31, denosumab PBAC minutes, July 2011, agenda item 5.6).*

6.15 This minor resubmission also identified a precedent from 2006 for the PBAC accepting $300-380 (estimated range[4]) as the cost for IV vinorelbine administration, the infusion of which is short (6-10 minute bolus or 20-30 minute infusion) and relatively straightforward. The Therapeutic Relativity sheets state:

> *"Vinorelbine tartrate capsules were recommended for listing on a cost minimisation basis versus intravenously administered vinorelbine. The equi-effective doses are one 3-week cycle at 60mg/m^2 and two 3-week cycles at 80mg/m^2 for oral vinorelbine and three 3-week cycles at 30mg/m^2 for intravenous vinorelbine."*

[3] Zoledronic acid 4mg and pamidronate 90mg dispensed prices with 32% of use in public hospital.

[4] Infusion cost estimated based the statement in the PBPA Therapeutic Relativity Sheets for the oral vs IV vinorelbine cost minimisation decision (March 2006 PBAC meeting) and August 2006 dispensed prices.

The March 2006 PBAC minutes for vinorelbine for locally advanced or metastatic non-small cell lung cancer stated:

> *"The PBAC did not agree that all patients receiving IV vinorelbine would be admitted as inpatients and therefore the cost offsets claimed for oral vinorelbine that were associated with administration of the IV formulation had been over-estimated. The price should be adjusted to take into account the proportion of patients receiving IV vinorelbine in the outpatient setting in calculating the administration cost-offsets." (section 12, vinorelbine, Public Summary Document, March 2006).*

Committee-in-confidence information

[redacted]

End Committee-in-confidence information

6.16 Advice from the Medical Benefits Division for this minor resubmission for denosumab was that administration of parenteral bisphosphonates is reimbursed on a consultation basis. Specialists would commonly bill either item 116 or 119 for a consultation of this nature; the Schedule Fees for these items as of September 2018 were $76.65 and $43.65, respectively.

6.17 The minor resubmission did not factor cost-savings from reduced infusion administration into the financial estimates (see below).

Drug cost/patient/year: $[redacted]

6.18 The estimated drug cost for denosumab 120 mg per patient per year was $[redacted] based on 9.5 scripts using the proposed DPMQ for multiple myeloma of $[redacted].

Estimated PBS usage & financial implications

6.19 Table 1 presents the estimated total use and costs of denosumab in the first 6 years of listing. The changes to financial estimates from the July 2018 major submission were:

- The assumption that all potentially eligible multiple myeloma patients are receiving bisphosphonates currently. This assumes that pamidronate and clodronate may be used for patients with CrCl < 30mL/min. In the July 2018 submission, an additional less than 10,000 patients were considered unsuitable for bisphosphonates in year 1 and 100% uptake with denosumab was assumed.

- An increase in the average script number for denosumab from 7.5 to 9.5 to reflect the view that compliance will be higher in the multiple myeloma population. In the July 2018 PBAC minutes it was suggested that compliance would not be as low as [redacted]% (which was based on the 10% Medicare sample) because in this indication therapy for skeletal-related events is given concomitantly with anti-myeloma therapy or timed with a review for patients on oral therapy (paragraph 6.42).
- Uptake of denosumab in year 1 has increased from [redacted]% to [redacted]%. The uptake in the years 2–6 remain the same as in July 2018, from [redacted]%–[redacted]%.
- A reduction in the denosumab price.
- Associated cost offsets from the reduction in price for existing denosumab 120 mg indications were included. The 10% April 2021 statutory price reduction is not included in the base case but is included in a separate analysis (Table 2).
- Updated bisphosphonate substitution distribution based on recent bisphosphonate use from the Myeloma and Related Diseases Registry.
- Updated prices for zoledronic acid and pamidronate.

6.20 The minor resubmission did not include cost offsets for infusion administration in the financial estimates.

Table 1: Estimated use and total cost of denosumab to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of denosumab MM patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of denosumab MM services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gross cost of denosumab for MM to the PBS/RPBS[a,b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offset from substitution[a]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost offset from existing indications[c]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost of denosumab MM listing to the PBS/RPBS[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: BP = bisphosphonate; MM = multiple myeloma; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Analysis assumes listing from 1 January 2019.
a. Costs represent DPMQ – copayment.
b. Based on proposed price that would apply across all denosumab 120 mg indications.
c. Based on forecast services for existing denosumab indications and the difference between current and proposed reduced DPMQ.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.

Table 2: Estimated use and total cost of denosumab including 10% statutory price reduction on April 2021

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Gross cost of denosumab for MM to the PBS/RPBS[a]	$	$	$	$	$	$
Net cost of denosumab MM listing to the PBS/RPBS[a]	$	$	$	$	$	$

Abbreviations: BP = bisphosphonate; MM = multiple myeloma; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Analysis assumes listing from 1 January 2019.
a. Costs represent DPMQ – copayment.

6.21 The estimated net cost to the PBS/RPBS for denosumab was less than $10 million in Year 1, increasing to less than $10 million in Year 6, with a total cost of $30 – $60 million in the first 6 years of listing. This compares with $60 – $100 million in the first 6 years of listing in the July 2018 major submission. The estimates including the 10% statutory discount from April 2021 were less than $10 million in Year 1, increasing to less than $10 million in Year 6, with a total of $30 – $60 million in the first 6 years of listing).

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

7 PBAC Outcome

7.1 The PBAC did not recommend the PBS listing of denosumab for the treatment of multiple myeloma on the basis that the price proposal did not meet the requirements of a cost minimisation analysis.

7.2 The PBAC accepted that zoledronic acid and pamidronate were appropriate comparators.

Committee-in-confidence information

End Committee-in-confidence information

7.3 The PBAC noted the modest clinical need, given the present availability of alternative treatments.

7.4 The PBAC considered that the claim of non-inferior comparative effectiveness and similar comparative safety to zoledronic acid was reasonably supported by the data.

7.5 The PBAC noted that the cost-minimisation approach proposed by the sponsor included substantial cost-offsets for the IV administration of zoledronic acid or pamidronate. The PBAC noted the advice from the Medical Benefits Division that administration of bisphosphonates is reimbursed on a consultation basis, and would attract Schedule Fees of $76.65 or $43.65. The PBAC noted that a higher cost for infusions to include activity-based costing for hospital funding is not routinely considered by PBAC for the purpose of cost-minimisation, as some costs associated with the prescribing and administration by other health professionals could apply to

all drugs on the PBS. The latest *Manual of resource items and their associated costs* (version 5.0) specifies a preference for using only the relevant Medicare Benefits Schedule (MBS) fee if the medicine or medicinal preparation is administered by infusion.

7.6 The PBAC is of the view that the proposed price of denosumab, underpinned by substantial and uncertain infusion cost off-sets, is not currently supported.

7.7 The PBAC advised that any subsequent submission should consider a cost-minimisation approach that applied previously accepted infusion costs for zoledronic acid and pamidronate, or a justification based on robust evidence for cost offsets that deviate from previously accepted costs.

7.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 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.

9 Sponsor's Comment

Amgen is disappointed with the outcome but will continue to work with the PBAC to address the clinical need for an alternative to bisphosphonate therapy in patients with multiple myeloma.