

**7.04 DENOSUMAB,  
Injection 120 mg in 1.7 mL,  
Xgeva<sup>®</sup>,  
Amgen Australia Pty Limited.**

**1 Purpose of Application**

- 1.1 The resubmission requested an extension of the current Section 85 Streamlined Authority Required listings for denosumab to include treatment of patients with multiple myeloma who have renal impairment (creatinine clearance  $\leq$  60 mL/min). Denosumab 120 mg is currently listed on the PBS for treatment of giant cell tumour of bone and bone metastases from breast and castration-resistant prostate cancer. The PBAC previously considered denosumab for multiple myeloma in July 2018 (item 6.03 refers) and November 2018 (item 7.07 refers, minor submission).
- 1.2 Listing was requested based on a cost-effectiveness analysis versus zoledronic acid (Table 1).

**Table 1: Key components of the clinical issue addressed in the resubmission**

<b>Component</b>	<b>Description</b>
Population	Patients with bone lesions due to multiple myeloma who have renal impairment (creatinine clearance $\leq$ 60 mL/min)
Intervention	Denosumab 120 mg subcutaneous injection every 4 weeks
Comparator	Zoledronic acid 4 mg intravenous infusion (main comparator) and pamidronate 90 mg intravenous infusion (secondary comparator) every 3-4 weeks
Outcomes	Prevention of skeletal related events and reduced incidence of renal adverse events
Clinical claim	Denosumab is non-inferior in terms of prevention of skeletal related events and superior in terms of safety due to lower incidence of renal adverse events compared to zoledronic acid Denosumab is non-inferior in terms of prevention of skeletal related events and superior in terms of safety due to lower incidence of renal adverse events compared to pamidronate

Source: Table 1.1.1, p11 of the resubmission

- 1.3 The sponsor also provided alternative pricing and financial estimates for the option of PBS listing for denosumab based on a lower creatinine clearance (CrCl) threshold of  $\leq$  30 mL/min. The resubmission proposed a higher price and lower financial caps for a Risk Sharing Arrangement for this listing. However, the resubmission did not provide clinical evidence or an economic analysis to support this indication.

## 2 Requested listing

2.1 Secretariat suggested additions are in italics and deletions are in strikethrough.

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	\$ [REDACTED]	Xgeva® Amgen
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)				
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
<b>Condition:</b>	Multiple Myeloma				
<b>PBS Indication:</b>	<i>Multiple myeloma</i>				
<b>Clinical criteria</b>	Patient <del>has</del> <i>must have</i> creatinine clearance of 60 millilitres per minute or less				
<b>Restriction Level / Method:</b>	<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				
<b>Administrative Advice</b>	<b>Continuing therapy only</b> 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.				

- 2.2 The proposed DPMQ was for a weighted price based on existing indications for denosumab 120 mg and the proposed listing for multiple myeloma. The Pre-Sub-Committee Response (PSCR) confirmed that the proposed price would apply to all indications including giant cell tumour of bone.
- 2.3 The requested listing was narrower than the TGA indication for use in any patients with multiple myeloma but broader than the clinical evidence presented in the resubmission, which excluded patients with severe renal impairment (creatinine clearance < 30 mL/min).
- 2.4 Given the differences in mode of administration and safety profile with existing therapies, there is potential for use of denosumab outside the requested restriction in the broader population with multiple myeloma (creatinine clearance > 60 mL/min).
- 2.5 The ESC noted the variability of creatinine measurements. Should the PBAC recommend listing in a population with renal impairment, the ESC considered that the requested listing should stipulate that a patient must have had either a 24-hour urine test, or a minimum of two independent serum tests, in order to meet the criterion of having a creatinine clearance rate of 60 millilitres per minute or less. Regardless, the ESC still considered there would be a risk of use outside the intended population of patients with renal impairment.

- 2.6 Across the broad multiple myeloma population, the ESC considered that denosumab (and zoledronic acid) would be suitable for nurse prescribing as continuing therapy only (although noting that nurse prescribing is not currently permitted for s100 drugs).

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

### **3 Background**

#### ***Registration status***

- 3.1 Denosumab 120 mg was registered for the prevention of skeletal related events in patients with multiple myeloma on 20 July 2018.

#### ***Previous PBAC consideration***

- 3.2 The sponsor presented a major submission to the July 2018 PBAC meeting to request an extension of listing for denosumab to include patients with multiple myeloma. Although the clinical evidence indicated non-inferiority to zoledronic acid for the outcome of skeletal related events, the PBAC rejected the request 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 was implausible (para 7.1, denosumab PSD July 2018). The PBAC also considered that the claim of similar comparative safety was reasonable (para 6.24 and 6.25, denosumab PSD July 2018). The July 2018 pre-PBAC response signalled an unwillingness to supply denosumab on a cost-minimisation basis with the comparator, zoledronic acid (para 7.9, denosumab PSD July 2018).
- 3.3 The sponsor subsequently presented a minor submission to the November 2018 PBAC meeting for the same indication with a cost-minimisation analysis against zoledronic acid and pamidronate. 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. The proposed price of denosumab was underpinned by substantial and uncertain infusion cost offsets (para 7.1 and 7.6, denosumab PSD November 2018).
- 3.4 The current resubmission has narrowed the requested PBS population to patients who have a creatinine clearance of  $\leq 60$  mL/min. The resubmission included a revised clinical claim that describes denosumab as superior in terms of safety due to lower incidence of renal adverse events compared to zoledronic acid and pamidronate. The cost-effectiveness analysis in the resubmission retains infusion cost offsets used in previous submissions.
- 3.5 The outstanding matters of concerns from the July 2018 and November 2018 (minor) PBAC meetings are summarised in Table 2.

**Table 2: Summary of outstanding matters of concern**

Matter of concern	How the resubmission addresses it
The PBAC noted the modest clinical need, given the present availability of alternative treatments [for the broader population with multiple myeloma] (7.3, November 2018 PSD)	The resubmission proposed a new listing for denosumab for the treatment of patients with multiple myeloma who have renal impairment, specifically creatinine clearance $\leq 60$ mL/min.
The PBAC did not recommend denosumab for the treatment of multiple myeloma on the basis that the price proposal did not meet the requirements of a cost minimisation analysis (7.1, November 2018 PSD) The PBAC advised that any subsequent submission should consider a cost-minimisation approach that applied previously accepted infusion costs for zoledronic acid or pamidronate, or a justification based on robust evidence for cost offsets that deviate from previously accepted costs (7.7, November 2018 PSD)	The resubmission presented a cost-effectiveness analysis based on a clinical claim of superior safety due to reduced incidence of renal toxicity for denosumab versus zoledronic acid.
The PBAC considered the proposed price of denosumab, underpinned by substantial and uncertain infusion cost offsets, was not supported (7.6, November 2018 PSD) The PBAC noted advice from the Medical Benefits Division that bisphosphonate administrations are reimbursed on a consultation basis and would attract Schedule Fees of \$76.65 or \$43.65 (7.5, November 2018 PSD)	The resubmission provided cost-effectiveness analyses using various intravenous infusion costs from \$43.65 to \$322.17.
The PBAC noted there were limited data regarding the optimal duration of therapy with denosumab and that there may be a potential quality use of medicines issue regarding rebound osteoclast activity (7.3, July 2018 PSD)	The resubmission acknowledged there were no data to indicate optimal duration of therapy for denosumab.
The PBAC noted no clinical evidence in the population with greatest clinical need (severe renal impairment with creatinine clearance $< 30$ mL/min) who were excluded from Study 482 (7.4, July 2018 PSD)	The resubmission provided post-hoc subgroup analyses from Study 482 in patients with creatinine clearance $\leq 60$ mL/min and $\leq 45$ mL/min.

Source: compiled during the evaluation

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

## 4 Population and disease

- 4.1 Multiple myeloma is a type of bone marrow cancer that is more common in people aged 60 years and older, and affects more men than women. The disease arises from uncontrolled growth of plasma cells, which are part of the immune system. The abnormal growth can affect multiple places in the body, leading to skeletal destruction, bone marrow failure, increased plasma volume and viscosity, suppression of normal immunoglobulin production and renal insufficiency.
- 4.2 Clinical progression of multiple myeloma results in the development of bone disease, which is typically characterised by the development of bone lesions. In multiple myeloma, the hypersecretion of RANK ligand (RANKL) increases osteoclast activity, which in turn leads to increased breakdown of bone tissue. Common complications of bone disease include bone pain, spinal cord compression and pathologic fractures. Bone lesions and bone pain are managed using localised radiotherapy or bisphosphonate treatment.

- 4.3 Kidney disease is a common complication of multiple myeloma which can manifest in a variety of ways including acute kidney injury, chronic kidney disease, albuminuria (or nephrotic syndrome) or electrolyte imbalances. Patients with multiple myeloma who also have renal impairment may have limited options for the treatment of bone disease given renal safety concerns with intravenous bisphosphonates, which are generally not recommended in patients with severe renal impairment.
- 4.4 The resubmission positioned denosumab as an alternative to IV bisphosphonates (zoledronic acid or pamidronate) in patients who can attend hospital and as an alternative to clodronate in those who cannot attend hospital. The PSCR claimed that with the recent removal of clodronate from the PBS (effective 1 May 2019), there is now no subsidised alternative to intravenous bisphosphonates for Australian myeloma patients with renal impairment. The ESC considered that this would increase the risk of leakage outside the proposed population, in rural and regional settings in particular.
- 4.5 The proposed algorithm did not clearly describe differences in treatment options according to degrees of renal impairment. The product information for IV bisphosphonates do not recommended use in severe renal impairment (creatinine clearance < 30 mL/min) but suggest lower doses with adjusted infusion times in those with mild to moderate impairment (creatinine clearance between 30-60 mL/min). Published Australian guidelines (Lee et al 2017) state that neither pamidronate nor zoledronic acid is recommended in patients with severe renal impairment; however they suggest that pamidronate may be used at slower infusion rates in cases of significant myeloma bone disease or life-threatening hypercalcaemia. The Australian guidelines were published prior to the availability of denosumab for this indication. More recent international guidelines (ASCO 2018, NCCN 2018) suggest that denosumab is preferred over bisphosphonates in cases of renal insufficiency (creatinine clearance < 40 mL/min).
- 4.6 Published guidelines note that following 1-2 years of therapy, the treatment regimen of IV bisphosphonates may be adjusted based on risk of skeletal related events (reduced to 3-monthly administration, cessation of therapy) (Lee et al 2017, ASCO 2018). The PBAC has noted the lack of data for denosumab in regards to optimal duration of therapy and was concerned about rebound osteoclast activity following cessation of treatment (para 7.3, denosumab PSD July 2018). The resubmission acknowledged there are no further data to inform this issue, however, updated safety data indicate that increased risk of fractures following cessation of denosumab remains an important identified risk. The ESC noted this concern, and also considered that the clinical management algorithm (and requested listing) did not explain how patients taking denosumab would be managed if their renal function improved whilst on therapy. For instance, it was unclear if they would be expected to take a treatment holiday, transition to intravenous bisphosphonate therapy, or remain on denosumab therapy. Published guidelines recommend that denosumab should not be stopped abruptly, and suggest at least one dose of IV bisphosphonates after cessation due to

the risk of rebound osteoclast activity (UpToDate – The use of osteoclast inhibitors in patients with multiple myeloma, May 2018). It was also unclear if the financial estimates accounted for these patients who may transition to IV bisphosphonates.

- 4.7 The target population for denosumab in the resubmission is patients with multiple myeloma who also have creatinine clearance  $\leq 60$  mL/min. The ESC considered there may be a greater clinical need for denosumab therapy in patients with severe renal insufficiency (CrCl  $< 30$  mL/min), than in with patients with mild to moderate impairment (CrCl of 30-60 mL/min), as the latter can still use intravenous (IV) bisphosphonates at slower infusion rates. Although no clinical evidence in this population was presented, the PSCR reiterated that international guidelines now include denosumab as a preferred bone targeted agent for patients with renal insufficiency ( $< 40$  mL/min) (NCCN, 2018; Anderson et al (ASCO), 2018).

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

## 5 Comparator

- 5.1 The resubmission nominated zoledronic acid as the main comparator and pamidronate as a secondary comparator.
- 5.2 The PBAC previously accepted zoledronic acid and pamidronate as appropriate comparators in the broader patient population with multiple myeloma but also suggested that pamidronate and clodronate may be used in patients with severe renal impairment (para 7.2, denosumab PSD, November 2018 and para 7.4, denosumab PSD July 2018).
- 5.3 The resubmission noted that the PBAC may nominate clodronate as a potential comparator. Clodronate was removed from the PBS on 1 May 2019 and was not considered a relevant comparator during the evaluation.
- 5.4 The ESC considered that placebo may be an appropriate comparator for a small proportion of patients with severe renal impairment and multiple myeloma (CrCl  $\leq 30$  mL/min). The ESC noted that the submission and PSCR identified that 13% of patients have CrCl  $\leq 30$  mL/min (from Ho et al, 2017). However, the ESC noted that there are case reports of patients with severe renal impairment being given IV bisphosphonates safely and once patients are on dialysis, they can have IV bisphosphonates. Thus, the ESC considered that the proportion of patients for whom placebo would be a suitable comparator was likely less than 13%.

*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.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (25) and health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with denosumab including the ability to use in patients with renal impairment, and how the subcutaneous form would be useful for patients away from hospitals or with poor veins. Comments also described how patients with multiple myeloma expect their disease to relapse, and that any additional treatment option provides hope for patients and flexibility for clinicians to offer the most suitable treatment according to individual needs.
- 6.3 The PBAC noted the advice received from Myeloma Australia and the Leukaemia Foundation. The PBAC noted the Leukaemia Foundation’s advice that patients with renal impairment would welcome a new treatment option, particularly if it could be delivered outside the hospital setting and reduce out-of-pocket costs associated with hospital visits. The PBAC also noted that Leukaemia Foundation conducted a patient insight survey, including almost 700 people with multiple myeloma. Responses highlighted the expenses associated with treatment, and concerns around understanding treatment options and the management of side effects.

### Clinical trials

- 6.4 The resubmission presented data for the whole trial population of Study 482, a head-to-head trial comparing denosumab with zoledronic acid that was previously considered by the PBAC in the July 2018 and November 2018 (minors) submissions.
- 6.5 The resubmission also presented new analyses from Study 482 based on a post-hoc subgroup analysis of patients with creatinine clearance  $\leq 60$  mL/min. These data had not previously been considered by the PBAC.
- 6.6 A formal comparison of the efficacy and safety of denosumab versus pamidronate was not provided as the resubmission claimed the pivotal trial for denosumab (Study 482; denosumab versus zoledronic acid) was the best evidence against IV bisphosphonates.
- 6.7 Details of Study 482 are provided in Table 3.

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
Study 482	Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study	<i>Lancet Oncology</i> , 2018; 19(3):370-81
	A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid in the Treatment of Bone Disease in Subjects With Newly Diagnosed Multiple Myeloma	2017 (Internal study report)

Source: Table 2.2-1, p21 of the resubmission

- 6.8 The key features of Study 482 are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in economic evaluation
<b>Denosumab vs. zoledronic acid</b>						
Study 482	1718	MC, R, DB, DD (max follow-up 45 months) + open-label extension (additional max follow-up 24 months)	Low	Patients with newly diagnosed multiple myeloma and ≥1 lytic bone lesion who did not have severe renal impairment (CrCl <30 mL/min)	Time to first on-study SRE (primary), renal adverse events (safety)	Renal adverse events from subgroup with CrCl ≤ 60 mL/min

Abbreviations: CrCl, creatinine clearance; DB, double-blind; DD, double-dummy; MC, multi-centre; R, randomised; SRE, skeletal related event

Source: Table 1, pp1-2, Appendix 1; Table 2.4-1, p24 and Table 2.4-2, pp24-25 of the resubmission

### **Comparative effectiveness**

- 6.9 Study 482 results based on time to first on-study skeletal related event (SRE) suggest no statistically significant difference when comparing denosumab with zoledronic acid (HR 0.98; 95% CI 0.85, 1.14). The non-inferiority margin was met for the fixed margin (upper limit of CI does not exceed 1.28) and synthesis approach (p=0.010). The PBAC previously considered that the claim of non-inferior efficacy between denosumab and zoledronic acid for prevention of SREs was adequately supported by the data (para 6.24, denosumab PSD July 2018). The ESC agreed, but noted that Study 482 included only newly diagnosed patients, and hence the comparative effectiveness in other multiple myeloma patients was unknown.
- 6.10 Results from exploratory quality of life and pain outcomes for the overall trial population (analgesic score, Brief Pain Inventory – Short Form questionnaire, EQ-5D-3L, EORTC QLQ-C30 and QLQ-MY20) suggest no statistically significant difference between denosumab and zoledronic acid between treatment arms in terms of pain or quality of life, except for one specific domain that favoured denosumab (Future Perspective; includes worry about death/health in future and thinking about illness which is part of the EORTC QLQ-MY20 instrument specific to multiple myeloma).
- 6.11 Subgroup results from pre-specified analyses of time to first on-study SRE suggest that the relative treatment effect of denosumab compared with zoledronic acid was generally consistent, with the exception of region (geographic and Japan versus non-Japan). However, the Japanese (n = 42) and other region subgroups (n = 251) were relatively small compared to their complement subgroups.
- 6.12 Results for post-hoc subgroup analyses based on a creatinine clearance threshold of 60 mL/min and supportive analyses based on a lower threshold of 45 mL/min are presented in Table 5.

Table 5: Post-hoc subgroup analyses of time to first on-study skeletal related event (Study 482)

Outcome	Denosumab n/N (%) <sup>a</sup>	Zoledronic acid n/N (%) <sup>a</sup>	Hazard ratio (95% CI)	Interaction p-value
<b>Renal impairment [post-hoc]</b>				
CrCl ≤ 60 mL/min	98/235 (41.7)	108/223 (48.4)	0.90 (0.68, 1.19)	0.37
CrCl > 60 mL/min	278/624 (44.6)	275/636 (43.2)	1.03 (0.87, 1.22)	
<b>Moderate renal impairment [post-hoc]</b>				
CrCl ≤ 45 mL/min	42/109 (38.5)	44/83 (53.0)	0.60 (0.37, 0.96)	0.044
CrCl > 45 mL/min	334/750 (44.5)	339/776 (43.7)	1.03 (0.89, 1.20)	

<sup>a</sup> Percentage (%) is the crude incidence of patients with first skeletal related event at cut-off.

Source: Table 14-4.114.1 of Appendix 5 of the resubmission

Abbreviations: CI, confidence interval; CrCl, creatinine clearance

- 6.13 Post-hoc subgroup analyses by creatinine clearance threshold of 60 mL/min suggest no difference in comparative treatment effect between denosumab and zoledronic acid. These results should be interpreted with caution as the analysis may be subject to bias and was not adjusted for multiplicity.
- 6.14 Supportive post-hoc subgroup analyses based on a creatinine clearance threshold of 45 mL/min suggest greater treatment effect with denosumab versus zoledronic acid in this subgroup compared to the whole trial population. The resubmission did not provide justification for the selected threshold of 45 mL/min, which only includes some patients with moderate renal impairment. The results were difficult to interpret given limitations with the post-hoc analysis (potential bias, no adjustment for multiplicity), relatively small patient numbers and events, and lack of information for both the subgroup and the complement subgroup (no drug exposure data, lack of patient characteristics for the complement group).
- 6.15 There were no data for denosumab in patients with severe renal impairment (creatinine clearance < 30 mL/min), however the ESC noted that evidence in other indications (for example, osteoporosis) may be considered supportive of a possible small benefit in this population compared with placebo<sup>1</sup>.

### Comparative harms

- 6.16 The overall incidence of adverse events was similar between denosumab and zoledronic acid. The most frequently reported adverse events for both treatment arms were diarrhoea, nausea, constipation, anaemia, fatigue, back pain and pyrexia.
- 6.17 For adverse events of interest, denosumab was more commonly associated with osteonecrosis of the jaw, infections and infestations, hypersensitivity events and hypocalcaemia; whereas zoledronic acid was more commonly associated with acute phase reactions (flu-like syndrome including pyrexia, chills, flushing, pain, arthralgia and myalgia) and renal toxicity. These events are consistent with those seen in other indications for these therapies.

<sup>1</sup> Jamal et al. (2011). Effects of Denosumab on Fracture and Bone Mineral Density by Level of Kidney Function. *Journal of Bone and Mineral Research*, 26 (8), 1829-1835.

- 6.18 The resubmission claimed that the incidence of adverse events potentially related to renal toxicity was statistically significantly higher with zoledronic acid compared to denosumab (17.1% versus 10.0% respectively,  $p < 0.001$ ). This analysis could not be identified in the trial report and appeared to be conducted post-hoc. It was unclear whether other adverse events were similarly tested for statistical significance.
- 6.19 The PBAC previously considered that denosumab and zoledronic acid were of similar comparative safety in the broader multiple myeloma population (para 6.25, denosumab PSD July 2018). The PBAC noted no new safety signals in the multiple myeloma population and that the most common adverse events were consistent with those seen in other indications for these therapies (para 7.8, denosumab PSD July 2018).
- 6.20 Post-hoc subgroup analyses of adverse events of interest based on creatinine clearance thresholds of  $\leq 60$  mL/min and  $> 60$  mL/min are presented in Table 6.

**Table 6: Post-hoc subgroup analyses of adverse events of interest based on CrCl of  $\leq 60$  or  $> 60$  mL/min**

	Patients with events, n (%)			
	Creatinine clearance $\leq 60$ mL/min		Creatinine clearance $> 60$ mL/min	
	Denosumab N = 233	Zoledronic acid N = 220	Denosumab N = 600	Zoledronic acid N = 614
<b>Adverse events (any severity)</b>				
Any adverse event	NR	NR	226 (97.0)	214 (97.3)
Adverse events potentially related to renal toxicity	30 (12.9)	58 (26.4)	53 (8.8)	87 (14.2)
- Blood creatinine increased	11 (4.7)	33 (15.0)	21 (3.5)	40 (6.5)
- Acute kidney injury	10 (4.3)	14 (6.4)	19 (2.0)	23 (3.7)
- Renal failure	6 (2.6)	11 (5.0)	12 (2.0)	27 (4.4)
- Renal impairment	3 (1.3)	6 (2.7)	3 (0.5)	8 (1.3)
Hypocalcaemia	46 (19.7)	28 (12.7)	94 (15.7)	77 (12.5)
Adjudicated positive ONJ	10 (4.3)	4 (1.8)	25 (4.2)	19 (3.1)
<b>Serious adverse events (fatal or life-threatening)</b>				
Any serious adverse event	NR	NR	125 (53.6)	124 (56.4)
Adverse events potentially related to renal toxicity	8 (3.4)	9 (4.1)	15 (2.5)	20 (3.3)
- Blood creatinine increased	7 (3.0)	5 (2.3)	10 (1.7)	15 (2.4)
- Acute kidney injury	1 (0.4)	2 (0.9)	3 (0.5)	3 (0.5)
- Renal failure	0 (0.0)	2 (0.9)	2 (0.3)	1 (0.2)
- Renal impairment	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Hypocalcaemia	4 (1.7)	0 (0.0)	3 (0.5)	2 (0.3)

Source: Tables 14-6.103.1, 14-6.103.2, 14-6.103.3 and 14-6.103.4, pp1586-1589, Appendix 5 of the resubmission

Abbreviation: NR, not reported; ONJ, osteonecrosis of the jaw

- 6.21 The resubmission presented selected comparative adverse event data for renal toxicity, hypocalcaemia and osteonecrosis of the jaw only. The trial report noted no patients in either treatment group experienced a positively adjudicated atypical femoral fracture. For the requested subgroup with creatinine clearance  $\leq 60$  mL/min, no comparative safety data were presented for the overall incidence of adverse events, nor for other known adverse events of interest including hypersensitivity and infections/infestations.

- 6.22 The results of the available analysis for each subgroup were broadly consistent with frequencies reported for the whole trial population. There were higher frequencies of renal adverse events associated with zoledronic acid compared to denosumab, and higher frequencies of hypocalcaemia and osteonecrosis of the jaw associated with denosumab compared with zoledronic acid.
- 6.23 In patients with creatinine clearance  $\leq 60$  mL/min, the frequency of any renal adverse event was higher in patients receiving zoledronic acid compared to denosumab (primarily mild to moderate severity). In the same subgroup, the frequency of hypocalcaemia events (primarily mild to moderate severity) and osteonecrosis of the jaw were higher in patients receiving denosumab compared to zoledronic acid.
- 6.24 No comparative safety data were provided for the subgroups with creatinine clearance  $\leq 45$  mL/min and  $> 45$  mL/min.
- 6.25 The resubmission did not provide additional safety data for the use of denosumab in patients with severe renal impairment (creatinine clearance  $< 30$  mL/min). During the evaluation, a Phase 1, open-label study evaluating the safety of multiple doses of denosumab 120 mg in patients with severe chronic kidney disease (creatinine clearance  $< 30$  mL/min) or on dialysis was identified (Block et al 2017, abstract only). The study suggested that denosumab was associated with a higher incidence of clinically significant hypocalcaemia in a subset of patients with severe renal impairment and the frequency of events was higher with increasing degrees of renal impairment.

### ***Benefits/harms***

- 6.26 The resubmission claimed non-inferior efficacy between denosumab and zoledronic acid in terms of prevention of skeletal events.
- 6.27 The resubmission did not provide data on the overall incidence of adverse events of interest for denosumab and zoledronic acid. However, there were differences in the incidence of specific adverse events of interest. For every 100 patients treated with denosumab compared with zoledronic acid over a maximum follow-up period of 45 months, approximately:
- 13 fewer patients would have renal toxicity, and 1 fewer patient would have serious renal toxicity;
  - 7 additional patients would have hypocalcaemia, and 2 additional patients would have serious hypocalcaemia;
  - 2 additional patients would have osteonecrosis of the jaw.

### ***Clinical claim***

- 6.28 The resubmission described denosumab as non-inferior in terms of prevention of skeletal related events compared to zoledronic acid. This was reasonable.

- 6.29 The resubmission described denosumab as superior in terms of safety due to a lower incidence of renal adverse events compared to zoledronic acid. The ESC considered that this claim may not be reasonable given differences in the overall safety profiles of the treatments.
- 6.30 The PBAC previously considered that denosumab and zoledronic acid were of similar comparative safety in the broader multiple myeloma population (para 6.25, denosumab PSD July 2018).
- 6.31 The resubmission described denosumab as non-inferior in terms of prevention of skeletal related events and superior in terms of safety due to a lower incidence of renal adverse events compared to pamidronate. The resubmission did not provide a formal comparison, noting that the pivotal trial of denosumab versus zoledronic acid (Study 482) was the best evidence for denosumab compared with IV bisphosphonates. The PBAC previously considered that zoledronic acid 4 mg was equivalent to pamidronate 90 mg in terms of efficacy and safety in patients with multiple myeloma (PBAC Outcomes, September 2002). In this context, the ESC considered the efficacy claim may be reasonable, but the safety claim was unsupported (as with zoledronic acid).
- 6.32 The PBAC considered that that the claim of non-inferior comparative effectiveness in terms of prevention of SREs was reasonable.
- 6.33 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

### ***Economic analysis***

#### Cost-effectiveness analysis

- 6.34 The resubmission presented a trial-based cost-effectiveness analysis based on a subgroup analysis of newly diagnosed multiple myeloma patients with creatinine clearance  $\leq 60$  mL/min from Study 482. This analysis has not previously been considered by the PBAC.
- 6.35 The resubmission did not adequately justify a cost-effectiveness analysis given the clinical claim of superior safety (due to lower incidence of renal adverse events) with denosumab compared to zoledronic acid was not adequately supported by the data. The PSCR reiterated that if the PBAC is unable to accept a cost-effectiveness claim for the proposed restricted population, it would not be possible to find a way forward with a listing for denosumab.
- 6.36 There were no data to inform a cost-effectiveness analysis comparing denosumab with zoledronic acid in patients with severe renal impairment (creatinine clearance  $< 30$  mL/min) as these patients were excluded from the pivotal trial.
- 6.37 In the context of the high risk of leakage outside the proposed listing, and the lack of support for the claim of superior safety in patients with renal insufficiency, the ESC considered that it may remain more appropriate to present a cost-minimisation

analysis for the broad multiple myeloma population.

- 6.38 Nonetheless, the ESC advised that it may be worth considering whether a small price premium would be justified for some patients with severe renal insufficiency (CrCl < 30 mL/min), noting that IV bisphosphonates are not recommended in this population, and that placebo may be an appropriate comparator for some of these patients (see ‘Comparator’ section).
- 6.39 Although denosumab is associated with a higher incidence of clinically significant hypocalcaemia in patients with severe renal impairment, these patients have the greatest need for an alternative to IV bisphosphonates. Furthermore, the ESC considered that evidence in other indications (for example, osteoporosis) may be considered supportive of a possible small benefit in this population compared with placebo.
- 6.40 No economic analysis was presented comparing denosumab with pamidronate.

**Table 7: Summary of parameters used in the economic evaluation**

Parameter	Description
<b>Denosumab 120 mg</b>	
Treatment costs	Based on proposed DPMQ for multiple myeloma (\$ [REDACTED]), average number of doses administered in the subgroup with CrCl ≤ 60 mL/min in Study 482 (16.5) and no administration costs
Renal events	Incidence of renal adverse events in the subgroup with CrCl ≤ 60 mL/min in Study 482 (12.9%)
<b>Zoledronic acid 4 mg</b>	
Treatment costs	Based on weighted DPMQ for zoledronic acid (\$183.58), average number of doses administered in the subgroup with CrCl ≤ 60 mL/min in Study 482 (15.5) and infusion costs of \$43.65, \$182.91 (midpoint) or \$322.17
Renal events	Incidence of renal adverse events in the subgroup with CrCl ≤ 60 mL/min in Study 482 (26.4%)

Source: Section 3.1, p41 of the resubmission

Abbreviations: CrCl, creatinine clearance; DPMQ, dispensed price maximum quantity

- 6.41 A trial-based analysis is unlikely to capture the cost-effectiveness of ongoing treatment beyond the trial duration (average follow-up of 1.5 years). The ESC agreed with the evaluation that a modelled analysis may be more informative as it has greater capacity to capture the costs and consequences of long-term use including all treatment-related adverse events, administration and monitoring costs.
- 6.42 The estimated drug costs may not be applicable to the target PBS population, particularly beyond the average study duration of 1.5 years. The use of treatments in the trial (monthly administration for up to 4 years) appears inconsistent with guidelines recommending that use of IV bisphosphonates should be reviewed after 1-2 years (ASCO 2018, Lee 2017). For some patients, treatment can be withdrawn and reintroduced if the disease relapses and for others the frequency of administrations could be reduced to 3-monthly in stable disease. The resubmission stated there were no data to inform the optimal duration of therapy with denosumab. Given that the resubmission did not explain how patients would be managed if their renal function improved whilst on therapy, the economic analysis did not adequately account for subsequent management, including for example, IV bisphosphate use to mitigate the risk of rebound osteoclast activity, or transition to IV bisphosphate therapy in general.

- 6.43 The resubmission did not adequately justify the inclusion of renal adverse events only, given the differences in safety profile between treatments. The ESC considered it unlikely that the lower incidence of renal adverse events offset the increased incidence of hypocalcaemia associated with denosumab in patients with mild-moderate renal impairment. The ESC noted that other potentially significant categories of adverse events (e.g. infection) were not included in the analysis.
- 6.44 The PBAC has previously noted advice from the Medical Benefits Division that administration of IV bisphosphonates is reimbursed on a consultation basis, and would attract MBS schedule fees of \$76.65 or \$43.65. The PBAC previously advised that any justification for higher infusion costs should be based on robust evidence (para 7.5 and 7.7, denosumab PSD, November 2018). The ESC believed that the higher end of the range of infusions costs for zoledronic acid was unlikely to be realistic because it was based on an older review (2010), which showed large disparities between treatment settings.
- 6.45 The resubmission argued that the cost of IV bisphosphonate infusions should be higher than the MBS schedule fees, particularly in the context of patients with renal impairment who may require longer infusion times. The highest estimate in the resubmission (\$322.17) was based on a 2010 review of zoledronic acid funding practices in private and public hospitals across the States and Territories (denosumab Commentary, July 2011). It was previously considered by the PBAC to be uncertain as there was a large disparity in zoledronic acid infusion costs between treatment settings [inpatient versus outpatient] and between the states and territories (para 5.6.29, denosumab PBAC minutes July 2011).
- 6.46 The results of the economic evaluation are presented in Table 8.

**Table 8: Results of the economic evaluation**

Component	Denosumab	Zoledronic acid	Increment
<b>Zoledronic acid infusion cost: \$43.65</b>			
Costs	████	████	████
Incidence of renal adverse events	0.129	0.264	0.135
<b>Incremental cost per renal adverse event avoided</b>			
<b>Zoledronic acid infusion cost: \$182.91 (midpoint)</b>			
Costs	████	████	████
Incidence of renal adverse events	0.129	0.264	0.135
<b>Incremental cost per renal adverse event avoided</b>			
<b>Zoledronic acid infusion cost: \$322.17</b>			
Costs	████	████	████
Incidence of renal adverse events	0.129	0.264	0.135
<b>Incremental cost per renal adverse event avoided</b>			Dominant

Source: Table 3.1-1, p41 of the resubmission

- 6.47 The incremental cost per renal adverse event avoided ranged from ‘dominant’ to \$15,000 -\$45,000. The ESC considered that the results were difficult to interpret given the difference in safety profiles between denosumab and zoledronic acid that was not fully captured in the analysis. The ESC also noted there was limited cost-effectiveness data against which the results could be benchmarked.

- 6.48 The difference in the incidence of renal adverse events in the trial was primarily due to events of mild to moderate severity. During the evaluation, sensitivity analyses were conducted using the incidence of serious renal adverse events (fatal or life-threatening). The economic analysis was highly sensitive to the selected outcome of interest with the incremental cost per serious renal adverse event avoided ranging from 'dominant' to \$345,286.
- 6.49 The November 2018 submission for denosumab presented cost-minimisation analyses for denosumab versus zoledronic acid and pamidronate (para 6.10-6.15, denosumab PSD, November 2018). The analyses assumed a zoledronic acid infusion cost of \$ [REDACTED] and pamidronate infusion cost of \$ [REDACTED], and were calculated using the DPMQ for each drug weighted by public/private hospital use.
- 6.50 During the evaluation, cost-minimisation analyses of denosumab versus zoledronic acid and pamidronate were conducted using ex-manufacturer prices and alternative infusion costs proposed in the resubmission (between \$43.65 and \$322.17). In the zoledronic acid comparison, analyses assuming infusion costs up to \$ [REDACTED] resulted in denosumab prices that were lower than proposed in the resubmission. In the pamidronate comparison, analyses with infusion costs up to \$ [REDACTED] resulted in denosumab prices that were lower than proposed in the resubmission.

#### Weighted denosumab price

- 6.51 The resubmission proposed a weighted overall price for denosumab 120 mg (ex-manufacturer price, \$ [REDACTED]) based on the predicted [REDACTED]%/ [REDACTED]% split in use between the proposed multiple myeloma population who have creatinine clearance  $\leq 60$  mL/min (ex-manufacturer price, \$ [REDACTED]) and existing indications for breast and prostate cancer (current ex-manufacturer price, \$446.50). The resubmission stated that the multiple myeloma-specific price was the same as proposed in the November 2018 submission. However, the weighted overall price in the resubmission was higher due to the change in distribution across indications (it was previously [REDACTED]% multiple myeloma and [REDACTED]% breast and prostate cancer; para 6.9 denosumab PBAC minutes November 2018). The ESC noted that reducing the eligible number of multiple myeloma patients would impact on both the numerator (multiple myeloma patients receiving denosumab) and denominator (all patients receiving denosumab), so the [REDACTED]%/ [REDACTED]% split was incorrect. Instead, the proportion of patients receiving denosumab who have multiple myeloma would likely be  $(0. [REDACTED] \times 0. [REDACTED]) / (0. [REDACTED] + (0. [REDACTED] \times 0. [REDACTED])) = 12.3\%$ . This would then impact on the weighted mean cost, giving a cost of  $(0. [REDACTED] \times \$ [REDACTED]) + (0. [REDACTED] \times \$446.50) = \$ [REDACTED]$ . The Pre-PBAC Response proposed a revised weighted overall ex-manufacturer price of \$ [REDACTED], if recommended for the population with creatinine clearance of 60 mL/min or less. The proposed price for a listing for patients with creatinine clearance of 30 mL/min or less was unchanged.
- 6.52 The weighted denosumab price was derived using a 10% Medicare sample analysis and an estimated proportion of patients with multiple myeloma who also have

creatinine clearance of 60 mL/min or less. The estimated price was highly uncertain due to the following reasons:

- The resubmission did not adequately justify the use of patient numbers to derive the relative distribution of use across denosumab indications. This approach does not account for differences in utilisation patterns between treatments which was assumed in the financial estimates of the resubmission (scripts/patient/year: denosumab, 9.5; zoledronic acid, 6.1; pamidronate, 5.9; clodronate, 7.5). This difference is likely due to differences between treatment regimens and patterns of long-term use. The relative distribution of use between indications is likely to vary substantially depending on the basis of the weights (i.e. patient numbers vs script numbers vs government expenditure) as the proposed drug cost of denosumab is higher than existing therapies.
- The weights used to determine the price were derived from an older (2014-15) 10% Medicare sample analysis of bone-targeting agents that may not be directly applicable given changing market dynamics over time. There were known limitations with the dataset including miscoding (half of the patients had an 'invalid' indication) that required redistribution to other indications based on an assumed pattern of use (e.g. a substantial number of 'invalid' patients from denosumab were redistributed to myeloma and hypercalcaemia, which it does not have current listings for);
- The market-share approach used to determine the weights does not account for potential growth of the multiple myeloma market due to the availability of denosumab, given IV bisphosphonates are generally not recommended in patients with severe renal impairment.
- The proportion of patients with multiple myeloma who have renal impairment (36%) is likely to be an underestimate as the data were based on newly diagnosed patients. The abstract on which the estimate is based noted that renal impairment was more prevalent in more advanced disease (Ho et al 2017). As renal deterioration is commonly associated with disease progression, the proportion of patients with renal impairment in the prevalent population with multiple myeloma is likely to be higher.

6.53 During the evaluation, sensitivity analyses were conducted using alternative estimates for the distribution of utilisation across the multiple myeloma, breast and prostate cancer indications as well as the proportion of patients who have creatinine clearance  $\leq 60$  mL/min. The results indicated that the weighted price is most sensitive to the expected proportion of patients who have creatinine clearance  $\leq 60$  mL/min.

6.54 The resubmission also proposed an alternative ex-manufacturer price for denosumab 120 mg of \$ [REDACTED] (DPMQ \$ [REDACTED]) should the PBAC consider a lower creatinine clearance threshold of  $\leq 30$  mL/min. No justification was provided for the proposed alternative price. No economic analysis was presented for the alternative price.

### Drug cost/patient/year

6.55 The drug cost per patient for denosumab and zoledronic acid is summarised in Table 9.

**Table 9: Drug cost per patient for denosumab and zoledronic acid**

	Denosumab			Zoledronic acid		
	Trial subgroup dose and duration	Economic analysis	Financial estimates	Trial subgroup dose and duration	Economic analysis	Financial estimates
Treatment regimen	120 mg/4 weeks	120 mg/4 weeks	120 mg/4 weeks	3-4 mg/4 weeks	3-4 mg/4 weeks	Unknown <sup>a</sup>
Mean duration of exposure	16.2 months <sup>b</sup>	16.2 months <sup>b</sup>	-	15.6 months <sup>b</sup>	15.6 months <sup>b</sup>	-
Mean number of doses	16.5 <sup>c</sup>	16.5 <sup>c</sup>	-	15.5 <sup>c</sup>	15.5 <sup>c</sup>	-
Annualised number of doses	12.2 <sup>d</sup>	12.2 <sup>d</sup>	9.5 <sup>e</sup>	11.9 <sup>d</sup>	11.9 <sup>d</sup>	6.1 <sup>e</sup>
Cost/patient/dose						
Cost/patient/year						

Source: Table 111-4.5.1, Appendix 5 of the resubmission

<sup>a</sup> The treatment schedule for zoledronic acid may vary due to the relapsing-remitting nature of multiple myeloma (temporary cessation, 4-weekly or 12-weekly administration)

<sup>b</sup> Cumulative investigational product exposure the subgroup of patients with creatinine clearance ≤ 60 mL/min in Study 482

<sup>c</sup> Mean number of doses received in the subgroup of patients with creatinine clearance ≤ 60 mL/min in Study 482

<sup>d</sup> Mean number of doses ÷ (mean duration of exposure ÷ 12 months)

<sup>e</sup> Assumed scripts/patient/yr

<sup>f</sup> Proposed DPMQ for multiple myeloma

<sup>g</sup> Proposed weighted DPMQ across all indications for denosumab 120 mg

<sup>h</sup> Weighted average DPMQ based on 32% public and 68% private hospital split

<sup>i</sup> Cost/patient/dose x annualised number of doses, calculated during the evaluation.

### Estimated PBS usage & financial implications

6.56 This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact for denosumab presented in the Table 10.

Table 10: Estimated use and financial implications

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
<b>Eligible multiple myeloma patients receiving denosumab</b>						
Patients receiving BP						
CrCl ≤ 60 mL/min (36%)						
Uptake rate						
Total patients receiving denosumab						
Total scripts (9.5/patient/yr)						
Total cost (DPMQ \$ )						
Patient co-pay (\$15.68)						
Net PBS cost less co-pay						
<b>Cost offsets due to denosumab substituting for bisphosphonates</b>						
ZA patients (68.3%)						
ZA scripts (6.1/patient/year)						
ZA cost (DPMQ \$183.58) <sup>a</sup>						
Pamidronate patients (29.5%)						
Pamidronate scripts (5.9/patient/yr)						
Pamidronate cost (DPMQ \$90.57) <sup>a</sup>						
Clodronate patients (2.2%)						
Clodronate scripts (7.5/patient/yr)						
Clodronate cost (DPMQ \$313.57)						
Total cost offsets (DPMQ)						
Patient co-payments (\$15.68)						
Net PBS cost less co-pay						
<b>Additional cost offsets due to proposed lower price of denosumab for existing indications</b>						
Denosumab scripts						
Total cost current DPMQ \$501.91						
Total cost proposed DPMQ \$ )						
Net additional cost offsets						
<b>Net costs to PBS/RPBS with denosumab listing</b>						
Net cost to PBS						

Source: Table 4.2-2, Table 4.2-3, Table 4.2-4, Table 4.3-1, Table 4.3-2 and Table 4.4-1, pp45-46 of the resubmission

Abbreviations: BP, bisphosphonates; CrCl, creatinine clearance; DPMQ, dispensed price for maximum quantity; ZA, zoledronic acid.

<sup>a</sup> Calculated using weighted average DPMQ based on 32% public hospital; 68% private hospital use

6.57 The estimated net cost to the PBS for denosumab was less than \$10 million in Year 1, increasing to less than \$10 million in Year 6, a total cost of \$30-\$60 million over 6 years. After cost offsets, the estimated net cost was less than \$10 million in Year 1, increasing to less than \$10 million in Year 6, a total cost of \$20-\$30 million over 6 years.

6.58 The additional cost offsets due to the proposed lower price of denosumab in existing indications could not be validated due to limited documentation in the resubmission (sponsor's internal forecast; source and methods not provided). It was unclear whether the estimates were based on all indications including giant cell tumour of bone. The weighted denosumab price was calculated based on the relative distribution of multiple myeloma, breast and prostate cancer only. The PSCR did not address this issue.

- 6.59 The resubmission also noted the April 2021 10% statutory price reduction was not included in the base case but provided sensitivity analyses based on a reduced price for denosumab of \$ [REDACTED] (DPMQ). The estimated net cost in the first 6 years of listing denosumab was \$30-\$60 million, and \$20-\$30 million with the inclusion of bisphosphonate cost offsets.
- 6.60 The estimated utilisation and financial implications were highly uncertain for the following key reasons:
- The resubmission's estimates of patients with multiple myeloma treated with bisphosphonates were unchanged from previous submissions (July 2018 and November 2018). There were multiple concerns previously noted with the analysis based on an older 10% Medicare sample from 2014-15 including the unsupported assumption of a stable market and approximately half of the sample were miscoded with 'invalid' or 'no dominant indication' that were then redistributed to other indications. This analysis was not updated for the resubmission;
  - The annual growth rate applied to the prevalent population was based on incidence of disease. Although no prevalence data were available, the total population with multiple myeloma is expected to grow over time with improved survival rates and availability of newer treatments;
  - The market share approach used does not account for potential growth of the multiple myeloma market due to the availability of denosumab, given IV bisphosphonates are generally not recommended in patients with severe renal impairment;
  - The risk of use outside the requested restriction may be high in the broader population with multiple myeloma given differences in mode of administration and safety profile between denosumab and existing therapies, and variability in creatinine measurements. The risk of leakage may be greater since the removal of oral clodronate from the PBS (1 May 2019), as there are no subsidised alternatives to IV bisphosphonates, and this risk may be greater in regional and rural settings.
  - The proportion of patients with multiple myeloma who have renal impairment is likely to be an underestimate as the data were based on a registry of newly diagnosed patients. The author of the abstract noted that renal impairment was more prevalent in more advanced disease (Ho et al 2017);
  - The uptake rates and average scripts per patient per year for denosumab were assumed. The estimated 9.5 scripts per patient per year was lower than the average number of doses per year of 12.2 in the pivotal trial (based on the average number of doses of 16.5 over a mean duration of 16.2 months in Study 482);
  - Cost offsets were based on substitution rates from zoledronic acid (68.3%), pamidronate (29.5%) and clodronate (2.2%), assuming flat uptake rates within a non-homogeneous market. This assumption may not be appropriate as the

distribution of the bisphosphonate market will vary according to degrees of renal impairment and stage of myeloma disease; and

- Cost offsets were calculated using scripts per patient per year estimated from the 10% Medicare sample analysis that was subject to the same uncertainties as the main analysis due to the large number of invalid scripts. It was unclear whether treatment persistence and treatment switching were appropriately accounted for due to poor documentation. This is a particular issue for zoledronic acid, which may have varying administration schedules. The scripts/patient/year estimate suggests potential differences in utilisation patterns for zoledronic acid in practice compared to the trial (6.1 versus 11.9 scripts per patient per year).

### ***Quality Use of Medicines***

- 6.61 The resubmission stated that denosumab is an alternative to bisphosphonates for the management of myeloma bone disease. The resubmission considered that both intravenous and oral bisphosphonates have limitations on their use due to renal safety concerns and administration requirements (e.g. hospital settings, complex oral regimen). Denosumab may reduce treatment burden in some patients as it is administered subcutaneously with no dose adjustments required in patients with renal impairment.
- 6.62 The resubmission noted that denosumab may be preferable in patients with renal impairment due to increased renal toxicity associated with IV bisphosphonates. Although denosumab was associated with reduced renal toxicity compared to IV bisphosphonates, there was also increased incidence of hypocalcaemia and osteonecrosis of the jaw.
- 6.63 The PBAC previously considered there may be potential quality use of medicines issues regarding rebound osteoclast activity associated with cessation of denosumab therapy (para 7.3, denosumab July 2018 PSD). The resubmission stated there were no new data to inform the optimal duration of therapy with denosumab. Based on updated safety data presented in the resubmission, the increased risk of fractures post treatment cessation remains an important identified risk. International guidelines recommend administration of at least one dose of IV bisphosphonate upon cessation of denosumab (UpToDate, Feb 2018 – The use of osteoclast inhibitors in patients with multiple myeloma). It was unclear if the financial estimates appropriately accounted for patients taking denosumab who then have improved renal function, cease denosumab and subsequently transition to IV bisphosphonate therapy.

### ***Financial Management – Risk Sharing Arrangements***

- 6.64 Table 11 presents the financial caps proposed in the resubmission to address the risk of denosumab use outside of the proposed restriction for patients with creatinine clearance  $\leq 60$  mL/min. The resubmission also presented alternative caps for a lower creatinine clearance threshold of  $\leq 30$  mL/min for PBAC consideration.

**Table 11: Proposed financial caps and rebate for the risk share agreement**

Listing	Year 1	Year 2	Year 3	Year 4	Year 5	Rebate
CrCl ≤ 60 mL/min	██████	██████	██████	██████	██████	██████
CrCl ≤ 30 mL/min	██████	██████	██████	██████	██████	██████

Source: Table 4.6-1, p47 of the resubmission

- 6.65 The nominated financial caps for the proposed restriction (creatinine clearance ≤ 60 mL/min) were based on the estimated government expenditure for denosumab use in multiple myeloma. The financial estimates for this threshold were calculated using the proposed weighted price of ██████ and estimated utilisation rates for Years 1 to 5.
- 6.66 The proposed financial caps for the lower creatinine clearance threshold of ≤ 30 mL/min could not be validated during the evaluation due to limited documentation in the resubmission. The PSCR confirmed that they were estimated using the same approach as presented for the higher threshold with adjusted assumptions (13% of patients have creatinine clearance ≤ 30 mL/min and 100% denosumab uptake). The estimates were also based on a higher proposed price of denosumab for this population (ex-manufacturer price of ██████, DPMQ ██████).
- 6.67 The resubmission proposed a ██████% rebate for any government expenditure above the nominated caps. The proposed rebate is designed to reduce the effective price of denosumab to match the cost of zoledronic acid with an additional price premium to account for infusion costs (weighted DPMQ ██████ + infusion cost ██████ = ██████). This may not be appropriate in the context of a weighted price where the price is a weighted average of the various indication specific prices for denosumab.
- 6.68 The nominated caps were also inflated by less than \$10 million in each year to allow for miscoding. The resubmission stated that the sponsor has experience with the occurrence of miscoding in indication-specific caps for denosumab in giant cell tumour of bone. The resubmission claimed that the giant cell tumour of bone caps have been exceeded by at least less than \$10 million each year and that this is due to miscoding from the breast and prostate cancer listings. Details of this analysis were not provided in the resubmission. The PSCR argued that it is reasonable to include a level of buffer above the financial estimates to allow for miscoding from the much larger established breast and prostate cancer listings, but that the sponsor would be willing to agree a reduced level of buffer or enter into a two-tier cap arrangement for the proposed moderate-severe renal impairment listing. The PSCR stated that the sponsor would not be willing to agree a reduced level of buffer were the PBAC to recommend a listing restricted to severe renal impairment given the small size of the population and likelihood of miscoding. The ESC considered that the less than \$10 million buffer was poorly justified, and is inappropriate as any potential miscoding is likely indication specific and it is unclear why it would be transposed to other indications. The ESC also noted that it may be more appropriate to resolve this issue through alternative RSA arrangements.

6.69 The Pre-PBAC Response proposed revised caps and removal of the buffer for the CrCl < 60 mL/min listing, but not the CrCl ≤ 30 mL/min listing, presented in the table below. The Pre-PBAC Response also proposed an increase to the rebate above the caps (from ██████% to ██████%) for both populations, which it stated reflected a lower zoledronic acid price from October 2019.

**Table 12: Financial caps and rebate for the risk share agreement presented in the Pre-PBAC Response**

Listing	Year 1	Year 2	Year 3	Year 4	Year 5	Rebate
CrCl ≤ 60 mL/min (new price and buffer removed)	██████	██████	██████	██████	██████	██████
CrCl ≤ 30 mL/min (unchanged)	██████	██████	██████	██████	██████	██████

Source: Pre-PBAC Response, p1.

6.70 The nominated financial caps were highly uncertain as they were based on the current bisphosphonate market that does not account for potential market growth due to denosumab; the prevalence of renal impairment (and severe renal impairment) is likely to be underestimated; and no justification was provided for the assumed 100% uptake rate in the patients with severe renal impairment.

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

## 7 PBAC Outcome

7.1 The PBAC did not recommend extending the current listing of denosumab to include the treatment of patients with multiple myeloma who have renal impairment. Although the clinical evidence indicated likely non-inferiority to zoledronic acid for the outcome of skeletal-related events (SREs), the PBAC considered there was an inadequate basis for accepting the claim of superior safety compared to zoledronic acid. The PBAC considered that the incremental cost-effectiveness based on renal adverse events avoided was not reasonable, as the submission did not adequately capture the differences in safety profiles between the therapies.

7.2 The PBAC recalled that it had previously accepted zoledronic acid and pamidronate as appropriate comparators in the broader patient population with multiple myeloma but also suggested that pamidronate may be used in patients with severe renal impairment. In the context of the current submission, the PBAC noted the ESC’s advice that placebo may be an appropriate comparator for a small proportion of patients with multiple myeloma and severe renal impairment (CrCl ≤ 30 mL/min). The PBAC considered that the proportion of patients for whom placebo may be a comparator was uncertain, and therefore reiterated that zoledronic acid (with a longer infusion time and less frequent dosing) and pamidronate may be used in patients with severe renal impairment.

7.3 The PBAC noted that the submission presented a new post-hoc subgroup analysis of patients with CrCl ≤ 60 mL/min from Study 482, to show that time to SRE for denosumab remained non-inferior compared with zoledronic acid for patients with renal impairment. The resubmission also provided a supportive post-hoc subgroup

analysis of patients with CrCl  $\leq$  45 mL/min, but no data for denosumab in patients with severe renal impairment (CrCl  $\leq$  30 mL/min). The PBAC considered that the evidence presented was difficult to interpret given the limitations with the post-hoc analysis, and thus the suggested difference in terms of prevention of SREs for patients with CrCl  $\leq$  45 mL/min was unreliable (paragraph 6.14). Therefore, the claim of non-inferiority in terms of SREs was likely reasonable for patients with moderate renal impairment.

7.4 The PBAC noted the post-hoc subgroup analysis of AEs of interest was based on a creatinine clearance threshold of  $\leq$  60 mL/min, and that no data were presented for the  $\leq$  45 mL/min and  $\leq$  30 mL/min subgroups. Again, the PBAC considered the post-hoc analysis was difficult to interpret. The PBAC considered that the data did not adequately support a claim of superior comparative safety due to a lower incidence of renal adverse events, noting that:

- In the broader Study 482 population, there were trends towards an increased risk of ONJ and clinically important hypocalcaemia, and that these were consistent with trends in the subgroup analysis presented in the resubmission.
- In the broader Study 482 population, there was limited difference in the rate of acute kidney injury (AKI) between patients taking denosumab and zoledronic acid. The PBAC was uncertain that AKI rates would be different for the subgroup of patients with renal impairment.
- In the broader Study 482 population, the serious AEs differed between the denosumab and zoledronic acid arms, and the subgroup analysis failed to capture the differences in safety profiles between the agents.

7.5 The PBAC recalled that it had previously advised that any subsequent submission should consider a cost-minimisation approach that applied previously accepted infusion costs for zoledronic acid or pamidronate, or a justification based on robust evidence for cost offsets that deviate from previously accepted costs (7.7, November 2018 PSD). The PBAC noted that the resubmission argued that the cost of IV bisphosphonate infusions should be higher than the MBS schedule fees, as patients with renal impairment who may require longer infusion times. Given that the clinical claim of superior safety was not supported by the data presented in this submission, and the lack of robust evidence to support higher infusion costs, the PBAC considered that the cost-utility analysis based on renal adverse event avoided was inappropriate, and the resulting ICER did not capture the differing AE profiles of the two therapies. The PBAC agreed with the evaluation and the ESC's view of the model structure and inputs (paragraphs 6.41-6.54).

7.6 The PBAC agreed with the ESC's advice that there was potential for use outside the proposed restriction – both due the restriction wording, which did not account for variability in creatinine measurements, and also due to different mode of administration and safety profiles, which may increase the risk of leakage in rural and

regional settings in particular. The PBAC noted the revised RSA caps for the CrCl  $\leq$  60 mL/min population and the higher [REDACTED] % rebate presented in the pre-PBAC response. However, it did not consider that these changes addressed the uncertainties outlined during the evaluation (paragraph 6.70).

- 7.7 The PBAC recalled that it had previously acknowledged the clinical need for treatment options to prevent SREs associated with multiple myeloma for patients who cannot receive bisphosphonates, particularly for those with severe renal impairment (CrCl < 30 mL/min) (paragraph 7.2, July 2018 PBAC meeting PSD). The PBAC reaffirmed this view, but it considered there was a lack of clinical evidence to support a superiority claim in that subgroup and that the need was modest given that pamidronate can be used in this population.
- 7.8 The PBAC noted that this was the third submission for denosumab for patients with multiple myeloma. The PBAC again recalled that it had previously provided advice about the acceptable parameters for a resubmission (7.7, November 2018 PSD), and that based on the sponsor's position reiterated in the pre-PBAC response, the commercially acceptable price and risk sharing arrangements for a PBS listing were not acceptable to the PBAC.
- 7.9 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 would like to clarify in relation to point 7.8 above that although this was the third submission for denosumab in multiple myeloma, it was the first submission which requested listing only for the subgroup of patients with renal impairment and on which the PBAC's advice had not been received.