

6.03 DENOSUMAB, injection, 120 mg in 1.7 mL vial, Xgeva[®], Amgen Australia Pty Ltd

1 Purpose of Application

- 1.1 The submission requested an extension of the current Section 85 Streamlined Authority Required listing for denosumab to include treatment of patients with multiple myeloma. Denosumab is currently listed on the PBS for treatment of giant cell tumour of bone and bone metastases from breast and castrate-resistant prostate cancer.
- 1.2 The submission requested PBS listing on the basis of a cost-effectiveness analysis compared with zoledronic acid.

Table 1: Key components of the clinical issue addressed in the submission

Component	Description
Population	Patients with bone lesions due to multiple myeloma
Intervention	Denosumab 120 mg subcutaneous injection every 4 weeks
Comparator	Zoledronic acid 4 mg intravenous infusion every 3-4 weeks
Outcomes	Prevention of skeletal related events, improved progression-free survival and reduced incidence of renal adverse events
Clinical claim	Denosumab is non-inferior to zoledronic acid in terms of prevention of skeletal-related events. Denosumab is superior to zoledronic acid in terms of progression-free survival. Denosumab is similar to zoledronic acid in terms of comparative safety but associated with a lower incidence of renal adverse events.

Source: Table 1.1-1, p12 of the submission

2 Requested listing

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
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:	Multiple Myeloma				
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				
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.				

- 2.1 The requested restriction was the same as for zoledronic acid but was broader than the proposed extension to the TGA indication for the prevention of skeletal related events (SREs) in patients with multiple myeloma. The use of denosumab for the treatment of multiple myeloma for indications other than for the prevention of SREs was not covered by the requested TGA indication.
- 2.2 The requested restriction was also broader than the proposed target population of patients with bone lesions due to multiple myeloma and the clinical evidence that only included newly diagnosed patients and excluded patients with severe renal impairment.

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

3 Background

Registration status

- 3.1 The submission was made under the TGA/PBAC Parallel Process. A positive TGA Delegate’s Overview was received with the pre-PBAC response in late June 2018. The TGA Delegate supported the application to extend the indications of denosumab (Xgeva) to include (underlined):
- Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumours.

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

4 Population and disease

- 4.1 Multiple myeloma (MM) is a type of cancer arising from plasma cells which are normally found in the bone marrow. MM is most common in people aged 60 years and older, and men are affected more often than women. MM is considered a relapsing and remitting disease and treatment will be recommended during active phases until the disease has stopped progressing or is no longer detectable. MM is a heterogeneous disease, with some patients progressing rapidly despite multiple lines of therapy and others not requiring therapy for a number of years. Although MM remains an incurable disease, survival for these patients has improved over time to a 5-year survival rate of approximately 50% (Cancer in Australia, AIHW 2017).
- 4.2 The uncontrolled growth of abnormal plasma cells can affect multiple places in the body, leading to bone destruction, bone marrow failure, increased plasma viscosity, suppression of normal immunoglobulin production and renal insufficiency. Bone destruction is mediated by osteoclasts, a type of bone cell that breaks down bone tissue which is activated by the receptor activator of nuclear factor kappa-B ligand (RANKL). In multiple myeloma, RANKL is hypersecreted by bone marrow cells, osteocytes and myeloma cells and therefore, increases activation of osteoclasts. The Pre-Sub-Committee Response (PSCR) noted that denosumab may directly prevent RANKL-mediated myeloma cell growth and reactivation of dormant myeloma cells, which may slow the progression of disease.
- 4.3 Myeloma bone disease typically manifests through the development of bone lesions. This process is characterised by the development of bone pain, spinal cord compression and pathologic fractures which are some of the most common complications in this disease. Radiation therapy or bone surgery are used to manage these complications.
- 4.4 The target population for denosumab in the submission is patients with bone lesions due to multiple myeloma. The submission positioned subcutaneous (SC) denosumab as an alternative to intravenous (IV) bisphosphonates and as a treatment option in the subpopulation who are unsuitable for IV bisphosphonates due to severe renal impairment (creatinine clearance <30 mL/min). The definition of patients unsuitable for IV bisphosphonates based on renal function alone was not completely consistent with Australian and international guidelines. Although IV zoledronic acid is not recommended in patients with severe renal impairment, low dose IV pamidronate remains an option in cases of significant disease and oral clodronate can still be used with dose adjustment in patients with creatinine clearance of 10-30 mL/min. No dose adjustments are necessary for denosumab in renal impairment.
- 4.5 The proposed algorithm described continuous monthly administration of IV bisphosphonates for 1-2 years followed by a review of therapy based on risk of SREs.

Consequently, some patients may spend a period of time on 3-monthly dosing or cease therapy and reinstate upon disease relapse.

- 4.6 The algorithm in the submission did not clearly describe the pattern of use of denosumab beyond 1-2 years of treatment. The differences in drug profile between IV bisphosphonates and denosumab (e.g. long-acting versus short-acting) suggest less flexibility with the dosing regimen of denosumab. Due to recent safety signals associated with rebound osteoclast activity, 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). There was limited data to indicate optimal duration of therapy with denosumab. The ESC noted the optimal duration of therapy is unknown, however it could be assumed that treatment would likely be continuous.
- 4.7 The submission noted that IV bisphosphonates are generally preferred over oral bisphosphonates due to improved efficacy, and that oral clodronate is recommended only for patients unable to attend hospitals for infusions based on Australian bisphosphonate guidelines for the treatment of myeloma bone disease (Lee et al 2017). There may be a preference to use subcutaneous denosumab in some patients as it does not require hospital attendance and may be preferred in those with stable disease. The preference will also extend to those who prefer to use a subcutaneous injection over IV infusion, which reduces nursing time and can potentially be self-administered.

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

5 Comparator

- 5.1 The submission nominated zoledronic acid as the main comparator. The submission argued that zoledronic acid is the most commonly used bisphosphonate in patients with multiple myeloma based on a 10% Medicare sample analysis of 2014-2015 utilisation data. Based on the analysis, the most commonly used therapy was zoledronic acid (70%), followed by pamidronate (17%) and clodronate (13%). Although there were limitations with the analysis (older data with adjustments due to the high proportion of invalid indications), it is likely that zoledronic acid is the most commonly used bisphosphonate treatment in the overall myeloma population.
- 5.2 In the proposed algorithm, the submission assumed that some patients would be unsuitable for intravenous (IV) bisphosphonates due to severe renal impairment, and have no available treatment options. The use of zoledronic acid is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min). However, Australian guidelines for bisphosphonates for the treatment of myeloma bone disease (Lee et al 2017) suggest pamidronate or clodronate as treatment options in these patients, which should be considered as alternative comparators in the subpopulation with severe renal impairment.

- 5.3 The submission further argued that zoledronic acid was accepted by the PBAC as an appropriate comparator when denosumab was considered for bone metastases in patients with breast and prostate cancer in the context of a superiority claim versus zoledronic acid in terms of efficacy (denosumab PSD, July 2011). However, the PBAC also considered pamidronate as an alternative comparator in more recent denosumab submissions for hypercalcaemia of malignancy:
- The PBAC accepted zoledronic acid as an appropriate comparator but also noted that pamidronate would also be replaced in practice, albeit to a lesser extent, and was therefore also a relevant comparator (paragraph 7.2, denosumab PSD, March 2016). This was considered in the context of a superior efficacy claim and non-inferior safety claim for denosumab compared with zoledronic acid that were not adequately supported by the data (paragraphs 6.22 and 6.23, denosumab PSD, March 2016)
 - The PBAC considered that pamidronate was the most reasonable comparator when denosumab was considered for the treatment of bisphosphonate-refractory hypercalcaemia of malignancy given the very poor quality of data presented for the comparison of denosumab and zoledronic acid (paragraph 7.4, denosumab PSD, July 2016).

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 (96), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with denosumab compared to zoledronic acid including less administrative burden, a different side effect profile perceived to be more favourable particularly with respect to renal toxicity.
- 6.3 The PBAC noted the advice received from Myeloma Australia which advised current treatments for bone disease are associated with renal toxicity and are therefore not suitable for patients with renal disease. Denosumab was considered safe for renally impaired patients, free from significant side effects, whilst improving progression free survival. The Myeloma Australia Medical and Scientific Advisory Group (MSAG) summarised the benefits of denosumab as being:
- not renally cleared and can be used in renally insufficient patients
 - associated with improved progression free survival (PFS)

- not associated with significant adverse events.

The PBAC noted that the claim of improved progression-free survival was not adequately supported by the evidence provided in the submission.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing denosumab to zoledronic acid (Study 482).

6.5 Details of the Study 482 trial are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 482	Raje N, Terpos E, Willenbacher W, et al (2018). Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study	Lancet Oncology, 19:370-81
	Clinical Study Report (2017). 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	Internal study report

Source: Table 2.2-1, p21 of the submission

6.6 The key features of Study 482 are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Denosumab vs. zoledronic acid						
Study 482	1718	Multi-centre, double-blind, double-dummy, randomised controlled trial (max follow-up 45 months) + open-label extension (additional max follow-up 24 months)	Low (SRE)/ High (PFS)	Patients with newly diagnosed multiple myeloma and ≥ 1 lytic bone lesion who did not have severe renal impairment (creatinine clearance < 30 mL/min)	Time to first on-study SRE (primary), OS (secondary), PFS (exploratory)	SRE outcomes not used. OS and PFS used in the economic model.

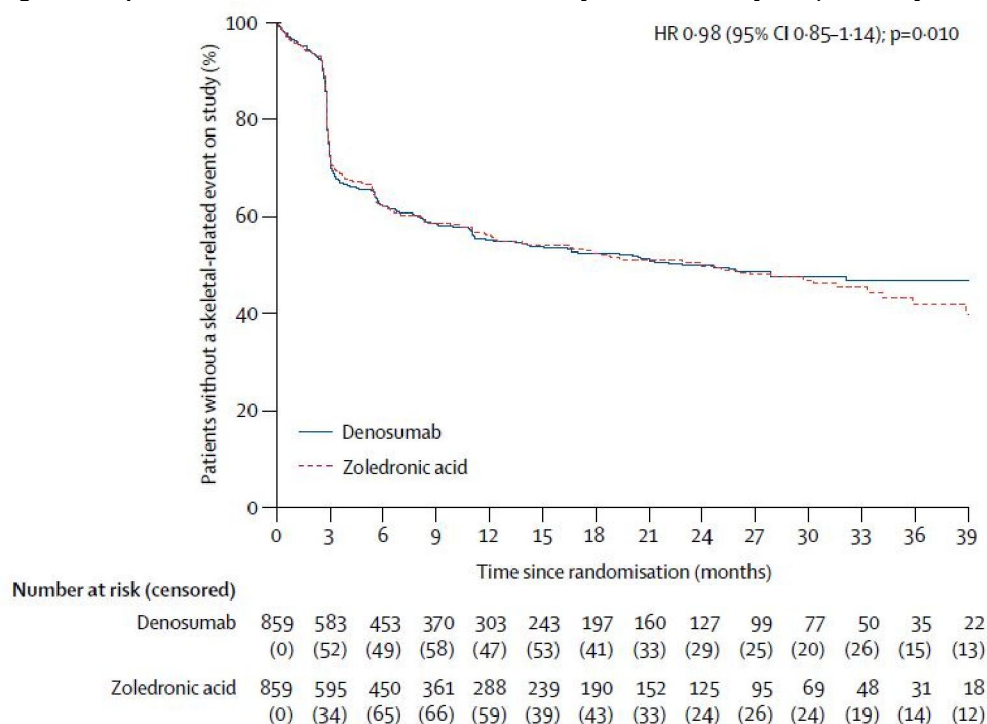
Source: Table 1, pp1-2, Appendix 1, Tables 2.2-1 and 2.3-1, pp21-23, Table 2.4-1, p24 and Table 2.4-2, pp24-25 of the submission
Abbreviations: OS, overall survival; PFS, progression-free survival; SRE, skeletal related event

6.7 Study 482 was primarily designed as a non-inferiority trial comparing denosumab with zoledronic acid when used for the prevention of SREs in patients with multiple myeloma who have evidence of bone disease. The risk of bias for Study 482 was low when considering SREs but high when considering progression-free survival. In this study, progression-free survival was an exploratory outcome that was non-centrally assessed and therefore did not meet regulatory requirements. Statistical analysis for progression-free survival was descriptive only without adjustment for multiplicity.

Comparative effectiveness

6.8 The primary outcome of time to first on-study SRE from Study 482 is summarised in Figure 1 and Table 4 below.

Figure 1: Kaplan-Meier estimates of time to first on-study SRE from Study 482 (Full Analysis Set)



Source: Figure 2, p375 of the Raje et al 2018 publication
Abbreviations: HR, hazard ratio; SRE, skeletal related event

Table 4: Time to first on-study SRE from Study 482

	Denosumab 120 mg N=859	Zoledronic acid 4 mg N=859
Patients with SRE (%)	376 (43.8)	383 (44.6)
- Spinal cord compressions (%)	3 (0.8)	3 (0.8)
- Surgery to bone (%)	21 (5.6)	26 (6.8)
- Pathological fractures (%)	323 (85.9)	314 (82.0)
- Radiation to bone (%)	29 (7.7)	40 (10.4)
Median time to event, months (95% CI)	22.8 (14.7, NE)	24.0 (16.6, 33.3)
Hazard Ratio (95% CI)	0.98 (0.85, 1.14)	
p-value, noninferiority	0.010	
p-value, superiority	0.82	
p-value, superiority (adjusted for multiplicity)	0.84	

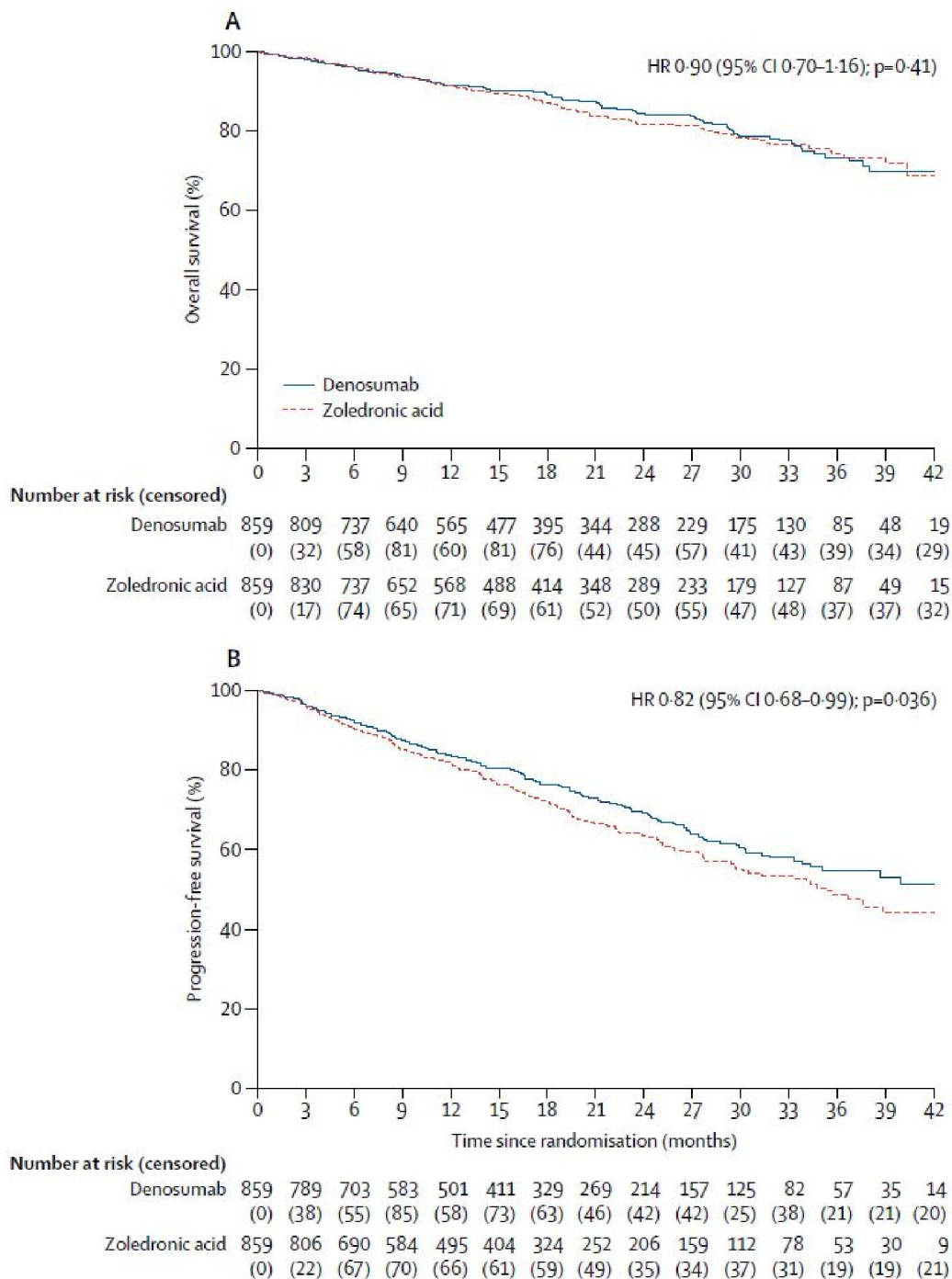
Source: Table 2.5-1, p26 of the submission
Abbreviations: CI, confidence interval; NE, not estimable; SRE, skeletal related event

6.9 There was no statistically significant difference in the risk of developing a first on-study SRE when comparing denosumab with zoledronic acid (HR 0.98; 95% CI 0.85, 1.14). The noninferiority margin was met for the fixed margin (upper limit of CI does not exceed 1.28) and synthesis approach (p=0.010). The median time to first SRE was

similar between denosumab and zoledronic acid, with 60% of all first SREs occurring within the first 3 months of the study and 81% occurring in the first 6 months of the study.

- 6.10 Results for overall survival (secondary outcome) and progression-free survival (exploratory outcome) from Study 482 are summarised in Figure 2 and Table 5 below.

Figure 2: Kaplan-Meier estimates of overall survival (A); and progression-free survival (B) of Study 482



Source: Figure 3, p376 of the Raje et al 2018 publication
Abbreviations: CI, confidence interval; HR, hazard ratio

Table 5: Overall survival and progression-free survival results from Study 482

	Denosumab 120 mg N=859	Zoledronic acid 4 mg N=859
Overall survival		
Deaths (%)	121 (14.1)	129 (15.0)
Median, months (95% CI)	49.5 (NE)	NE
Hazard Ratio (95% CI) ^a	0.90 (0.70, 1.16), p=0.41	
Progression-free survival		
Disease progression or death (%)	219 (25.5)	260 (30.3)
Median, months (95% CI)	46.1 (34.3, NE)	35.4 (30.2, NE)
Hazard Ratio (95% CI) ^a	0.82 (0.68, 0.99), p=0.036	

Source: Table 2.5-7, p33

Abbreviations: CI, confidence interval; NE, not estimable

^a Based on Cox proportional hazards model with treatment groups, age, geographic region (North America, Europe, or other), race group, risk per cytogenetic based prognosis, baseline creatinine clearance (≤ 60 vs > 60 mL/min), baseline ECOG (≤ 1 vs 2) as the independent variables and stratified by the randomisation stratification factors

- 6.11 There was no statistically significant difference in overall survival between treatment arms. The overall survival data were not mature with only 14.6% of subjects having died by the primary analysis cut-off (19 July 2016).
- 6.12 An 18% reduction in the risk of progression or death was observed in those receiving denosumab compared with zoledronic acid (HR 0.82, 95% CI 0.68, 0.99). The estimated increase in median progression free survival was 10.7 months, however this estimate was considered unreliable given the observed number of events. The evaluation considered that these results might not be robust as the outcome was an exploratory endpoint; there was a high risk of bias as the outcome was not centrally assessed; and the observed effect was of marginal statistical significance (upper limit of confidence interval close to 1) that was not adjusted for multiplicity. The cut-off for the primary analysis was mid-2016 and the pre-PBAC response indicated that no further analysis from the double-blind period would be forthcoming, with the final analysis of the open-label follow-up for survival and safety outcomes to become available at the end of 2019.
- 6.13 The evaluation was concerned with the applicability of survival outcomes from the trial to the target Australian population, with the trial publication noting particularly long progression-free survival that could be attributed to the high proportion of patients with early-stage disease, and the use of combination regimens in first-line treatment which are not currently subsidised by the PBS (Raje et al 2018). The ESC agreed with the evaluation on these applicability issues, noting for first-line therapies, “1712 (>99%) received front-line antimyeloma therapy, with 893 (52%) receiving a proteasome inhibitor (441 in the denosumab group vs 452 in the zoledronic acid group), 287 (17%) receiving an immunomodulatory drug (133 vs 154), 463 (27%) receiving both (248 vs 215), and 69 (4%) receiving other therapies (33 vs 36). Maintenance therapy was given to 320 (19%) patients (158 vs 162)” Raje et al 2018, p7. Further noted in the Raje et al 2018 publication, patients treated with denosumab had approximately one month longer median cumulative exposure to treatment versus zoledronic acid and this may have resulted in a reduced anti-

myeloma effect. This was due to increased withholding and dose delays in the zoledronic acid group.

- 6.14 Exploratory quality of life and pain outcomes were also assessed in Study 482 (analgesic score, Brief Pain Inventory – Short Form questionnaire, EQ-5D-3L, EORTC QLQ-C30 and QLQ-MY20). In the trial, both arms showed improvements in analgesic and pain scores at Week 113 compared to baseline. Consistent with measures of pain, both treatment arms showed improvement in health related quality of life outcomes from baseline to Week 113 in the trial. There was no statistically significant difference 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).

Comparative harms

- 6.15 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.
- 6.16 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.

Benefits/harms

- 6.17 A summary of the comparative benefits and harms for denosumab versus zoledronic acid is presented in the table below.

Table 6: Summary of comparative benefits and harms for denosumab and zoledronic acid

Benefits	Denosumab	Zoledronic acid	Absolute Difference	HR (95% CI)
Skeletal related events				
Patients with events	376 (43.8)	383 (44.6)	No difference	0.98 (0.85, 1.14)
Median time to event (months)	22.8 (14.7, NE)	24.0 (16.6, 33.3)		
Harms				
			Fatal or life-threatening	
			Denosumab	Zoledronic acid
Any adverse event	816/850 (96.0)	825/852 (96.8)	391/850 (46.0)	403/852 (47.3)
Hypersensitivity	219/850 (25.8)	189/852 (22.2)	5/850 (0.6)	9/852 (1.1)
Hypocalcaemia	144/850 (16.9)	106/852 (12.4)	8/850 (0.9)	2/852 (0.2)
Infections and infestations	537/850 (63.2)	500/852 (58.7)	165/850 (19.4)	163/852 (19.1)
Osteonecrosis of the jaw	35/850 (4.1)	24/852 (2.8)	6/850 (0.7)	2/852 (0.2)
Renal toxicity	85/850 (10.0)	146/852 (17.1)	23/850 (2.7)	30/852 (3.5)
Acute phase reactions	46/850 (5.4)	74/852 (8.7)	NR	NR

Source: Table 2.5-1, p26, Table 2.5-7, p33, Table 2.5-10, pp36-37 of the submission; Table 12-6, p100, Table 14-6.11.3, p1578, Table 14-6.11.4, p1579 of the Study 482 trial report and Raje 2018 publication

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression-free survival

6.18 On the basis of the direct evidence presented in the submission, there was no difference in the incidence of skeletal related events or overall survival. The ESC considered the submission’s claim of an increase in progression free survival with denosumab compared with zoledronic acid to be inadequately supported.

6.19 On the basis of the direct evidence presented in the submission, the incidence of any adverse event and any serious adverse event (fatal or life-threatening) were similar between denosumab and zoledronic acid. However, there were differences in the incidence of 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:

- 3 additional patients would have hypersensitivity;
- 3 additional patients would have hypocalcaemia;
- 4 additional patients would have an infection or infestation;
- 1 additional patient would have osteonecrosis of the jaw;
- 7 fewer patients would have renal toxicity;
- 4 fewer patients would have acute phase reactions.

Clinical claim

6.20 The submission described denosumab as non-inferior in terms of prevention of SREs compared to zoledronic acid.

6.21 The submission described denosumab as superior in terms of progression-free survival compared to zoledronic acid. The ESC did not consider the claim of superior efficacy in terms of progression-free survival was adequately supported by the data presented in the submission. There were major limitations associated with results

based on an exploratory outcome that was non-centrally assessed and of marginal statistical significance (HR 0.82, 95% CI: 0.68, 0.99) with no adjustment for multiplicity.

- 6.22 The submission described denosumab as similar in terms of safety compared with zoledronic acid but associated with a lower incidence of renal adverse events. The ESC noted overall incidence of adverse events was similar between denosumab and zoledronic acid. However, denosumab was more commonly associated with hypocalcaemia, hypersensitivity reactions, infections and infestations, and osteonecrosis of the jaw while zoledronic acid was more commonly associated with renal adverse events and acute phase reactions.
- 6.23 The risk-benefit profile of denosumab in patients with severe renal impairment was unclear. The pivotal trial excluded patients with severe impairment (creatinine clearance <30 mL/min). Although denosumab is not significantly affected by renal function, treatment with denosumab is associated with increased incidence of hypocalcaemia which is of greater risk in patients with renal impairment. The Pre-sub-committee response noted some patients with moderate renal impairment (baseline CrCl <60ml/min) were enrolled in the trial and the incidence of renal events in this group was 26.4% in the zoledronic acid arm and 12.9% in the denosumab arm.
- 6.24 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.
- 6.25 The PBAC considered that the claim of similar comparative safety was reasonable.

Economic analysis

- 6.26 The submission presented a modelled economic evaluation assessing the cost-effectiveness of denosumab compared with zoledronic acid based on the whole trial population with newly diagnosed symptomatic multiple myeloma (≥ 1 bone lesion) who are receiving antimyeloma treatment. The comparison was based on the denosumab and zoledronic acid trial arms from Study 482.

Table 7: Summary of model structure and rationale

Component	Description
Type of analysis	Cost-utility analysis
Methods used to generate results	Cohort expected value, partitioned survival model
Time horizon	20 years in the model base case vs. maximum follow-up of 45 months in the key trial
Cycle length	28 days
Discounting	5% for costs and outcomes, applied per 28-day cycle
Population	Study 482 trial population; newly diagnosed multiple myeloma patients with bone lesions who are receiving antimyeloma treatment
Health states	On treatment, off treatment, pre-progression, post-progression, death
Outcomes	Months of progression-free survival, quality-adjusted life years
Extrapolation method	Overall survival was extrapolated using a Weibull curve based on pooled data from both trial arms in Study 482 (same curve for both arms in the model). Progression-free survival curves were extrapolated using a generalised gamma curve based on individual arms in Study 482 (separate curves for each arm in the model). Time on treatment was extrapolated using a Weibull curve based on pooled data from both trial arms in Study 482 (same curve for both arms in the model).
Software package	Excel 2010

Source: Table 3.1-1, p43 and 'XGEVA MM economic model' Excel workbook, Appendix 7 of the submission

- 6.27 The ESC considered the submission did not adequately justify a cost-utility analysis comparing denosumab with zoledronic acid given the clinical evidence presented supported a non-inferiority claim between treatments for the prevention of skeletal related events and lack of robust evidence to support the submission's claim of superiority in terms of progression-free survival. It may have been more appropriate to present a cost-minimisation analysis. The ESC noted from the PSCR that the sponsor is willing to reduce the price of denosumab to address the economic issues and secure a listing in multiple myeloma however, would not be able to move forward with a listing at a price based on a cost-minimisation recommendation.
- 6.28 The model structure had three health states; on/off treatment, progressed/not progressed disease and the absorbing state of death. The submission stated that the health states were modelled independently, however, they were not mutually exclusive. There was no direct relationship between the on/off treatment states and the pre/post-progression states. The model structure implicitly assumes no treatment effect on the risk of disease progression which appears inconsistent with the submission's claim of improved progression-free survival associated with denosumab treatment. The impact of this structural uncertainty is unclear as it was not possible to derive the proportions of patients in mutually exclusive states (e.g. pre-progression on treatment or pre-progression off treatment).
- 6.29 Key issues with the economic model in the submission are summarised in the following table.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Progression-free survival	<p>Modelled estimate of 8.3 months incremental gain in PFS associated with denosumab. It was unclear whether the incremental PFS from the trial could be directly applied in the model given the outcome was of marginal statistical significance, not adjusted for multiplicity and subject to high risk of bias. The ESC did not consider the modelled approach based on this PFS outcome was appropriate. There were major concerns with the applicability of trial data to the target population (e.g. dosing regimens and duration of therapy for bone disease treatments beyond 1-2 years, background antimyeloma treatment regimens not used in Australian practice).</p>	High, favours denosumab
Time horizon	<p>20 years. The submission claimed this was reasonable based on previous PBAC considerations of first-line myeloma treatments that included 15 year time horizons (lenalidomide PSD, November 2015; thalidomide PSD, March 2009). The submission also noted that the population in Study 482 was younger than the trial population considered in the November 2015 lenalidomide submission. While it is possible that a longer time horizon (e.g. 15 years) is appropriate for younger patients, this was previously considered in the context of improved overall survival. The submission claimed no survival advantage for denosumab compared to zoledronic acid.</p>	High, favours denosumab
Utilities	<p>Baseline (pre-progression) utility of █████ based on average utility score across both trial arms over the trial duration. Post-progression utility of █████ calculated using relative reduction of 19.5% applied to baseline estimate based on van Agthoven (2004) publication. This method is not consistent with what is stated in van Agthoven et al, where the reduction should be applied to age/sex adjusted population norm. Furthermore, the baseline utility estimate was unlikely to represent patients remaining progression-free in the trial as it was based on data with substantial proportions of patients in each arm (approximately 30% in denosumab and 40% in the zoledronic acid arm) experiencing a progression event in that period.</p> <p>The submission stated that the PBAC previously accepted the 19.5% approach from the van Agthoven (2004) publication (carfilzomib PSD, July 2017). The PBAC did not accept the approach used but accepted the modelled estimates given additional analyses suggested they were consistent with trial estimates (paragraph 6.34, carfilzomib PSD, July 2017).</p> <p>There were substantial inconsistencies between trial-based estimates from Study 482 and modelled estimates suggesting this approach may not be appropriate. Trial-based estimates suggested improvements in pain and quality of life outcomes in both arms over time, and no statistically significant difference between treatment arms. The utility values in the model were inconsistent with the trial based utility values where on average patients were improving over time.</p> <p>The disutilities associated with mode of administration may be inappropriately counted as the baseline utility value was from the trial and based on patients who were already receiving the drugs (and thus mode of administration was already accounted for).</p>	High, favours denosumab
Extrapolation	<p>Modelled curves for OS (Weibull, identical for both arms), PFS (generalised gamma, separate curves for each arm) and time on treatment (Weibull, identical for both arms). The submission did not provide justification for the use of modelled data only, which is inconsistent with the PBAC Guidelines v5.0 recommending the use of observed time to event data up to the time point at which the observed data become unreliable as a result of small number of patients remaining event-free.</p> <p>Overall, the assessment for goodness of fit of the parametric distributions to the observed data was inadequate (e.g. lack of detail justifying clinical plausibility of extrapolations, no BIC assessment, no log-cumulative hazards plot). The approach used in the submission to determine the suitability of various parametric distributions was poorly documented (e.g. missing data for Gompertz model, missing AIC values for PFS models).</p> <p>The model assumed sustained benefits in PFS with denosumab treatment versus zoledronic acid over the model lifetime, beyond the point of which all patients have ceased</p>	High, favours denosumab

Description	Method/Value	Impact
	therapy. The assumption that the PFS curves never converge may not be reasonable.	
Monitoring costs	Based on a relatively old data from a US study (Usmani et al, 2016) which has not been validated for the Australian context.	Moderate, direction of advantage is unclear.

Source: compiled during the evaluation

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival; PFS, progression-free survival

6.30 The results of the economic evaluation are summarised in the table below.

Table 9: Results of the economic evaluation

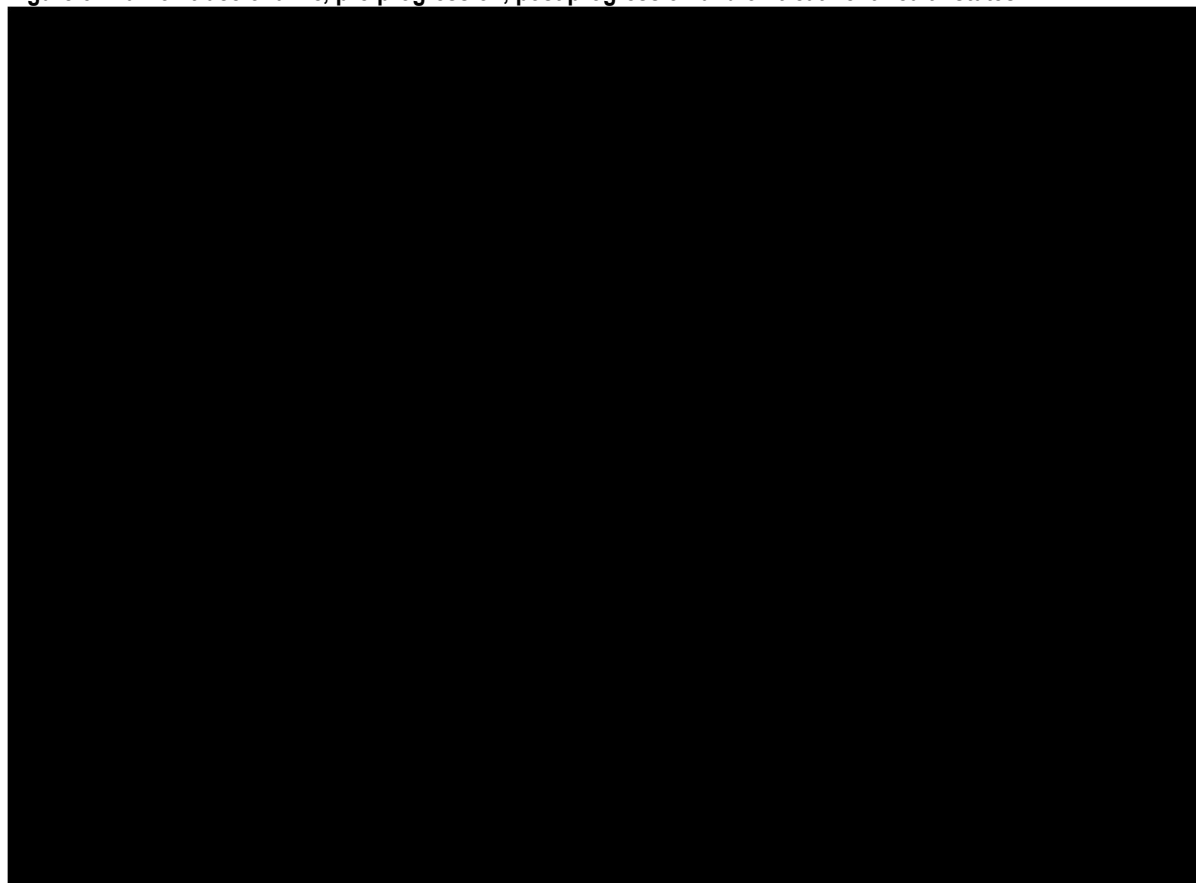
Component	Denosumab	Zoledronic acid	Increment
Costs	\$ [REDACTED]	\$21,563	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per quality adjusted life year			\$ [REDACTED]

Source: Table 3.8-4, p59 and 'XGEVA MM economic model' Excel workbook, Appendix 7 of the submission

6.31 In patients with bone lesions due to multiple myeloma, treatment with denosumab was associated with an incremental cost per QALY gained of \$15,000/QALY - \$45,000/QALY compared to zoledronic acid.

6.32 Markov traces constructed during the evaluation are summarised in the figure below, showing the proportion of patients remaining in each health state (pre-progression, post-progression, alive and on treatment) over the model duration.

Figure 3: Markov trace of alive, pre-progression, post progression and on treatment health states



Source: constructed during the evaluation using the 'XGEVA MM economic model' Excel workbook, Appendix 7 of the submission
Note: The model used the same overall survival and time on treatment curves for denosumab and zoledronic acid.

- 6.33 The association between time on treatment and survival benefits in the model appear implausible when considering the incremental benefit in progression-free survival associated with denosumab treatment that persists over the model lifetime of 20 years, beyond the point of which all patients have ceased therapy. The difference in progression-free survival appears to increase over time, peaking at between 6-7 years in the model when the majority of patients have stopped therapy. Due to the limitations of the model structure, it was not possible to derive the proportions of patients in mutually exclusive states (e.g. pre-progression on treatment or pre-progression off treatment).
- 6.34 The submission did not present a comparison of results from a trial-based cost-effectiveness analysis with the modelled economic analysis. Based on the modelled analysis, the majority of the incremental QALY gain associated with denosumab was derived from the extrapolation beyond the trial duration (maximum follow-up in the trial of 42 months, see sensitivity analyses results below).
- 6.35 The results of key sensitivity analyses are summarised below.

Table 10: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.1539	\$ [REDACTED]
Time horizon (base case 20 years; 261 28-day cycles)			
5 years (66 cycles)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
10 years (131 cycles)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
15 years (196 cycles)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PFS extrapolation (base case generalised gamma extrapolation, separate curves, unrestricted)			
Generalised gamma (restricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Exponential (unrestricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Exponential (restricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Weibull (unrestricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Weibull (restricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Log-logistic (unrestricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Log-logistic (restricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Log-normal (unrestricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Log-normal (restricted)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PFS extrapolation (base case generalised gamma extrapolation, separate curves, unrestricted)			
PH assumption (HR 0.82), exponential (unrestricted) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PH assumption (HR 0.82), exponential (restricted) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PH assumption (HR 0.82), Weibull (unrestricted) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
PH assumption (HR 0.82), Weibull (restricted) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Progression-free survival (base case mean estimates: 62 months for denosumab arm, 47 months for zoledronic acid; 15.1 months difference)			
No PFS difference	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Difference between pre- and post-progression utility values (base case 0.675 pre-progression, 0.543 post-progression; 0.132 difference)			
75% of difference (0.675 pre-progression, 0.576 post-progression)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
50% of difference (0.675 pre-progression, 0.609 post-progression)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
25% of difference (0.675 pre-progression, 0.609 post-progression)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
No difference between pre- and post-progression	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3.9-1, pp60-11 and 'XGEVA MM economic model' Excel workbook, Appendix 7 of the submission

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; QALY, quality adjusted life year

^a Rather than independently fitted curves in the model, the PFS curve for denosumab was derived from the zoledronic acid curve, assuming proportional hazards and using the hazard ratio of 0.82 for denosumab versus zoledronic acid reported in Study 482

Note: When testing the impact of extrapolation using different parametric distributions, restricted analyses refers to the assumption of a treatment effect on only one of the parameters defining the shape and scale of a distribution. For example, a restricted Weibull extrapolation assumes a change in scale due to treatment effect but maintains the same shape parameter.

The redacted table shows ICERS in the range of \$15,000/QALY - \$105,000/QALY.

6.36 The results of sensitivity analyses indicate that the model was most sensitive to the difference in progression-free survival between arms, the modelled time horizon, the magnitude of difference in pre- and post-progression health state utilities and the use of different parametric distributions for the extrapolation of progression-free survival.

Drug cost/patient/year

- 6.37 The estimated drug cost for denosumab 120 mg per patient per year was \$ [REDACTED] based on 13.04 scripts using the proposed DPMQ \$ [REDACTED]. The submission claimed that from April 2021, the statutory 10% (10-year anniversary) price reduction for denosumab would come into effect, resulting in a DPMQ of \$ [REDACTED]. The drug cost per patient per year with the price reduction based on 13.04 scripts would be \$ [REDACTED].
- 6.38 The estimated drug cost for zoledronic acid 4 mg per patient per year was \$2,345.67 based on 13.04 scripts, weighted by 42.33% private hospital use at a DPMQ of \$188.00 and 57.67% public hospital use at a DPMQ of \$173.89. This estimate was lower than presented in the submission that was based on a higher price for zoledronic acid (weighted DPMQ \$245.33) prior to the 1 April 2018 price disclosure reduction. The updated cost estimates were used in a revised base case for the economic model and financial estimates during the evaluation.

Estimated PBS usage & financial implications

- 6.39 This submission was not considered by DUSC. The submission used a mixed market share and epidemiological approach to estimate the utilisation and financial impact of denosumab. The key source for the approach was a 10% Medicare sample analysis of bisphosphonate prescriptions for multiple myeloma from 2014-2015. The 10% Medicare sample analysis was the same as presented in the March 2016 submission for denosumab in hypercalcaemia of malignancy, and has not been updated for the current submission.
- 6.40 Table 11 presents the estimated total use and costs of denosumab in the first 6 years of listing. The submission's estimates of costs incorporated a 10% statutory price reduction effective April 2021 for denosumab. During the evaluation, the 10% price reduction was removed from the base case estimates but was included in sensitivity analyses. During the evaluation, zoledronic acid prices were updated to reflect the 1 April 2018 price disclosure reduction and the updated estimates were included in the revised base case and any additional sensitivity analyses.

Table 11: Estimated use and total cost of denosumab to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Denosumab uptake – from patients currently treated with bisphosphonates (BPs)						
Currently BP treated						
Uptake rate	%	%	%	%	%	%
Uptake from BP treated						
Denosumab uptake – from patients unsuitable for BPs						
Unsuitable for BPs						
Uptake rate	%	%	%	%	%	%
Uptake from BP unsuitable						
Total uptake (patients)						
Total scripts (7.5/patient/yr)						
Denosumab total costs to PBS/RPBS (DPMQ \$501.67 across all years of listing)						
Total cost (DPMQ)	\$	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$	\$
Net PBS/RPBS cost	\$	\$	\$	\$	\$	\$
Cost offsets due to denosumab substituting for BPs (proportion of patients for each therapy x scripts/patient/year)^a						
Zoledronic acid scripts (70%)						
Zoledronic acid cost offset ^b	\$	\$	\$	\$	\$	\$
Pamidronate scripts (17%)						
Pamidronate cost offset ^b	\$	\$	\$	\$	\$	\$
Clodronate scripts (13%)						
Clodronate cost offset	\$	\$	\$	\$	\$	\$
Total cost offsets (DPMQ)	\$	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$	\$
Net (DPMQ less co-payment)	\$	\$	\$	\$	\$	\$
Net costs to PBS/RPBS with denosumab listing						
Net (DPMQ less co-payment)	\$	\$	\$	\$	\$	\$

Source: XGEVA MM financial estimates.xlsx, and compiled during the evaluation.

Abbreviations: BP, bisphosphonates; DPMQ, dispensed price for maximum quantity; MM, multiple myeloma

^a Assuming scripts/patient/year for bisphosphonates as follows: zoledronic acid 6.1; pamidronate 5.9; clodronate 7.5.

^b Calculated using weighted average DPMQ based on 32% public hospital; 68% private hospital use

6.41 The estimated net cost to the PBS/RPBS for denosumab was less than \$10 million in Year 1, increasing to \$10 - \$20 million in Year 6, a total cost of \$60 - \$100 million in the first 6 years of listing. After cost-offsets for the substitution of denosumab for bisphosphonates, the estimated net cost to the PBS/RPBS for listing denosumab was less than \$10 million in Year 1 of listing, increasing to \$10 - \$20 million in Year 6, a total of \$30 - \$60 million in the first 6 years of listing (submission's original 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, a total of \$30 - \$60 million in the first 6 years of listing).

6.42 The estimated utilisation and financial implications were highly uncertain for the following key reasons:

- Use of older 10% Medicare sample analysis from 2014-15 as the basis for current patient estimates rather than more recent data assumes the market is stable. Market dynamics are changing in recent years with the introduction of new myeloma treatments as well as improvement in 5-year survival rates (Cancer in Australia, AIHW 2017);

- Approximately half of the total number of patients were categorised as ‘invalid’ and ‘no dominant indication’ which were then redistributed across the indications using the weighted proportions. The appropriateness of this approach was unclear;
- The 10% Medicare sample estimate included patients receiving denosumab and ibandronate, which are currently not PBS-listed for the treatment of multiple myeloma. Approximately half of the total ‘invalid’ category was from denosumab utilisation data which were redistributed amongst all treatments. The submission’s estimate of the bisphosphonate market may therefore include patients not treated with bisphosphonates and/or with conditions other than multiple myeloma;
- The population who are unsuitable for bisphosphonates was poorly defined. It is unclear whether all patients with severe renal impairment would avoid treatment with bisphosphonates, in the absence of any other available treatment. While the use of zoledronic acid is not recommended in patients with severe renal impairment, Australian guidelines suggest that pamidronate and clodronate remain as treatment options;
- Denosumab uptake rates from the bisphosphonate market and from the unsuitable for bisphosphonate population were based on unsubstantiated assumptions;
- Denosumab script estimates of [REDACTED] per patient per year were broadly based on scripts per patient per year estimated for denosumab indications for breast and prostate cancer from the 10% Medicare sample analysis. It was unclear whether data based on solid tumour conditions would be applicable to the use of denosumab in a haematological condition. The scripts/patient/year estimate indicates substantially lower compliance than in the trial and economic model ([REDACTED]% versus [REDACTED]% respectively). The ESC did not consider compliance would be as low as [REDACTED]% in this indication. Most therapy for skeletal-related events is given concomitantly with anti-myeloma therapy or timed with a review for patients on oral therapy.
- Cost offsets due to denosumab substituting for bisphosphonates were substantial and highly uncertain:
 - The submission assumed similar uptake rates of denosumab across a non-homogeneous bisphosphonate market, which is likely to have differential uptake due to patient-related issues (e.g. hospital access) and compliance factors (IV versus oral);
 - Displaced bisphosphonate script numbers were derived from the 10% Medicare sample analysis and were therefore subject to the same uncertainties associated with the overall population estimates (high proportions of invalid indications). The yearly script estimate for zoledronic acid indicates substantially lower compliance than in the trial ([REDACTED]% versus [REDACTED]% respectively). As noted above for denosumab, most therapy for skeletal-related events is given concomitantly with anti-

myeloma therapy or timed with a review for patients on oral therapy. Therefore, the ESC did not consider compliance would be as low as ■■■% in this indication;

- There were no cost offsets attributed to a likely reduction in administration costs due to substitution of IV bisphosphonates with denosumab. This was inconsistent with the economic analysis (\$59.15 per infusion). The cost of administration of zoledronic acid remains unclear.

Quality Use of Medicines

- 6.43 The submission stated that the burden of bone lesions in multiple myeloma patients is high and treatment is necessary, with the aim being to delay the onset and/or reduce recurrence of SREs, control bone pain and preserve quality of life. The use of pharmacological therapy in multiple myeloma patients with bone lesions is standard practice in Australia and consistent with recommendations in clinical guidelines.
- 6.44 The submission claimed that denosumab offers multiple myeloma patients a choice of therapy from a different class to currently available bisphosphonates and a new option for patients who cannot take bisphosphonates due to severe renal impairment. Denosumab is administered subcutaneously meaning patients or carers may be trained in administration, compared to intravenous bisphosphonates which must be administered in a hospital setting. Clodronate is administered orally but the submission argued that compliance is difficult due to complicated administration instructions.
- 6.45 The submission noted that denosumab is administered as a subcutaneous injection once every 4 weeks, claiming the reversibility of denosumab provides the ability to moderate treatment as required. The submission claimed that denosumab has similar overall safety to existing treatments and a positive risk-benefit profile in the proposed population.

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

7 PBAC Outcome

- 7.1 The PBAC decided not to recommend extending the current Section 85 Streamlined Authority Required listing for denosumab to include treatment of patients with multiple myeloma. Although the clinical evidence indicated 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 effectiveness compared to zoledronic acid and the incremental cost-effectiveness based on superior progression-free survival was implausible.
- 7.2 The PBAC 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. The PBAC noted that low dose IV

pamidronate and oral clodronate can be used with dose adjustment in patients with creatinine clearance of 10-30 mL/min. The submission also stated that there was a clinical need for patients unsuitable for bisphosphonate therapy, although the proposed PBS listing was not limited to second line.

- 7.3 The PBAC noted there were limited data available regarding the optimal duration of therapy with denosumab and that the International Myeloma Working Group (IMWG) and MSAG guidelines suggested two years. The PBAC considered there may be a potential quality use of medicines issues regarding rebound osteoclast activity.
- 7.4 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 patients¹. The PBAC noted no clinical evidence was presented in this population, as patients with renal disease were excluded from Study 482, and no clinical claim was presented in relation to these alternative comparators.
- 7.5 The PBAC noted that Study 482 was designed as a non-inferiority trial comparing denosumab with zoledronic acid when used for the prevention of SREs in patients with multiple myeloma who have evidence of bone disease. The primary outcome of time to first on-study SRE showed there was no statistically significant difference in the risk of developing a first on-study SRE when comparing denosumab with zoledronic acid (HR 0.98; 95% CI 0.85, 1.14).
- 7.6 The exploratory analysis of progression-free survival in Study 482 was not considered reliable given the observed number of events. This outcome was determined locally by investigators, the data was immature with only 28% of subjects experiencing a progression-free survival event at the time of primary analysis, and the observed effect was of marginal statistical significance (HR 0.82, 95% CI 0.68, 0.99; p=0.036) based on statistical testing that was not adjusted for multiplicity. Furthermore, the PBAC noted that there were concerns with the applicability of survival outcomes from the trial to the target Australian population, with the trial publication noting particularly long progression-free survival that could be due to the high proportion of patients at an early disease stage and the use of combination regimens in first-line treatment which is not currently subsidised by the PBS (Raje et al 2018).
- 7.7 The PBAC noted the claim that denosumab may directly prevent RANKL-mediated myeloma cell growth and reactivation of dormant myeloma cells, which may slow the

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

progression of disease. However, the Committee did not consider this biological argument provided strong evidence to support that denosumab would have a disease-modifying effect.

- 7.8 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.
- 7.9 Given the rejection of the clinical claim of superior effectiveness, the PBAC did not accept the rationale for the modelled cost-effectiveness of denosumab compared to zoledronic acid. The PBAC noted the pre-PBAC response signalled an unwillingness to supply denosumab on a cost-minimisation basis with the comparator, zoledronic acid.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review as the PBAC has declined to recommend an extension of the listing of an already listed drug.

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 pleased that the PBAC has recognised that there is an unmet clinical need for treatment options to prevent SREs associated with multiple myeloma, particularly for patients who cannot receive bisphosphonates. A resubmission for denosumab will be considered at the November 2018 PBAC meeting.