6.03 DENOSUMAB, 120 mg/1.7mL injection, Xgeva®, Amgen.

1 Purpose of Application

1.1 The submission requested an Authority Required (Streamlined) listing for denosumab for treatment of hypercalcaemia of malignancy that was refractory to intravenous bisphosphonate.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
DENOSUMAB 120 mg/1.7 mL injection, 1 x 1.7mL vial	1	5	$[redacted]	Xgeva	AN

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ ~~Nurse practitioners~~ ☐ Optometrists ☐ Midwives
Condition:	Hypercalcaemia of malignancy
PBS Indication:	Hypercalcaemia of malignancy
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	The condition must be refractory to treatment with an intravenous bisphosphonate.
Administrative Advice	*A patient is considered refractory to Intravenous (IV) bisphosphonates if their corrected serum calcium (CSC) level is not lowered to ≤11.5 mg/dL following treatment with an IV bisphosphonate.*

2.1 The Pre-PBAC response clarified that the corrected serum calcium level should be presented in SI units rather than conventional units i.e. 2.9 mmol/L rather than 11.5 mg/dL.

2.2 The listing was requested on a cost-effectiveness basis compared to zoledronic acid.

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

3 Background

3.1 Denosumab was approved for registration by the TGA for the treatment of hypercalcaemia of malignancy that is refractory to intravenous bisphosphonate on 22 July 2015.

3.2 Denosumab has not previously been considered by the PBAC for the treatment of hypercalcaemia of malignancy.

3.3 Administration is via a subcutaneous injection of 120 mg on days 1, 8 and 15 (loading doses) in the initial 4-week period followed by 120 mg every 4 weeks.

4 Clinical place for the proposed therapy

4.1 Hypercalcaemia of malignancy is a rare complication associated with advanced cancer characterised by elevated serum calcium levels (measured by albumin-corrected serum calcium). The excessive release of calcium is primarily a result of increased bone resorption due to the cancer cytokine environment. Clinical manifestations range from asymptomatic in mild hypercalcaemia to coma or death in severe cases. Treatment is aimed at reduction of serum calcium and severe cases are usually managed in an acute, emergency setting using intravenous fluid rehydration and intravenous bisphosphonates.

4.2 The proposed treatment algorithm appeared to be broadly consistent with published literature for the treatment of severe hypercalcaemia of malignancy in an acute, emergency setting. It was unclear from the algorithm how patients who have mild to moderate hypercalcaemia or who are asymptomatic would be managed.

4.3 Typically, first-line treatment for severe cases included an intravenous bisphosphonate. The use of intravenous bisphosphonates was less clear in a non-acute setting. The recommended dosing regimen for intravenous bisphosphonates was a single dose infusion with repeat doses should patients relapse. This was in contrast to denosumab, with the product information recommending regular dosing every 4 weeks. Following initial treatment, the treatment goals of denosumab and zoledronic acid were inconsistent (maintenance versus episodic treatment, respectively). The complexity of the proposed denosumab listing (with its alternative dosing regimen and mode of administration) and how it may affect the clinical algorithm was unclear.

4.4 The submission positioned denosumab as an alternative therapy in patients who are refractory to initial intravenous bisphosphonate treatment. The proposed current therapy for retreatment was an intravenous bisphosphonate such as pamidronate or

zoledronic acid (4 mg and 8 mg). The zoledronic acid product information states that doses should not exceed 4 mg due to safety concerns such as increased risk of renal impairment.

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

5 Comparator

5.1 Zoledronic acid. This was the appropriate comparator.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on a naïve indirect comparison between a single-arm denosumab observational study and a pooled subgroup analysis of zoledronic acid 8mg retreatment from two randomised controlled trials.

6.4 The submission also presented a supportive comparison of denosumab and zoledronic acid for the prevention of hypercalcaemia of malignancy based on a retrospective, pooled analysis of two randomised controlled trials.

6.5 No data were available to support a comparison of zoledronic acid 4 mg with denosumab for retreatment of hypercalcaemia of malignancy.

Table 1: Studies and pooled analyses presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Treatment of hypercalcaemia of malignancy		
Denosumab single arm observational study		
Study 315	A Single-arm, Multicenter, Proof-of-concept Study of Denosumab in the Treatment of Hypercalcemia of Malignancy in Subjects with Elevated Serum Calcium Despite Recent Treatment with Intravenous (IV) Bisphosphonates	Internal study report
	Hu et al (2014). Denosumab for treatment of hypercalcemia of malignancy	Journal of Clinical Endocrinology & Metabolism, 99:3144-3152
	Hu et al (2013). Denosumab for patients with persistent or relapsed hypercalcemia of malignancy despite recent bisphosphonate treatment	Journal of the National Cancer Institute, 105 (18):1417-20
Main comparator		
Zoledronic acid pooled analysis of 2 randomised trials		
Major 2001 (overall and retreatment phase)	Major P et al (2001). Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomised, controlled clinical trials	Journal of Clinical Oncology, 9(2):558-67
	Major P and Coleman R (2001). Zoledronic acid in the treatment of hypercalcemia of malignancy: Results of the international clinical development program	Seminars in Oncology, 28 (suppl6):17-24
Prevention of hypercalcaemia of malignancy (supportive analysis)		
Denosumab pooled analysis of 2 randomised trials		
Diel 2015	Diel et al (2015). The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease	European Journal of Cancer, 51(11):1467-75

Source: Table B.2-2 (p13) of the submission

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

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design	Dosing regimen	Risk of bias	Patient population	Outcome(s)
Treatment of hypercalcaemia of malignancy						
Study 315	33	Open-label, single arm, multi-centre observational study	Denosumab 120 mg on day 1, 8, 15 (loading doses) in initial 4 weeks then 120 mg every 4 weeks thereafter	High	- HCM - CSC>3.1 mmol/L - Recently received IV bisphosphonate and refractory/relapsed	Response rate and duration
Major 2001 (overall)	287	Pooled analysis of 2 double-blinded, double-dummy, multi-centre RCTs	Single dose zoledronic acid 4 mg vs Single dose zoledronic acid 8 mg vs Single dose pamidronate 90 mg	Unclear	- HCM - CSC≥3.0 mmol/L - Have not recently received IV bisphosphonate	Response rate and duration
Major 2001 (retreatment)	69[a]	Pooled subgroup analysis of 2 double-blinded, double-dummy, multi-centre RCTs	Single dose zoledronic acid 8 mg	High	- HCM - Refractory or relapsed after single dose IV bisphosphonate	Response rate and duration
Prevention of hypercalcaemia of malignancy (supportive analysis)						
Diel 2015	3822	Retrospective pooled analysis of 2 double-blinded, multi-centre RCTs	Denosumab 120 mg every 4 weeks vs zoledronic acid 4 mg every 4 weeks	High	- Not previously diagnosed with HCM - CSC between 2.0-2.9mmol/L - Not previously received IV bisphosphonates	Incidence of HCM and time to HCM

Source: Table B.2-3 (p13) of submission, Study 315 clinical study report (p3), Major 2001 and Major and Coleman 2001 publications

Abbreviations: CSC=corrected serum calcium; HCM=hypercalcaemia of malignancy; RCT=randomised controlled trial

[a]Patients not achieving a response to initial treatment (relapsed/refractory) received retreatment with zoledronic acid 8mg: 22 refractory, 47 relapsed

Comparative effectiveness

6.7 **Table 3: Summary of results in Study 315 and Major 2001**

Outcomes	Study 315	Major 2001 (overall)		Major 2001 (retreatment phase)	
	Denosumab (refractory/ relapsed)	Zoledronic acid 4 mg	Zoledronic acid 8 mg	Zoledronic acid 8 mg (refractory /relapsed)	Zoledronic acid 8 mg (refractory only)
Proportion of patients with a complete response (CSC ≤2.7 mmol/L) by day 10, n/N (%)	12/33 (36) *95%CI 0.20-0.55*	76/88 (86)	78/90 (87)	36/69 (52) *95%CI 0.40-0.64*	NR
Proportion of patients with a complete response (CSC ≤2.7 mmol/L) over study duration, n/N (%)	21/33 (64) *95%CI 0.45-0.80*	NR	NR	NR	NR
Proportion of patients with any response (CSC ≤2.9 mmol/L), %	70 *95% CI 0.51-0.84* (max follow-up 57 days)	NR	NR	NR	23 *If 5/22 then 95%CI 0.08-0.45* (max follow-up 28 days)
Duration of complete response, median, days	11.5[a] (max follow-up 57 days)	32.0 (max follow-up 56 days)[b]	43.0 (max follow-up 56 days)[b]	10.5 (max follow-up 28 days)	NR
Duration of complete response, mean, days	50.6	NR	NR	NR	NR

Source: Study 315 clinical study report (pp74, 75, 76, 163), Major 2001 and Major and Coleman 2001 publications
Abbreviations: CSC=corrected serum calcium; NR=not reported
[a]Median from summary statistics Table 14-4.6.2 (p163), Study 315 clinical study report
[b]During 56 day follow-up, patients who relapsed or were refractory entered the retreatment phase. Patients were retreated with zoledronic acid 8mg and followed-up for 28 days.
Note: Shaded values were used in the economic evaluation, *95% CI calculated during evaluation*.

6.8 The submission claimed higher response rates with denosumab compared to zoledronic acid in patients refractory to bisphosphonate treatment. Although a higher proportion of refractory/relapsing patients treated with denosumab achieved any response at any time (70%) compared with refractory patients treated with zoledronic acid 8mg (23%), there were higher complete response rates in patients receiving zoledronic acid compared with denosumab. The median durations of response for denosumab and zoledronic acid 8mg (retreatment) were similar.

6.9 The total population from Major/Major-Coleman (N=287), was bisphosphonate naïve and therefore not representative of the requested PBS population (patients refractory to IV bisphosphonates). A subgroup from the Major/Major-Coleman study was re-treated in a second round of therapy (N=69), and this may be considered similar to the Study 315 population. This group included both refractory and relapsed patients. Nonetheless, there is outcome data for this group that were compatible with Study 315 (complete response at day 10 and duration of complete response).

6.10 The submission (p 19) incorrectly assumes a sub-population of the re-treated population of Major *et al* (2001) is a homogeneous refractory population: "In Major *et*

al, 69 patients who were refractory to or relapsed after one dose of zoledronic acid or pamidronate, the complete response rate to retreatment with zoledronic acid 8 mg was 52% (Major *et al*, page 562). The median duration of response was 10.5 days (Major *et al*, page 562). In the subgroup of 22 refractory patients, the response rate was 23% (Major and Coleman, page 21). The duration of response in the refractory subgroup was not reported." However (Major and Coleman, p 21) defines the refractory patients as "Retreatment was successful in normalizing CSC in more than half (52.2%) of these patients. While the majority (68%) of the 69 retreated patients had experienced a CR after initial treatment with zoledronic acid or pamidronate, 22 patients had had refractory hypercalcemia (N = 6), a partial response (N = 13), or were unclassified (N = 3) after initial treatment. The response rate to retreatment was 23% in these 22 patients."

6.11 The 23% response rate figure is key to all subsequent analyses, however the actual response rate of true refractory hypercalcaemia patients (N=6) from Major and Coleman is unknown. The analyses that follow are therefore not informative to decision making for the requested PBS population.

6.12 The Pre-PBAC response (page 1) accepted the above interpretation of the data from Major *et al*, stating that subset of 22 patients from Major and Coleman is mainly a mix of patients who did not respond or only partially responded to zoledronic acid. The response argued that the subgroup is most, but not 100%, representative of the proposed PBS population.

6.13 Dosing regimens and treatment durations in each study suggested different treatment goals between Study 315 and Major 2001, (multiple regular doses for maintenance vs single dose for episodic treatment). Response rates were likely to favour denosumab given the observed increased response with increased number of doses that suggested a possible dose-response relationship between denosumab and treatment effect.

6.14 Patient populations between the studies were not directly comparable. Study 315 enrolled patients who were heavily treatment-experienced with prior intravenous bisphosphonate therapy. In contrast, patients in Major 2001 were naïve to bisphosphonate treatment or received a single dose prior to retreatment. Treatment experience may have had an impact on response rates, with results favouring zoledronic acid.

6.15 The different definitions of treatment failure in both studies favoured denosumab, given patients had longer time frames for response. Follow-up periods were also longer for patients in Study 315 compared with Major 2001, which biased the duration of response in favour of denosumab.

6.16 The studies were not sufficiently comparable in terms of study design, patient populations, dosing regimens, treatment intent and outcome definitions to justify an indirect comparison.

6.17 The Pre-PBAC response acknowledged that the lack of comparative data made an economic comparison of denosumab and zoledronic acid challenging. The response presented an incremental efficacy and cost comparison that it asserted supported the claim that denosumab is more effective and cheaper than zoledronic acid 8 mg. This is summarised below in table 4.

Table 4: Incremental efficacy and cost comparison

	Zoledronic acid 4 mg vs pamidronate 90 mg (2003 costs)	Denosumab vs zoledronic 4 mg (current costs)	Denosumab vs zoledronic 8 mg (current costs)
Percentage of patients with complete response	Z = 88% P = 64.9% Δ = 23.1.%	Z = 23% (max.) D = 64% Δ = 41% (min.)	Z = 23% (max.) D = 64% Δ = 41% (min.)
Cost per dose	Z = $[redacted] + $[redacted]* P = $[redacted] + $[redacted]* Δ = $[redacted]	Z = $[redacted] + $[redacted]* D = $[redacted] Δ = $[redacted]	Z = $[redacted] + $[redacted]* D = $[redacted] Δ = -$[redacted]

Source: Table 2 (p2) of the Pre-PBAC response

Comparative harms

Table 5: Overall summary of adverse events in included studies

Summary of adverse events, n (%)	Study 315	Major 2001 (overall)		Major 2001 (retreatment)
	Denosumab 120 mg N=33	Zoledronic acid 4 mg N=86	Zoledronic acid 8 mg N=98	Zoledronic acid 8 mg N=70
Adverse event	32 (97.0)	81 (94.2)	94 (95.9)	50 (71.4)
Treatment-related adverse event	13 (39.4)	NR	NR	NR
- Hypocalcaemia	3 (9.1)	5 (5.8)	6 (6.1)	1 (1.4)
- Hypophosphataemia	4 (12.1)	3 (3.5)	3 (3.1)	0
- Nausea	4 (12.1)	1 (1.2)	3 (3.1)	0
- Peripheral oedema	3 (9.1)	NR	NR	NR
- Serum creatinine Grade 3 or more	NR	2 (2.3)	3 (3.1)	1 (1.5)
- Fever	NR	6 (7.0)	10 (10.2)	2 (2.9)
- Colitis	1 (3.0)	NR	NR	NR
- Cardiac arrest	1 (3.0)	NR	NR	NR
Serious adverse event	30 (90.9)	NR	NR	NR
Adverse event leading to trial discontinuation	8 (24.2)	NR	NR	NR
Deaths	26 (78.8)	NR	NR	NR

Source: Table B.6-2 (p22) of the submission, Table 14-6.6.2 (p486) of Study 315 clinical study report, TGA clinical evaluation report (pp19-27), Major 2001 and Major and Coleman 2001 publications
Abbreviations: NR=not reported

6.18 The most common treatment-related adverse events for denosumab were hypophosphatemia, nausea and peripheral oedema. Serious adverse events that occurred most frequently were neoplasms (52% related to underlying cancer), hypercalcaemia, dyspnoea, diarrhoea and tachycardia. Two serious adverse events considered by the investigator to be possibly related to denosumab were cardiac arrest (with fatal outcome) and colitis (with pre-existing Clostridium difficile infection). All other deaths and serious adverse events were not considered to be treatment-related by the investigator.

6.19 There were insufficient data from the naïve indirect comparison to justify the submission's claim of similar comparative safety between denosumab and zoledronic acid.

Benefits/harms

6.20 There was insufficient information from the naïve indirect comparison to quantify the benefits and harms of denosumab compared to zoledronic acid in absolute terms.

Clinical claim

6.21 The submission described denosumab as superior in terms of comparative effectiveness and similar in terms of comparative safety compared with zoledronic acid. This claim was not adequately supported:

- it was difficult to draw reliable conclusions regarding the relative efficacy of denosumab and zoledronic acid given the uncertainties and discrepancies in the clinical evidence (high risk of bias, different treatment goals, limited applicability and exchangeability of patient populations and non-comparable outcomes).
- the clinical importance of the 'complete response' and 'duration of response' efficacy outcomes and whether there was an association with patient-relevant outcomes was unclear.
- it may not have been reasonable to use zoledronic acid 8 mg retreatment as a comparator as doses above 4 mg are not recommended due to safety concerns.

6.22 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.

6.23 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.24 The submission presented a trial-based cost-effectiveness analysis, based on a naïve indirect comparison between the included studies (Study 315 and refractory subset of Major 2001 pooled subgroup analysis). The cost-effectiveness analysis presented an 'incremental drug cost per day of response'.

6.25 The submission compared denosumab with two dose strengths of zoledronic acid (4 mg or 8 mg). It is unlikely that zoledronic acid 8 mg would be used in practice due to safety concerns and was excluded from the main analysis. The ESC noted that some patients that were refractory may be treated with higher the 4 mg doses of zoledronic acid however, the number of patients possibly treated as such was unknown.

6.26 The drug costs for zoledronic acid were updated during the evaluation due to generic availability from 1 December 2015.

6.27 The numbers of doses of denosumab (4.8) and zoledronic acid (1) were based on the mean number of doses in the included studies. It was unclear if this would reflect clinical practice.

6.28 The parameters used in the cost-effectiveness analysis were inconsistent and non-comparable in terms of patient populations, outcome definitions and follow-up durations in each study. The proportions used in the analysis were based on different outcome definitions in each study (i.e. any response versus complete response) and lengths of follow-up. A median value was used for zoledronic as opposed a mean value for denosumab (10.5 days vs 50.6 days respectively). Lower median values were reported in Study 315 (11.5 and 34 days). Use of median values for denosumab would reduce the incremental benefit to 5 days and would consequently increase the incremental cost/day (see Table 6 below).

6.29 **Table 6: Results of trial-based cost-effectiveness analysis**

	Incremental cost	Incremental benefit (days of response)	Incremental cost per day of response
Base case			
Denosumab vs zoledronic acid 4mg	$ [redacted]	30	$ [redacted]
Use of median CR values for both denosumab and zoledronic acid (10.5 vs 11.5)			
Denosumab vs zoledronic acid 4mg	*$ [redacted]*	*5*	*$ [redacted]*

Source: Table D.4-1 (p28) of the submission
Values in italics were recalculated using 1 December 2015 PBS prices for zoledronic acid 4 mg

6.30 The result from the analysis was uninformative given the difficulty in interpreting 'incremental cost per day of response'.

6.31 The submission acknowledged the inability to construct a robust economic model given the limited clinical evidence available. The cost-effectiveness analysis was unreliable and uninformative due to clinical uncertainties and lack of robustness.

Denosumab cost/patient/course: $[redacted]

6.32 The estimated cost of denosumab assumed 5 scripts of denosumab at $[redacted] per script. The comparative cost of zoledronic acid was $[redacted], assuming 1 script of zoledronic acid 4 mg (50:50 mix of public and private hospital administration) per course of therapy.

Estimated PBS usage & financial implications

6.33 The submission used a market share approach to estimate the utilisation and financial implications of listing denosumab. Key sources used were the 10% Medicare sample including Authority indications of use to estimate the number of patients receiving treatment for hypercalcaemia of malignancy; the AIHW Australian Cancer Incidence and Mortality books to estimate the annual growth of patients with hypercalcaemia of malignancy; and the Major 2001 study to estimate the proportion of refractory patients.

6.34 The submission was not considered by DUSC. However, the DUSC Secretariat provided updated estimates of expected patients with hypercalcaemia of malignancy based on available PBS patient data that were incorporated in the estimated use and financial implications.

6.35 **Table 7: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use (submission estimates)					
Number of patients on bisphosphonates for HCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of refractory HCM patients (32%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of denosumab to PBS/RPBS (less patient co-payment[b])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost with 50:50 mix of zoledronic acid 4 mg and 8 mg offset *(Average cost: $[redacted])*[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated extent of use (DUSC Secretariat estimates)					
Number of patients on bisphosphonates for HCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of refractory HCM patients (32%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost of denosumab to PBS/RPBS (less patient co-payment[b])	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost with 50:50 mix of zoledronic acid 4 mg and 8 mg offset *(Average cost: $[redacted])*[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Error addressed in PSCR (net cost with 50:50 mix of zoledronic acid 4 mg and 8 mg offset)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Sensitivity analysis					
Net cost with zoledronic acid 4 mg offset *(Average cost: $[redacted])*[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a]Assuming 5 scripts per patient as estimated in the submission
[b]Assuming patient co-payments were only from denosumab scripts
[c]Average cost calculated assuming 50:50 mix of public and private hospital administration
Source: Table E.2-2, E.3-1, E.4-1, E.6-1 (pp31-32) of the submission and compiled during the evaluation
Estimates in italics were recalculated using December 2015 PBS prices for zoledronic acid 4mg

The redacted table above shows that in year 5, the estimated number of scripts was less than 10,000 and the net cost to PBS would be less than $10 million.

6.36 The PSCR revised net cost of listing denosumab on the PBS was estimated to be up to less than $10 million in the fifth year of listing, including all cost offsets proposed in the submission. The estimated utilisation and financial implications of listing denosumab on the PBS were highly uncertain due to the following issues:

- Given the limitations of the 10% Medicare sample in estimating the total patient population with hypercalcaemia of malignancy, an epidemiological approach may have been more appropriate. Denosumab may be used in settings different to zoledronic acid (due to differences mode of administration, dosing regimen and renal restrictions).
- The average cost of zoledronic acid based on a 50:50 mix of 4mg and 8mg is unlikely to represent utilisation in practice as doses above 4mg are not recommended.
- The number of denosumab scripts per patient, based on Study 315 may not represent the number of prescriptions per year of treatment.
- Cost offsets from zoledronic acid substitution were based on an assumption of two prescriptions per substituted patient, which was inconsistent with the assumption of one dose in the economic evaluation.

- The proportion of refractory patients (32%) based on the refractory rate in Major 2001 may not reflect the proportion of patients who would qualify for retreatment in practice.
- It was unclear whether a co-payment offset would be applicable should primary access to denosumab occur in a public hospital setting.
- There could be potential for market growth as denosumab has an alternative dosing regimen to currently listed treatments, no restrictions on use in renal impairment and can be administered outside of a hospital setting.

6.37 The submission did not provide an estimate for the potential affects to the MBS or other government health budgets but suggested that any additional cost to the PBS would be offset by savings in the avoidance of the day admission required for intravenous zoledronic acid administration. The submission did not consider the potential costs to the MBS for denosumab administration (5 doses).

Financial Management – Risk Sharing Arrangements

6.38 The submission claimed that a Risk Share Arrangement was unnecessary for the indication of treatment of hypercalcaemia of malignancy.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the PBS listing of denosumab for hypercalcaemia of malignancy based on low quality clinical data that did not support the claim of superior efficacy, and the lack of a clear clinical place for denosumab.

7.2 The PBAC accepted that zoledronic was an appropriate comparator, however also noted that pamidronate is also PBS-listed for hypercalcaemia of malignancy. The PBAC considered that as pamidronate would also be replaced in practice, albeit to a lesser extent, it was also a relevant comparator.

7.3 PBAC noted that the listing of denosumab would impact the clinical treatment algorithm and treatment setting, given its alternative treatment goal and administration outside of a hospital setting, however considered that the benefit of this impact had not been justified by the submission.

7.4 The PBAC considered that the clinical place for denosumab had not been clearly defined, particularly in the context of refractory and relapsed patients, where patients who initially respond to treatment with intravenous bisphosphonates are likely to relapse, and considered there was potential for use of denosumab in this patient group. The PBAC also considered that there was a high likelihood of ongoing denosumab use in patients once they present with malignant hypercalcaemia, when they are still responsive to bisphosphonates, and/or where hypercalcaemia would be well controlled by the specific treatment targeting the underlying condition.

7.5 The PBAC noted the submission's claim of superior efficacy and non-inferior safety was based on a naïve indirect comparison between a single-arm denosumab

observational study (Study 315) and a pooled subgroup analysis of zoledronic acid 8 mg retreatment from two randomised controlled trials (Major 2001), which were conducted more than 10 years apart. While difficult to compare across studies given the lack of data in both studies, the PBAC considered that there were similarities between the 33 patients in Study 315 and the 69 patients with relapsed or refractory HCM in Major:

- the mix of different malignancies was similar, although patients in Study 315 were heavily pre-treated; and
- refractoriness was defined as minimal response by day 7 in Major, and approximately 1/3 patients fell into that category; while in Study 315, 25% of patients had last received a bisphosphonate in the previous 8 – <13 days, a group most analogous to the refractory group in Major.

7.6 The PBAC considered that the clinical data was of low quality with respect to comparative efficacy and safety, and did not form an adequate basis to support the clinical claim of superior efficacy and non-inferior safety. Based on the evidence, the PBAC considered that denosumab is likely to be effective in patients who have previously received bisphosphonates for malignant hypercalcaemia. The PBAC did not consider the data in this clinical setting allowed conclusions to be drawn about the relative benefit/harm of denosumab compared to zoledronic acid. The PBAC also noted that denosumab was proposed as ongoing therapy, whereas zoledronic acid was episodic, this further exacerbated the difficulty of comparison between treatments.

7.7 The PBAC considered that the values selected for use in the economic model were not justified, as the data did not support superior efficacy for denosumab over zoledronic acid. The PBAC also noted the incremental efficacy and cost comparison presented in the Pre-PBAC response, however considered that this comparison was not informative as it also did not provide new data to support greater efficacy.

7.8 PBAC noted that the lack of comparative clinical data made an economic comparison between denosumab and zoledronic acid challenging, and further noted that no further head to head trials of denosumab and zoledronic acid were planned. In this context the PBAC considered that a future major submission should include a cost-minimisation analysis between denosumab and bisphosphonates and further identify the patient group for which PBS listing is sought. It was noted that bisphosphonates are contraindicated in patients with a GFR < 30ml/min.

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 intends to address the issues raised by the PBAC in a resubmission to enable PBS listing of denosumab for this small population with limited treatment options and high clinical need.