PUBLIC SUMMARY DOCUMENT

Product: Denosumab, solution for injection, 120 mg in 1.7 mL, Xgeva®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission requested an Authority Required (Streamlined) listing for the treatment of giant cell tumour of bone in adult and skeletally mature adolescent patients.

The submission was made under TGA/PBAC parallel process. At the time of PBAC consideration the TGA Clinical Evaluation Report and positive Delegate's Summary were available.

2. Background

Denosumab had not previously been considered by the PBAC for this indication.

Denosumab 120 mg is currently available on the PBS for the treatment of bone metastases from breast cancer and castration-resistant prostate cancer.

3. Registration Status

Denosumab was TGA registered on 15 January 2014 for the treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.

Denosumab is also TGA approved for the prevention of skeletal related events in patients with bone metastases from solid tumours.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
For the treatment of giant cell tumour of bone in adult and skeletally mature adolescent patients.

Listing was requested on a cost-effectiveness basis over 'no treatment'/placebo.

The PBAC considered that listing specifying use in adults and skeletally mature adolescents was appropriate and consistent with the proposed TGA indication. The PBAC considered that it was not appropriate that denosumab be used in adolescents with an open bone growth plate.

The PBAC considered that the listing should allow use of denosumab in patients for whom surgical resection is not feasible and in patients for whom surgery is possible, but would

result in significant morbidity. Additionally, the listing should specify that denosumab is not PBS-subsidised for patients who have undergone curative surgical resection.

5. Clinical Place for the Proposed Therapy

Giant cell tumour (GCT) of bone is histologically classified as a benign neoplasm which behaves aggressively as a locally osteolytic bone tumour. GCTs occur most frequently in the bones of the lower and upper limbs. Approximately 20% of cases occur in the axial skeleton (sacrum, spine) or pelvis, where it is particularly difficult to manage.

Surgical resection is considered curative and is the treatment of choice. Currently in patients for whom surgery is not feasible a variety of salvage therapies are used (which may include radiation therapy, chemotherapy and interferon, or bisphosphonates) but there is no definitive therapy. The submission stated that in patients for whom resection is feasible denosumab will be used as an adjuvant to surgery alone and in patients for whom resection is not feasible, denosumab will become the standard of care. The aim of treatment appears to be improvement in quality of life through pain improvement, improved mobility and function, as well as reduced morbidity due to reduced need for salvage therapy and surgery.

6. Comparator

The submission nominated 'no treatment'/placebo as the main comparator. The PBAC accepted that this was the appropriate comparator for patients in whom resection is feasible and surgery would not result in significant morbidity. However, the PBAC agreed with the Economic Sub-Committee (ESC) and Commentary that 'salvage therapies' also represented a relevant comparator for patients in whom resection is feasible and surgery would not result in severe morbidity and in those in whom resection is not feasible.

7. Clinical Trials

The submission presented two single arm, non-randomised studies enrolling a total of 309 patients with giant cell tumour. All patients were treated with denosumab 120 mg injections once every 4 weeks including additional loading doses at days 8 and 15. Study 20040215 enrolled patients with recurrent GCT or those with GCT where resection was not feasible, whilst Study 20062004 enrolled patients who had surgically unsalvageable disease or had GCT for which planned surgery included joint resection, limb amputation, hemipelvectomy or another procedure which would result in severe morbidity. The risk of bias in studies 20040215 and 20062004 are high as they are both single arm, non-randomised, open-label studies. Details of the studies are presented in the table below.

Studies and associated reports presented in the submission

Study	Protocol title/ Publication title	Publication citation
Single arm phase II studies		
Study 20040215	An open-label, multicenter, phase 2 safety and efficacy study of denosumab (AMG162) in subjects with recurrent or unresectable giant cell tumour (GCT) of bone. Report date: 19 June 2011.	Branstetter, D. G., Nelson, S. D., et al. (2012). "Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone." Clinical Cancer Research 18(16): 4415-4424. Fenton, M., Murphey, M. D., et al. (2011a). "Imaging findings of patients with giant cell tumor after treatment with denosumab." Skeletal Radiology 40(8): 1125. Fenton, M. E., Jelinek, J. S., et al. (2011b). "Imaging findings of patients with giant cell tumor after treatment with denosumab." Skeletal Radiology 40(4): 486. Thomas, D., Henshaw, R., et al. (2010). "Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study." The Lancet Oncology 11(3): 275-280. Thomas, D. M., Chawla, S., et al. (2009). "Denosumab for the treatment of giant cell tumor (GCT) of bone: Final results from a proof-of-concept, phase II study." Journal of Clinical Oncology 27(15): 10510.
Study 20062004	An open-label, multi-center, phase 2 study of denosumab in subjects with Giant Cell Tumour of Bone. Report date: 29 February 2012.	Blay, J., Chawla, S. P., et al. (2011). "Denosumab safety and efficacy in giant cell tumor of bone (GCTB): Interim results from a phase II study." Journal of Clinical Oncology 29(15). Cleeland, C. S., Staddon, A. P., et al. (2011). "Effects of denosumab on pain reduction in giant cell tumor of bone (GCTB): Interim phase II study results." Journal of Clinical Oncology 29(15). Engellau, J., Chawla, S., et al. (2011). "Denosumab treatment for giant cell tumor of bone (GCTB) in adolescent patients: Interim results from a phase II study." European Journal of Cancer 47: 15-16. Powell, A., Cleeland, C. S., et al. (2011). "Pain reduction in giant cell tumour of bone: Interim analysis of a phase 2 trial with denosumab." Asia-Pacific Journal of Clinical Oncology 7: 144. Thomas, D., Blay, J. Y., et al. (2011). "Safety and efficacy of denosumab in Giant Cell Tumour of Bone (GCTB)." Osteoporosis International 22: S558.

The submission also presented an "integrated tumour response analysis" (referred to as the "Tumour response analysis"), conducted by the sponsor, which included all patients enrolled in Studies 20040215 and 20062004 who received at least one dose of denosumab and who had radiopathological images (n=190), referred to as the 'tumour analysis response set'. A control group was determined post hoc and included all patients in the tumour analysis response set with at least three pre-treatment images available for assessment. There was no

consistency in the time between images, imaging modality or the assessment technique for the pre-treatment images. The PBAC did not consider that this analysis was informative given the issues raised in the ESC and Commentary about the selection of the control group.

The sponsor requested a hearing for this item. The surgeon gave case studies and discussed the natural history of the disease, how the drug would be used in practice and other matters in response to the Committee's question. The PBAC noted the perspective of the orthopaedic surgeon's presentation in relation to the high clinical need for denosumab treatment.

8. Results of Trials

With regard to comparative effectiveness, the PBAC acknowledged the results of the tumour response analysis presented in the submission, which showed a higher rate of tumour response in patients treated with denosumab than those in the control group. However, given the issues with the construction of the control group, and the lack of information about the patient relevance of this outcome, the Committee did not consider that these results provided a strong basis to inform the assessment of comparative efficacy of denosumab in GCT.

The PBAC noted that Study 20062004 (Chawla et al 2013[1]) reported results in terms of surgeries performed compared to planned in a cohort of 'surgically salvageable' patients treated with denosumab, and considered that these results better informed their consideration of the efficacy of denosumab in GCT. The results are presented in the table below.

Planned vs Actual surgeries in 'surgically salvageable' patients

	Planned (n=100)	Actual total (n=26)
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint or prosthesis replacement	9	1
Joint resection	14	2
En-bloc resection	37	6
En-bloc excision	4	0
Marginal excision	1	0
Curettage	13	16
Other	1	1
No surgery	NA	74

The PBAC considered that the Chawla 2013 data of planned versus actual surgeries supported the clinical effectiveness of denosumab in the treatment of GCT in terms of the clinically relevant outcome of avoidance of surgery.

With regard to comparative harms, overall, 259/304 patients (85.2%) in Studies 20040215 and 20062004 experienced at least one adverse event. The incidence of adverse events in the two clinical studies was consistent with the known safety profile of denosumab and no new safety risks associated with denosumab treatment were identified.

[1] Chawla S et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013; 14: 901-908,

The Committee noted from the hearing presentation that use of denosumab for the treatment of GCT was likely to be long term, at least for some patients. The safety of prolonged use of denosumab at the recommended dose for treatment of GCT remains unknown.

9. Clinical Claim

The submission described denosumab as superior in terms of comparative effectiveness and inferior (but manageable) in terms of comparative safety over no treatment/placebo.

This claim was not well supported by the tumour response analysis presented in the submission, given the issues with the construction of the control group and the patient relevance of the 'tumour response' outcome.

However, whilst the submission had not attempted to quantify the magnitude of any improvement in quality of life, the PBAC considered that patient relevance of avoiding major surgeries such as hemipelvectomy and amputation was clear. The Committee considered that in the context of a rare and potentially invasive condition such as GCT, the data on surgeries avoided were sufficient to support the claim of superior efficacy over placebo.

10. Economic Analysis

The submission presented a cost-effectiveness analysis, expressed as a cost per responder based on the results of the adjusted objective response of the Tumour response analysis, and a cost analysis based on the actual versus planned surgeries reported in Study 20062004.

The estimated incremental cost per responder was less than $15,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of patients treated to be less than 10,000 in the first 5 years of listing, at an estimated net cost to Government over the first five years of listing of less than $10 million.

The PBAC acknowledged the concerns in the Commentary that the use of denosumab may have been underestimated in the submission, but noted that the total number of eligible patients was unlikely to be high, given the rarity of the condition, and that the submission's estimated net cost to the Government did not include any cost-offsets associated with the likely reduction in surgeries performed.

The PBAC noted that the duration that an individual patient is treated with denosumab is not yet known and could range from 2-3 years to a lifetime. The Committee considered that it was appropriate that a risk share arrangement is implemented to manage the uncertainty of the long term cost to the Commonwealth budget because the patient number and treatment duration are unknown.

12. Recommendation and Reasons

The PBAC recommended extending the current Authority Required (Streamlined) listing of denosumab to include treatment of giant cell tumour of bone in adults and skeletally mature adolescent patients on a cost-effectiveness basis over 'no treatment'/placebo.

The PBAC acknowledged that GCT of bone was a rare tumour for which there are no other effective medical treatments, and that a high clinical need exists.

The PBAC was satisfied that denosumab provides, for some patients, a significant improvement in efficacy over no treatment/placebo.

The PBAC acknowledged the difficulties associated with the collection of data in rare conditions such as giant cell tumour, but noted that clinical trials are being undertaken in the area of bone tumours.

The PBAC acknowledged the results of the tumour response analysis presented in the submission, however, given the issues with the construction of the control group, and the lack of information about the patient relevance of this outcome, the Committee did not consider that these results provided a strong basis to inform the efficacy of denosumab in GCT.

The PBAC noted that Study 20062004 (Chawla et al 2013) reported results in terms of surgeries performed compared to planned in a cohort of 'surgically salvageable' patients treated with denosumab. Whilst the submission had not attempted to quantify the magnitude of any improvement in quality of life, the PBAC considered that patient relevance of avoiding major surgeries such as hemipelvectomy and amputation was clear. The Committee considered that in the context of a rare and potentially invasive condition such as GCT, the data on surgeries avoided were sufficient to support the claim of superior efficacy over placebo.

The PBAC suggested that a review of the use of denosumab be undertaken in 5 years to address the uncertainty of the long-term safety of prolonged use of denosumab, the duration of treatment and the financial risk to the Commonwealth.

The Committee considered that it was appropriate that a risk share arrangement is implemented to manage the uncertainty of the long term cost to the Commonwealth budget because the patient number and treatment duration are unknown.

The PBAC noted and welcomed in input from a health care professional (1) via the Consumer Comments facility on the PBS website. The input described the perceived benefits of denosumab in terms of tumour shrinkage/disappearance and improvement of symptoms, together with the possibility of less extensive surgery.

The PBAC noted that denosumab is currently available for prescribing by nurse practitioners as continuing therapy only.

The PBAC recommended the Safety Net 20 Day Rule should not apply.

In accordance with subsection 101 3BA of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to it at its November 2013 meeting, denosumab should not be treated as interchangeable on an individual patient basis with any other drug or medicinal preparation.

Outcome:
Recommended

Extend the current listing of denosumab to include the following:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
DENOSUMAB denosumab 120 mg / 1.7 mL injection, 1 x 1.7 mL vial	1	5	Xgeva	AN

Condition:	Giant cell tumour of bone
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must be one in whom surgical resection is not feasible; OR Patient must be one in whom surgical resection is possible but surgery would result in significant morbidity AND
Population criteria:	Patient must be an adult; OR Patient must be a skeletally mature adolescent
Prescriber instructions:	Denosumab is not PBS-subsidised for use in patients who have undergone curative surgical resection.
Administrative Advice:	Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for patient has been initiated by a medical practitioner.

13. 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.

14. Sponsor's Comment

Amgen is pleased that denosumab will be available on the PBS for patients with giant cell tumour of bone