

**7.08 ROMOSUZUMAB,
Injection 105 mg in 1.17 mL single use pre-filled
syringe,
Evenity[®],
Amgen Australia Pty Ltd.**

1 Purpose of Application

- 1.1 The resubmission requested a Section 85 (Authority Required) PBS listing for romosozumab for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti-resorptive therapy (later-line setting). The PBAC previously considered romosozumab for the broader severe osteoporosis population (first and later-line settings) in November 2018 and the later-line setting only in July 2019.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis compared to teriparatide and a cost-effectiveness analysis compared to alendronate (Table 1).

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

Component	Description
Population	Patients with severe osteoporosis (multiple minimal trauma fractures, at least one symptomatic fracture, and BMD T-score \leq -3.0) who have experienced a fracture while on at least 12 months of anti-resorptive therapy
Intervention	Romosozumab, 210 mg monthly subcutaneous injection for 12 months followed by anti-resorptive therapy
Comparator	Teriparatide, 20 mg daily subcutaneous injection for 18 months followed by anti-resorptive therapy Alendronate 70 mg weekly oral tablet (as a proxy for long term anti-resorptive therapy)
Outcomes	Increased bone strength, prevention of osteoporosis-related fractures and mortality
Clinical claim	Romosozumab is similar (potentially superior) in terms of efficacy and potentially inferior in terms safety compared to teriparatide Romosozumab is superior in terms of efficacy compared to alendronate. The resubmission did not specify a comparative safety claim for romosozumab versus alendronate, however, an increased incidence of cardiovascular events associated with romosozumab was noted.

Source: Table 1.1-1, p 11 of the submission

2 Background

Registration status

- 2.1 Romosozumab was approved by the TGA on 21 June 2019 for the following indications:
- treatment of osteoporosis in postmenopausal women at high risk of fracture.
 - treatment to increase bone mass in men with osteoporosis at high risk of fracture.

- 2.2 In July 2019, the PBAC noted the ACM considered romosozumab to have an overall positive benefit-risk profile but noted cardiovascular concerns and were of the opinion that a long term cardiovascular safety study was necessary. The TGA delegate was previously reluctant to register romosozumab without a plan and firm commitment for active post market pharmacovigilance (paragraph 3.2, romosozumab Public Summary Document (PSD), July 2019 PBAC meeting).
- 2.3 The TGA approved product information states the need to consider an individual benefit-risk assessment prior to initiating romosozumab treatment (particularly in patients at high cardiovascular risk).
- 2.4 The FDA approved romosozumab on 9 April 2019 for the treatment of osteoporosis in postmenopausal women at higher risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. The FDA approval included a requirement for the sponsor to conduct a 5-year observational cardiovascular feasibility study, potentially followed by a comparative safety study or trial. Romosozumab does not currently have an approved FDA indication for the treatment of men with osteoporosis.
- 2.5 The FDA approved product information includes a black boxed warning for the potential risk of myocardial infarction, stroke and cardiovascular death. The warning recommends that romosozumab should not be used in patients who have had a recent myocardial infarction or stroke (≤ 1 year); and that patients experiencing a myocardial infarction or stroke while on treatment should cease therapy.
- 2.6 The PBAC noted that on 17 October 2019, the Committee for Medicinal Products for Human Use (CHMP) recommended marketing approval for romosozumab in Europe for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture (following a rejection in June 2019 due to concerns with increased risk of cardiovascular events). It was proposed that romosozumab treatment be initiated and supervised by specialist physicians experienced in the treatment of osteoporosis.

Previous PBAC consideration

- 2.7 The key matters of concern from the previous November 2018 and July 2019 submissions for severe osteoporosis (later-line therapy) are summarised in Table 2.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
<p>The PBAC considered that the nominated comparator, teriparatide, was appropriate for the restricted population proposed in the resubmission. However, if romosozumab is likely to be used in a much broader population than teriparatide, as predicted in the resubmission (i.e. an approximate ■-fold increase in the market size with the introduction of romosozumab), a comparison with anti-resorptives is relevant (paragraph 7.3, romosozumab, PSD, July 2019 PBAC meeting)</p>	<p>The resubmission nominated alendronate as a relevant comparator, as a proxy for anti-resorptives.</p>
<p>The PBAC considered the clinical claim of non-inferior efficacy for romosozumab and teriparatide to be uncertain given the issues with the indirect comparison versus teriparatide, including the impact of the requirement for continued anti-resorptive therapy following cessation of romosozumab (paragraphs 7.4 and 7.18, romosozumab PSD, July 2019 PBAC meeting). The PBAC also advised that any additional information regarding the cardiovascular safety profile of romosozumab should be provided (paragraph 7.18, romosozumab, PSD, July 2019 PBAC meeting).</p>	<p>The resubmission described romosozumab as similar (potentially superior) in terms of efficacy and potentially inferior in terms of safety compared to teriparatide.</p> <p>The resubmission did not provide additional data to inform the impact of the requirement for anti-resorptive therapy following discontinuation of romosozumab.</p> <p>Additional information from the first Periodic Safety Update Report (PSUR) for romosozumab was presented in the resubmission.</p>
<p>The sponsor provided updates to the cost-minimisation analysis in the July 2019 submission, in both the PSCR and Pre-PBAC response. Although some key areas of concern from the ESC were addressed in the Pre-PBAC response in July 2019 (costs associated with monitoring and treatment of cardiovascular events), the PBAC remained concerned around the trial-based equi-effective doses used, the additional costs for anti-resorptive therapy following cessation of romosozumab and administration costs (paragraph 6.58, romosozumab, PSD, July 2019 PBAC meeting)</p>	<p>The resubmission included further adjustments to the cost-minimisation analysis (teriparatide drug cost, equi-effective doses, additional anti-resorptive therapy cost) that also include changes from the revised base case in the July 2019 Pre-PBAC response (cardiovascular event management cost, romosozumab administration cost).</p>
<p>The PBAC considered that any resubmission would need to address concerns regarding the cost-effectiveness of romosozumab use in a much broader population than teriparatide (paragraph 7.18, romosozumab, PSD, July 2019 PBAC meeting).</p>	<p>The resubmission included an economic model comparing romosozumab/alendronate versus alendronate from the November 2018 submission.</p>
<p>The PBAC noted the significant concerns regarding the economic model comparing romosozumab and alendronate and considered that it did not form a reliable basis for decision making due to the overestimation of fracture risk and treatment effect, the assumption of continuing treatment effect (which relied on adherence and persistence rates unlikely to be achieved in the PBS population), and potentially unreliable fracture disutilities (paragraph 7.13, romosozumab, PSD, November 2018 PBAC meeting).</p>	<p>The resubmission did not address the concerns raised by the PBAC. Key changes include a reduced price for romosozumab (based on the cost-minimised price versus teriparatide), changes to the fatal and non-fatal cardiovascular event costs, cardiovascular monitoring cost and romosozumab administration cost.</p>
<p>The PBAC considered that any resubmission would need to provide revised financial estimates and include a Risk Sharing Arrangement which addresses concerns regarding use in a larger population compared to teriparatide (paragraph 7.18, romosozumab, PSD, July 2019 PBAC meeting).</p>	<p>The resubmission provided revised financial estimates based on the cost-minimised romosozumab drug price versus teriparatide.</p> <p>The resubmission provided an updated risk-sharing arrangement which included a ■% rebate for use beyond the utilisation caps.</p>

Matter of concern	How the resubmission addresses it
The PBAC considered that any resubmission would need to include details of a comprehensive and robust quality use of medicines implementation strategy to address concerns regarding ensuring on-going use of anti-resorptive therapy following cessation of romosozumab (paragraph 7.18, romosozumab, PSD, July 2019 PBAC meeting).	The resubmission provided additional details regarding the sponsor's quality use of medicines strategy.

Source: compiled during the evaluation

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

3 Requested listing

3.1 The proposed listing is outlined below and is essentially the same as that requested in July 2019. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for maximum quantity	Proprietary Name and Manufacturer
ROMOSOZUMAB 105mg/1.17mL injection, 2 x 1.17mL pre-filled syringes	1	1	5	\$618.09 (published price)	EVENTY® Amgen Australia Pty Ltd

Initial treatment Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
	Severity: Severe
	Condition: Established osteoporosis
7712	Indication: Severe established osteoporosis
	Treatment Phase: Initial treatment
7717	Clinical criteria:
7716	Patient must be at very high risk of fracture
	AND
7719	Clinical criteria:
7718	Patient must have a bone mineral density (BMD) T-score of -3.0 or less
	AND
7721	Clinical criteria:
7720	Patient must have had 2 or more fractures due to minimal trauma
	AND
7723	Clinical criteria:

Public Summary Document – March 2020 PBAC Meeting

7722	Patient must have experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses
	AND
19937	Clinical criteria: The treatment must be the sole PBS-subsidised agent <i>for this condition</i> .
	AND
NEW	Clinical criteria: The treatment must not exceed a lifetime maximum of 12 months therapy
	AND
NEW	Clinical criteria: Patient must not have received treatment with teriparatide; OR Patient must have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy
7736	Treatment criteria:
7735	Must be treated by a specialist; or
7714	Must be treated by a consultant physician
7729	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
NEW	Prescribing Instructions: If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with romosuzumab <i>this drug</i> is initiated.
NEW	Prescribing Instructions: If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialed so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with romosuzumab <i>this drug</i> is initiated
19003	Prescribing Instructions: Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
7733	Prescribing Instructions: Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
7734	Administrative Advice: Details of accepted toxicities including severity can be found on the Department of Human Services website at www.humanservices.gov.au .
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

Continuing treatment Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
	Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
	Severity: Severe
	Condition: Established osteoporosis
7712	Indication: Severe established osteoporosis
	Treatment Phase: Continuing treatment
7738	Clinical criteria:
7737	Patient must have previously been issued with an authority prescription for this drug,
	AND
NEW	Clinical criteria: The treatment must not exceed a lifetime maximum of 12 months therapy
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.
7608	Administrative Advice: Special Pricing Arrangements apply.

- 3.2 The resubmission stated that teriparatide is currently subject to a special pricing arrangement (SPA) and noted that a SPA would also be required for romosozumab. The resubmission did not estimate an effective price for romosozumab as the SPA in place for teriparatide would need to be taken into consideration in the agreement of an effective price for romosozumab.
- 3.3 The requested PBS restriction is narrower than the approved TGA indication (patients at high risk of fracture) as it is limited to a subset of patients with severe osteoporosis who meet specific clinical criteria relating to fracture history, BMD T-scores and prior therapies.
- 3.4 The proposed restriction is broadly consistent with the current PBS listing of teriparatide, which limits treatment to patients with severe osteoporosis who have experienced a prior symptomatic fracture while receiving anti-resorptive therapy.
- 3.5 The PBAC noted that the requested listing would allow prescribing of romosozumab only by a Specialist or a Consultant Physician, which is consistent with the current teriparatide restriction. The PBAC noted advice from the Department that that both ‘Specialists’ and ‘Consultant Physicians’ are intended to cover the same eligible prescriber type. As such, the PBAC considered the treatment criteria proposed appropriate for both the initial and continuing restriction.
- 3.6 The proposed restriction does not allow for sequential use of romosozumab following treatment with teriparatide, but allows for use of romosozumab in patients who are intolerant to teriparatide after a trial of 6 months or less. There were no available data

on the sequential use of anabolic agents. A corresponding statement will be required in the restriction for teriparatide to prevent sequential use following treatment with romosozumab.

- 3.7 The ESC noted that the resubmission provided updated information regarding the cardiovascular safety profile of romosozumab based on the Periodic Safety Update Report (PSUR). The ESC considered the PSUR indicated that serious events of myocardial infarction and stroke remain an important potential risk with romosozumab (see paragraph 6.34). The ESC noted that in relation to myocardial infarction and stroke the TGA approved product information states a ‘causal relationship between EVENITY and these events has not been established’ and romosozumab ‘should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year’. The ESC considered that it may be appropriate to include a criterion in the proposed PBS restriction to exclude patients with prior cardiovascular events to mitigate this risk while awaiting results of the 5-year observational cardiovascular feasibility study required by the FDA. The pre-PBAC response argued that details regarding contraindications, special warnings or precautions are best outlined in the product information for medicines and that romosozumab educational programs will clearly outline the breadth of matters relating to quality use of medicines. The PBAC considered that inclusion of a criterion excluding patients with prior cardiovascular events in the proposed PBS restriction was not required as prescribing would be restricted to Specialists or Consultant Physicians with the need to consider an individual’s benefit-risk assessment prior to initiating romosozumab treatment clearly stated in the product information.
- 3.8 The ESC considered that the addition of anti-resorptive therapy following cessation of romosozumab was important to the consideration of effectiveness and subsequent cost-effectiveness for this drug. The ESC suggested including a requirement in the restriction for enrolment in a patient support program that involves an alert to the need to transition to anti-resorptive therapy on cessation of romosozumab. The pre-PBAC response argued that extensive education efforts and formal guidance, combined with an optional patient support program, will ensure that prescribers are well aware of the need for anti-resorptive therapy following cessation of romosozumab. The pre-PBAC response also stated that PBS listings which have included a mandated requirement for patient enrolment into a program mainly do so because of safety concerns, whereas the issue here is one of ensuring bone mass is optimised into the future. In addition, the pre-PBAC response argued that a mandatory requirement for participation in a patient support program may deny access for patients who would choose not to enrol (e.g. for personal or privacy reasons). The PBAC considered that, with prescribing restricted to Specialists or Consultant Physicians, mandatory participation in a patient support program to provide an alert to the need to transition to anti-resorptive therapy was not required. However, the PBAC considered that the utilisation of anti-resorptive therapy following

cessation of romosozumab should be reviewed after an appropriate period post listing to investigate the success of transitioning patients.

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

4 Population and disease

- 4.1 Osteoporosis is a condition that occurs when the bones lose minerals more quickly than the body can replace them, leading to enhanced bone fragility (due to reduced bone mass and micro-architectural deterioration of bone tissue) and a consequent increase in fracture risk. Loss of bone strength occurs gradually over many years and usually shows no symptoms. The most common fractures occur at the hip, spine and wrist and can lead to increased mortality, long-lasting pain, reduced mobility and possible disability.
- 4.2 Romosozumab is a dual acting anabolic agent/anti-resorptive therapy while teriparatide is an anabolic agent and alendronate is an anti-resorptive therapy.
- 4.3 The target population for romosozumab is patients with severe osteoporosis in the later-line setting, defined in the resubmission as patients with multiple minimal trauma fractures who have a BMD T-score ≤ -3.0 , with at least one symptomatic fracture after at least 12 months of anti-resorptive therapy. The resubmission identified this population as a group with high clinical need given their high risk of additional fractures.
- 4.4 The resubmission positioned romosozumab as an alternative to teriparatide for subsequent treatment of patients who develop severe osteoporosis while on anti-resorptive therapy for at least 12 months.

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

5 Comparator

- 5.1 The resubmission nominated teriparatide as the main comparator. The PBAC previously considered teriparatide as an appropriate comparator for the requested population (paragraph 7.3, romosozumab, PSD, July 2019 PBAC meeting).
- 5.2 The resubmission nominated alendronate as a relevant comparator, as a proxy for anti-resorptive therapy. The previous submissions (November 2018 and July 2019) and current resubmission forecast an approximate ■-fold increase in the anabolic agent market with the introduction of romosozumab. Based on this assumption, the majority of romosozumab utilisation will be captured from patients not currently receiving teriparatide. The PBAC previously considered that if romosozumab is likely to be used in a much broader population than teriparatide, a comparison with anti-resorptives is relevant (paragraph 7.3, romosozumab, PSD, July 2019 PBAC meeting). In November 2018, the PBAC considered alendronate as an appropriate comparator but noted comparative evidence against denosumab would have been informative (paragraph 7.9, romosozumab, PSD, November 2018 PBAC meeting). The ESC considered alendronate was probably a reasonable proxy for anti-resorptive therapy but also agreed with the November 2018 PBAC advice that denosumab was the treatment most likely to be replaced in practice.

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 (5), health care professionals (17) and organisations (8) via the Consumer Comments facility on the PBS website. The comments highlight the cost of fragility fractures to the Australian health care system and the impact of such fractures on patients' quality of life. In particular, the comments highlight the potential pain associated with such fractures and the loss of confidence and reduced mobility that can arise. The comments also highlight the dosing convenience of romosozumab compared with teriparatide with some comments suggesting the current uptake of teriparatide is limited by the requirement for daily injections.
- 6.3 The PBAC noted the advice received from the Australia and New Zealand Bone and Mineral Society (ANZBMS) Therapeutics Committee clarifying the likely use of romosozumab in clinical practice and highlighting the novel mechanism of action of this agent. The PBAC specifically noted that according to ANZBMS recent evidence has reported that the magnitude of increase of areal BMD compared to placebo is a

statistically and clinically significant predictor of the magnitude of fracture reduction.¹ In addition, the ANZBMS stated that for patients who would benefit from anabolic therapy but have contra-indications to teriparatide (e.g, those unable to tolerate the side effects of teriparatide or those with a previous history of radiotherapy), romosozumab may be a suitable alternative. The ANZBMS agreed with the view that clinicians should refrain from prescribing romosozumab in those at high risk of cardiovascular disease, in particular those with a history of myocardial infarction or stroke.

Clinical trials

- 6.4 There were no changes to the clinical evidence provided in the resubmission compared to the November 2018 and July 2019 submissions.
- 6.5 The resubmission was based on the following comparisons:
- Direct comparison of BMD outcomes with romosozumab versus teriparatide in postmenopausal women with osteoporosis who were previously treated with anti-resorptive therapy (STRUCTURE).
 - Direct comparison of fracture outcomes with romosozumab versus alendronate in postmenopausal women with osteoporosis who were predominantly naïve to anti-resorptive therapy (ARCH).
 - Indirect comparison of fracture outcomes with romosozumab (FRAME) versus teriparatide (GHAC, ACTIVE) using placebo as the common comparator in postmenopausal women with osteoporosis who were predominantly naïve to anti-resorptive therapy.
- 6.6 The resubmission presented a supportive analysis of BMD outcomes with romosozumab versus placebo in men with osteoporosis (BRIDGE) and a supportive non-inferiority analysis of BMD outcomes with the marketed formulation of romosozumab compared to the trial formulation (Study 156).
- 6.7 During the evaluation, an additional Phase 2 dose ranging study (Study 326) comparing BMD outcomes with romosozumab, alendronate, teriparatide and placebo was considered as supportive evidence as it provided the only clinical data on longer-term treatment with romosozumab and maintenance of treatment effect without ongoing anti-resorptive therapy.
- 6.8 The resubmission also excluded a Phase 4 study comparing fracture outcomes with teriparatide and risedronate in postmenopausal women with severe osteoporosis (VERO) as there was no common reference for an indirect comparison with romosozumab trials. Although the trial may not be useful for an indirect comparison,

¹ Bouxsein M et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials J Bone Miner Res 2019;34:632-642

it is the only trial with fracture outcomes for treatment with anabolic agents after anti-resorptive therapy (Kendler 2017; Geusens 2018) and was included during the evaluation.

- 6.9 The main comparisons and supportive analyses noted above were previously considered by the PBAC at the November 2018 and July 2019 meetings.
- 6.10 All clinical data presented in the resubmission were based on romosozumab administered by a healthcare professional. During the evaluation, it was noted that there is an RCT assessing the efficacy and safety of romosozumab when administered by a patient (using auto-injector) rather than a healthcare professional (using pre-filled syringe) (NCT03432533, completed June 2019, results not available).
- 6.11 Details of the included trials are provided in Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
ARCH	Amgen clinical study report (2017). A Multicenter, International, Randomized, Double-blind, Alendronate-controlled Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis	Internal study report
	Saag K et al (2017). Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis.	New England Journal of Medicine 377: 1417-1427
BRIDGE	Amgen clinical study report (2016). A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Compare the Efficacy and Safety of Romosozumab With Placebo in Men With Osteoporosis	Internal study report
	Lewiecki EM et al (2018). A Phase 3 Randomized Placebo-controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis	The Journal of Clinical Endocrinology & Metabolism DOI 10.1210/jc.2017-02163
FRAME	Amgen clinical study report (2017). A Multicenter, International, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis	Internal study report
	Cosman F et al (2016). Romosozumab Treatment in Postmenopausal Women with Osteoporosis.	New England Journal of Medicine 375: 1532-1543
	Cosman F et al (2018). FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab	Journal of Bone and Mineral Research DOI 10.1002/jbmr.3427
STRUCTURE	Amgen clinical study report (2015). An Open-label, Randomized, Teriparatide-controlled Study to Evaluate the Effect of Treatment With Romosozumab in Postmenopausal Women With Osteoporosis Previously Treated With Bisphosphonate Therapy	Internal study report
	Langdahl B et al (2017). Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial.	Lancet 390: 1585–1594
Study 156	Amgen clinical study report (2015). A Multicenter, Randomized, Multiple-dose Phase 3 Study to Evaluate the Noninferiority of Romosozumab at a 90 mg/mL Concentration Compared With a 70 mg/mL Concentration in Postmenopausal Women With Osteoporosis	Internal study report

Public Summary Document – March 2020 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
Study 326	Amgen clinical study report (2016). A Randomized, Placebo-controlled, Multi-dose Phase 2 Study to Determine the Efficacy, Safety and Tolerability of AMG 785 in the Treatment of Postmenopausal Women With Low Bone Mineral Density McClung M et al (2014). Romosozumab in Postmenopausal Women with Low Bone Mineral Density. McClung M et al (2018). Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study Ishibashi H et al (2017). Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study.	Internal study report New England Journal of Medicine 370: 412-420 Journal of Bone and Mineral Research 33: 1-10 Bone 103: 209–215
GHAC	Neer et al (2001). Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. Gallagher JC et al (2005). Teriparatide Reduces the Fracture Risk Associated with Increasing Number and Severity of Osteoporotic Fractures.	New England Journal of Medicine 344: 1434-1441 The Journal of Clinical Endocrinology & Metabolism 90: 1583–1587
ACTIVE	Miller P et al (2016). Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis A Randomized Clinical Trial.	JAMA 316:722-733
VERO	Kendler et al (2018). Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Geusens et al (2018). Effects of teriparatide compared with risedronate on the risk of fractures in subgroups of postmenopausal women with severe osteoporosis: The VERO trial.	Lancet 391:230-40 Journal of Bone and Mineral Research 33 (5):783-794

Source: Table 2.2-1, p23-25, Table 2.2-4, p27 of the resubmission

6.12 The key features of the included trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Romozosumab vs. teriparatide						
STRUCTURE	436	MC, R, OL, AC 12 months	Unclear	PMO with prior treatment	BMD	Not used
Romozosumab followed by alendronate vs. alendronate followed by alendronate						
ARCH	4,093	MC, R, AC First year: DB Later years: OL Median 33 months	Low	PMO with prevalent fracture	Fractures	Patient characteristics, fracture risk, treatment efficacy, incidence of cardiovascular events
Romozosumab followed by denosumab vs. placebo followed by denosumab						
FRAME	7,180	MC, R, PC First year: DB Later years: OL 3 years	Low	PMO	Fractures	Not used
Teriparatide vs. placebo						
GHAC	1,637	MC, R, DB, PC Median 19 months ^a	Unclear	PMO with prevalent fracture	Fractures	Not used
ACTIVE	2,463	MC, R, PC, AC Aba vs Pbo: DB Teri: OL 18 months	Unclear	PMO	Fractures	Not used
Meta-analysis	2,724	Included vertebral fractures and non-vertebral fractures from the teriparatide 20mcg and placebo arms of the GHAC and ACTIVE trials				Not used
Teriparatide vs. risedronate						
VERO	1,360	MC, R, AC, DB 24 months	Low	PMO with prevalent fracture	Fractures	Not used

Source: Table 2.3-1 (p 30), Table 2.3-2 (p 31), Table 2.4-1 (p 36), Table 2.4-2 (p 37), Table 2.4-3 (p 39-44), Table 2.4-4 (p 45-46) of the resubmission; p 1-6 Appendix 1 of the resubmission; Kendler et al 2018 publication

Abbreviations; Aba, abaloparatide; AC, active-controlled; DB, double blind; MC, multi-centre; OL, open label; Pbo, placebo; PMO, postmenopausal osteoporosis; R, randomised; Teri, teriparatide

^a Trial stopped prematurely due to the potential risk of osteosarcoma identified in animal studies

Comparative effectiveness

Romozosumab versus teriparatide

- 6.13 Results based on BMD outcomes from the STRUCTURE trial suggest that treatment with romozosumab was associated with a statistically significant increase in total hip, femoral neck and lumbar spine BMD over one year compared to teriparatide. The PBAC previously noted that the clinical importance of this difference was unclear as changes in BMD T-scores may not reflect changes in fracture risk with different therapies (para 7.3, romozosumab PBAC PSD November 2018).
- 6.14 The Pre-Sub-Committee Response (PSCR) acknowledged the PBACs preference for fracture outcomes and argued that a recent meta-regression of 38 placebo-controlled trials of 19 therapeutic agents had shown a strong correlation between increasing

BMD at the total hip or femoral neck and reduced risk of hip and vertebral fracture.² The PSCR further argued that a trend was also evident for non-vertebral fracture. The ESC considered the applicability of the meta-regression to a comparison between romosozumab and teriparatide was unclear given the small amount of data from these agents included in the analysis.

- 6.15 The PSCR noted the larger gains in BMD reported in the STRUCTURE trial for romosozumab compared with teriparatide in patients who transitioned from alendronate. The PSCR argued that the increase in BMD observed with romosozumab in the pre-treated STRUCTURE patients was similar to that observed in treatment-naïve patients in the fracture outcomes trials. The PSCR argued that the same was not true for teriparatide and noted a decline in hip BMD observed with teriparatide in the STRUCTURE trial. The ESC noted that the STRUCTURE trial assessed the effect of teriparatide on BMD at 12 months and advised that there is increasing evidence that longer durations are required (18-24 months) for the full BMD benefit of this drug to be reached³ and hence the comparison was suboptimal. The ESC noted that the current PBS listing for teriparatide allows a maximum of 18 months of subsidised treatment.
- 6.16 The indirect comparison of fracture outcomes with romosozumab versus teriparatide is summarised in Table 5.

² Bouxsein M et al. Change in Bone Density and Reduction in Fracture Risk: A Meta-Regression of Published Trials *J Bone Miner Res* 2019;34:632-642

³ Lindsay R et al. Teriparatide for osteoporosis: importance of the full course. *Osteoporos Int* 2016;27: 2395-2410

Table 5: Indirect comparison of fracture outcomes with romosozumab (12 months) and teriparatide (approximately 18 months) when used as the primary osteoporosis treatment

Trial	Romosozumab n/N (%)	Placebo, n/N (%)	Teriparatide, n/N (%)	Odds ratio (95% CI)
Cumulative incidence of new vertebral fracture				
FRAME	16/3321 (0.5)	59/3322 (1.8)	-	0.27 (0.15, 0.47)
GHAC	-	64/448 (14.3)	22/444 (5.0)	0.31 (0.19, 0.52)
ACTIVE	-	30/711 (4.2)	6/717 (0.8)	0.19 (0.08, 0.46)
Meta-analysis of the teriparatide trials ($I^2 = 0\%$)				0.28 (0.18, 0.43)
Indirect analysis of romosozumab vs. teriparatide (results < 1 favour romosozumab)				0.97 (0.5, 2.0)
Cumulative incidence of non-vertebral fracture				
FRAME	56/3589 (1.6)	75/3591 (2.1)	-	0.74 (0.52, 1.05)
GHAC	-	30/544 (5.5)	14/541 (2.6)	0.46 (0.24, 0.87)
ACTIVE	-	33/821 (4.0)	24/818 (2.9)	0.72 (0.42, 1.23)
Meta-analysis of the teriparatide trials ($I^2 = 14\%$)				0.69 (0.38, 0.93)
Indirect analysis of romosozumab vs. teriparatide (results < 1 favour romosozumab)				1.25 (0.7, 2.2)
Cumulative incidence of clinical fracture^a				
FRAME	58/3589 (1.6)	90/3591 (2.5)	-	0.64 (0.46, 0.89)
ACTIVE	-	49/821 (6.0)	35/818 (4.3)	0.70 (0.45, 1.10)
Indirect analysis of romosozumab vs. teriparatide (results < 1 favour romosozumab)				0.91 (0.5, 1.6)

Source: Table 2.6-4 (p 69) of the resubmission

^a The definition of clinical fractures was not consistent between clinical trials. FRAME defined clinical fractures as any clinical vertebral fracture as well as non-vertebral fractures excluding skull, face, hand, fingers, toes, pathologic fractures and severe trauma fractures. ACTIVE defined clinical fractures all fractures that would cause a patient to seek medical care regardless of the level of trauma including skull, face, hand, fingers and toe fractures

- 6.17 The indirect analyses suggest there were no statistically significant differences in fracture outcomes between romosozumab and teriparatide.
- 6.18 The resubmission also provided an indirect comparison of the primary and residual effect of romosozumab (12 months romosozumab and 12 months denosumab treatments) to the primary effect of teriparatide (approximately 18 months treatment) based on fracture outcomes. The results were consistent with the main indirect analyses.
- 6.19 The PBAC previously noted issues of exchangeability and applicability with the indirect analyses of fracture outcomes (para 7.3, romosozumab, PSD, November 2018 PBAC meeting). There were differences in study design, patient characteristics, treatment characteristics and outcome definitions between trials. The incidence of fracture in the common comparator arm also varied substantially between trials (particularly for vertebral fractures). The GHAC trial included patients with a substantially higher risk of fracture (based on FRAX scores) compared to the FRAME and ACTIVE trials. While the overall risk of fracture was broadly similar between FRAME and ACTIVE trials there were differences between the populations, with the FRAME trial generally having lower femoral neck/total hip BMD T-scores versus the ACTIVE trial, which had a higher proportion of patients with prior fracture.
- 6.20 The resubmission did not nominate a non-inferiority margin. The lack of a statistically significant difference between treatments is not a robust methodology for

determining non-inferiority and may not adequately justify the claim of similar efficacy given the wide confidence intervals for fracture outcomes, which indicate substantial uncertainty around the indirect estimate of effects.

Romozosumab versus alendronate

6.21 Key fracture outcomes reported with romozosumab versus alendronate (both followed by alendronate treatment) in the ARCH trial (which was conducted in patients who were predominantly naïve to anti-resorptive therapy) are summarised in Table 6.

Table 6: Key fracture outcomes reported in the ARCH trial

Outcome	Romosozumab/ alendronate	Alendronate/ alendronate	Relative difference (95% CI)	Multiplicity adjusted p-values
New vertebral fracture (includes radiographic and clinical fractures), n/N (%)				
Cumulative incidence to 12 months	55/1696 (3.2)	85/1703 (5.0)	RR 0.64 (0.46, 0.89)	-
Cumulative incidence to 24 months (co-primary outcome)	74/1825 (4.1)	147/1834 (8.0)	RR 0.50 (0.38, 0.66)	p < 0.001
Non-vertebral fracture (includes all non-vertebral fractures except skull, face, hand, fingers, toes, pathologic fractures and severe trauma fractures), n/N (%)				
Cumulative incidence to 12 months	70/2046 (3.4)	95/2047 (4.6)	HR 0.74 (0.54, 1.01)	-
Cumulative incidence to 24 months	129/2046 (6.3)	159/2047 (7.8)	HR 0.81 (0.64, 1.02)	-
Cumulative incidence to primary analysis (median 33 months)	178/2046 (8.7)	217/2047 (10.6)	HR 0.81 (0.66, 0.99)	p = 0.040
Clinical fracture (includes non-vertebral fractures and clinical vertebral fractures), n/N (%)				
Cumulative incidence to 12 months	79/2046 (3.9)	110/2047 (5.4)	HR 0.72 (0.54, 0.96)	-
Cumulative incidence to 24 months	146/2046 (7.1)	197/2047 (9.6)	HR 0.74 (0.59, 0.91)	-
Cumulative incidence to primary analysis (co-primary outcome) (median 33 months)	198/2046 (9.7)	266/2047 (13.0)	HR 0.73 (0.61, 0.88)	p < 0.001
Clinical vertebral fracture, n/N (%)				
Cumulative incidence to 12 months	10/2046 (0.5)	18/2047 (0.9)	RR 0.56 (0.26, 1.22)	-
Cumulative incidence to 24 months	18/2046 (0.9)	44/2047 (2.1)	RR 0.41 (0.24, 0.71)	-
Hip fracture, n/N (%)				
Cumulative incidence to 12 months	14/2046 (0.7)	22/2047 (1.1)	HR 0.64 (0.33, 1.26)	-
Cumulative incidence to 24 months	31/2046 (1.5)	43/2047 (2.1)	HR 0.72 (0.46, 1.15)	-
Cumulative incidence to primary analysis (median 33 months)	41/2046 (2.0)	66/2047 (3.2)	HR 0.62 (0.42, 0.92)	-

Source: Table 2.5-5 (p 52), Table 2.5-6 (p 52), Table 2.5-7 (p 53) of the resubmission

Abbreviations: HR, hazard ratio; NR, not reported; RR, risk ratio

Bolding indicates results that remained statistically significant after adjustments for multiplicity testing. Exploratory outcomes (e.g. clinical vertebral fractures and hip fractures) were not adjusted for multiplicity. Short term (12 month) fracture outcomes were not adjusted for multiplicity.

6.22 Treatment with romosozumab followed by alendronate was associated with statistically significant decreases in vertebral (including clinical vertebral) fractures, clinical fractures and non-vertebral fractures (including hip) over a median of 33 months compared to alendronate alone.

6.23 There were no data on fracture outcomes with romosozumab compared to alendronate in patients with previous anti-resorptive treatment (which may be a treatment effect modifier).

- 6.24 There were no consistent differences in quality of life outcomes associated with romosozumab treatment in the clinical trials.

Other data

- 6.25 Treatment with romosozumab was associated with statistically significant changes in total hip, femoral neck and lumbar spine BMD over one year compared to placebo in male patients with osteoporosis (BRIDGE). The resubmission noted that the BMD changes reported in males with romosozumab treatment were similar to those reported for postmenopausal women.
- 6.26 Treatment with romosozumab 210 mg monthly was associated with larger improvements in BMD outcomes compared to other romosozumab dosing regimens and was superior to placebo, alendronate and teriparatide over 12 months (Study 326). The results also indicated that the majority of BMD gains occurred in the first year but also demonstrated that BMD improvements associated with romosozumab are rapidly lost after discontinuation of osteoporosis treatment.
- 6.27 The PBAC previously noted a lack of comparative data in patients with prior anti-resorptive therapy (paragraph 7.3, romosozumab, PSD, November 2018 PBAC meeting) as there were no data on fracture outcomes with romosozumab compared with teriparatide in patients who had received prior anti-resorptive therapy. No new data were provided in the resubmission.
- 6.28 The PBAC previously noted a lack of comparative data on residual treatment effects with or without subsequent anti-resorptive therapy (paragraph 6.17, romosozumab, PSD, November 2018 PBAC meeting). In July 2019, the PBAC considered that the limited available data from Study 326 suggest that treatment effects associated with romosozumab are rapidly lost after discontinuation of subsequent anti-resorptive therapy. In comparison, the PBAC considered that available data suggest the treatment benefits associated with teriparatide were maintained regardless of follow-up osteoporosis treatment. At that time the PBAC considered that the addition of anti-resorptive therapy following cessation of romosozumab treatment was important to the claim of similar comparative efficacy with teriparatide and considered it was difficult to ensure that patients received and adhered to subsequent anti-resorptive therapy (paragraph 7.5, romosozumab, PSD, July 2019 PBAC meeting). No new data were provided in the resubmission.

Comparative harms

- 6.29 There was no clear pattern in the overall incidence of adverse events between romosozumab and comparators (teriparatide, alendronate and placebo) during the initial 12-month treatment period. The incidence of adverse events over the full trial period (including primary treatment and subsequent anti-resorptive therapy) was generally similar between treatment arms.
- 6.30 The most frequently reported adverse events in the romosozumab trials were musculoskeletal disorders (osteoarthritis, arthralgia, back pain, musculoskeletal pain, pain in the extremity), infections (nasopharyngitis, upper respiratory tract infection), injury (falls), vascular disorders (hypertension), nervous system disorders (headache) and metabolism disorders (hypercalcaemia; higher incidence with teriparatide). Individual serious adverse events and adverse events leading to discontinuation were generally low in all treatment arms.
- 6.31 In regards to adverse events of special interest, treatment with romosozumab was associated with an increased risk of injection site reactions and serious cardiovascular events (primarily cardiac ischaemic and cerebrovascular events). Table 7 shows a summary of serious cardiovascular events reported in the ARCH trial.

Table 7: Summary of serious cardiovascular events reported in the ARCH trial

	Patients with events, n (%)	
	Romosozumab/alendronate N=2040	Alendronate/alendronate N=2014
Initial treatment period (12 months)		
Any cardiovascular event	50 (2.5)	38 (1.9)
Cardiac ischaemic event	16 (0.8)	6 (0.3)
Heart failure	4 (0.2)	8 (0.4)
Non-coronary revascularisation	3 (0.1)	5 (0.2)
Cerebrovascular event	16 (0.8)	7 (0.3)
Peripheral vascular ischaemic event not requiring revascularisation	0 (0.0)	2 (<0.1)
Cardiovascular death	17 (0.8)	12 (0.6)
Full trial period (median 33 months)		
Any cardiovascular event	133 (6.5)	122 (6.1)
Cardiac ischaemic event	30 (1.5)	20 (1.0)
Heart failure	12 (0.6)	23 (1.1)
Non-coronary revascularisation	6 (0.3)	10 (0.5)
Cerebrovascular event	45 (2.2)	27 (1.3)
Peripheral vascular ischaemic event not requiring revascularisation	2 (<0.1)	5 (0.2)
Cardiovascular death	58 (2.8)	55 (2.7)

Source: Table 2.5-15 (p 64) and Table 2.5-16 (p 65) of the resubmission

- 6.32 The resubmission also provided an overall summary from a sponsor-conducted report on the cardiovascular safety of romosozumab. The report aimed to further investigate the imbalance in serious cardiovascular events observed in the ARCH and BRIDGE

clinical trials but not in the FRAME trial. This was previously considered by the PBAC in the November 2018 and July 2019 submissions.

- 6.33 The report noted that a blinded re-adjudication of cardiovascular events was consistent with the original analysis reported in the ARCH, BRIDGE and FRAME trials. The report presented extensive re-analysis of cardiovascular event data (including meta-analyses, subgroup analyses and use of different composite outcomes) which did not identify a population at consistently increased risk with romosozumab treatment. However, the report noted that the incidence of cardiovascular events in the alendronate arm of the ARCH trial was unexpectedly low in the first year and that the relative difference between treatments reduced over time. The report also explored plausible biological mechanisms for the increase in cardiovascular events but stated that no specific mechanism could be identified based on genetic studies, pre-clinical models or epidemiological data. The report concluded that a causal relationship between romosozumab and serious cardiovascular events could not be confirmed or refuted based on the available data.
- 6.34 During the reporting period of the first PSUR, there were 2 reports of myocardial infarction (1 from post-marketing data and 1 from a trial, unrelated to treatment) and 10 reports of stroke from post-marketing sources, none of which were fatal. A review of the stroke reports suggests that 9 out of the 10 patients had 1 or more confounding factors. Serious cardiovascular events of myocardial infarction and stroke have been incorporated in the benefit-risk assessment with the PSUR noting that overall benefit-risk balance remains positive. These data have not previously been considered by the PBAC. The ESC considered the PSUR indicated that serious events of myocardial infarction and stroke remained an important potential risk with romosozumab.

Benefits/harms

- 6.35 A benefits/harms summary was not presented for romosozumab versus teriparatide due to the claim of non-inferiority.

Clinical claim

- 6.36 There were no changes to the clinical evidence provided in the resubmission compared to previous submissions (November 2018 and July 2019).

Romosozumab versus teriparatide

- 6.37 The PBAC previously considered that the claim of non-inferior comparative efficacy between romosozumab and teriparatide was inadequately justified given the issues with the indirect comparison and the uncertainty in the benefits of romosozumab following cessation of treatment (paragraph 7.6, romosozumab, PSD, July 2019 PBAC meeting). In July 2019 the PBAC remained concerned regarding the cardiovascular safety signals observed with romosozumab and considered the claim of inferior comparative safety was reasonable (paragraph 7.7, romosozumab, PSD, July 2019 PBAC meeting).

- 6.38 The resubmission claimed that romosozumab is similar (potentially superior) in terms of efficacy compared to teriparatide. The ESC noted that no new clinical trial data was presented in the resubmission and agreed with the evaluation that this claim was not adequately supported.
- 6.39 The resubmission described romosozumab as potentially inferior in terms of safety compared to teriparatide due to cardiovascular safety signals observed with romosozumab. The ESC agreed with the evaluation that this claim appeared reasonable based on available data.
- 6.40 The PBAC considered that the claim of non-inferior effectiveness compared to teriparatide remained uncertain given the issues with the indirect comparison.
- 6.41 The PBAC considered that the claim of inferior safety compared to teriparatide was reasonable.

Romosozumab versus alendronate

- 6.42 The PBAC previously considered the claim of superior efficacy versus alendronate was adequately supported based on trial data (median 33 months follow-up), however, the long-term comparative efficacy of romosozumab was uncertain as maintenance of treatment effect following romosozumab cessation would likely depend on persistence with anti-resorptive therapy (paragraph 7.10, romosozumab, PSD, November 2018 PBAC meeting). The PBAC considered that romosozumab was likely to be of inferior safety compared to alendronate given the number of serious cardiovascular events reported in the romosozumab arm of the ARCH trial (paragraph 7.11, romosozumab, PSD, November 2018 PBAC meeting).
- 6.43 The resubmission described romosozumab as superior in terms of efficacy compared to alendronate. The submission did not specify a comparative safety claim for romosozumab compared to alendronate. The PBAC agreed with the evaluation that the efficacy claim may be reasonable but the clinical data suggest that romosozumab is inferior in terms of safety compared to alendronate.

Economic analysis

- 6.44 The resubmission presented a cost-minimisation analysis as the basis for establishing the price of romosozumab relative to teriparatide (presented below).
- 6.45 The resubmission also included a cost-utility analysis of romosozumab compared to alendronate to address the PBAC's concerns in July 2019 about the cost-effectiveness of romosozumab use in a much broader population than teriparatide (including a population of people who are currently eligible for teriparatide but not accessing it due to convenience or other issues). This analysis was originally presented in the romosozumab November 2018 submission that requested a broader listing for severe osteoporosis (first-line and later-line settings). The model was largely unchanged except for drug costs and was based on the ARCH trial population of patients who

were predominantly naïve to anti-resorptive therapy (first-line setting) (details presented below).

- 6.46 In November 2018, the PBAC considered that the economic model did not form a reliable basis for decision-making due to the overestimation of fracture risk and treatment effect (e.g. due to adjustments to the underlying fracture risk using a poorly justified application of the Garvan risk calculator), the assumption of continuing treatment effect (which relied on adherence and persistence rates unlikely to be achieved in the PBS population), and potentially unreliable fracture disutilities (paragraph 7.13, romosozumab, PSD, November 2018 PBAC meeting).
- 6.47 The PSCR argued that the cost-effectiveness analysis versus alendronate was included in the resubmission as supportive information only and that an anti-resorptive comparator was not necessary due to the established cost-effectiveness of teriparatide. The ESC noted that this assumption required acceptance that romosozumab is non-inferior to teriparatide. In addition, the ESC maintained that the additional comparison was relevant to understand the cost-effectiveness of romosozumab use in a much broader population than teriparatide. However, the ESC considered that the applicability of the model to a broader population outside of current teriparatide use was not addressed in the resubmission.

Cost-minimisation analysis versus teriparatide

- 6.48 In July 2019, the PBAC noted that a cost-minimisation analysis would only be appropriate with a conservative base case given the uncertainty with the clinical claim of non-inferior efficacy for romosozumab versus teriparatide (paragraph 7.8, romosozumab, PSD, July 2019 PBAC meeting). The ESC considered that a conservative base case was also important as the evidence presented indicated romosozumab has an inferior safety profile compared to teriparatide.
- 6.49 The PBAC previously considered that the revised base case proposed in the July 2019 pre-PBAC response addressed some key areas of concern with the cost-minimisation analysis (costs associated with monitoring and treatment of cardiovascular events). However, in July 2019 the PBAC remained concerned around the trial-based equi-effective doses used, the additional costs for anti-resorptive therapy following cessation of romosozumab and administration costs (paragraph 6.58, romosozumab, PSD, July 2019 PBAC meeting).
- 6.50 Compared to the previous submission, the following changes were made which include changes from the revised base case presented in the pre-PBAC response in July 2019:
- The use of ex-manufacturer prices in the cost-minimisation analysis instead of DPMQs;

- Reduced drug acquisition cost for teriparatide from \$365.75 (published AEMP) to \$329.18 (estimated in the resubmission to include 10-year anniversary 10% statutory price reduction from April 2020);
- Teriparatide adherence rate reduced to 79% from 87%, used to estimate the equi-effective dose. The revised base case in the July 2019 pre-PBAC response used an adherence rate of 85%;
- An additional cost for ■ months of anti-resorptive therapy in ■% of patients who discontinue romosozumab prematurely (\$■■■■);
- Increased cost of cardiovascular event management from \$■■■■ to \$■■■■ over 365 days (included in pre-PBAC response July 2019);
- Inclusion of romosozumab administration costs of \$■■■■ for 10.8 doses (included in pre-PBAC response July 2019).

6.51 The equi-effective doses provided in the resubmission were based on maximum PBS quantities that were adjusted using trial-based adherence estimates:

- 10.8 scripts of romosozumab 210 mg once monthly over 365 days of therapy = 14.22 scripts of teriparatide 20 mcg once daily over 504 days of therapy

6.52 In July 2019, the PBAC noted the equi-effective doses may not be reliable given concerns with: the robustness of the indirect comparison; the applicability of the included trials; not accounting for treatment persistence; uncertain treatment benefit following cessation of romosozumab; and the uncertain impact of self-administration on treatment compliance (paragraphs 6.43, 6.67 and 7.5, romosozumab, PSD, July 2019 PBAC meeting).

6.53 Compared to the previous submission, the resubmission used the same adherence rate for romosozumab (90%) and a lower adherence rate for teriparatide (79%) based on the lowest estimate reported of the included trials (from the GHAC trial, stopped prematurely) as a conservative assumption to address the PBAC's concerns regarding the equi-effective doses. The PBAC previously considered that adherence in clinical practice would likely be lower than reported in trials particularly given the method and frequency of administration required for teriparatide (paragraph 7.10, romosozumab PSD, July 2019 PBAC meeting).

6.54 In July 2019, the PBAC noted the limited data from Study 326 suggesting that treatment effects associated with romosozumab are rapidly lost after discontinuation of subsequent anti-resorptive therapy. In comparison, the PBAC considered available data suggest the treatment benefits associated with teriparatide were maintained regardless of follow-up osteoporosis treatment. The PBAC considered that the estimated cost of subsequent anti-resorptive therapy following cessation of romosozumab treatment was not conservative and that a longer duration of treatment would be required in practice (paragraph 6.5, romosozumab PSD, July 2019

PBAC meeting).

- 6.55 The resubmission included additional anti-resorptive therapy costs for █ months in █% of patients who do not transition to anti-resorptive therapy upon completion of romosozumab. The resubmission noted the additional cost was intended to address the potential for residual treatment effects following cessation of teriparatide but not romosozumab. The proportion of patients who do not receive subsequent anti-resorptive therapy is likely to be underestimated given the broad definitions used to determine treatment switching and persistence in the 10% Medicare sample analysis (e.g. at least 1 script of any anti-resorptive following teriparatide; and allowing a gap of 6 months). There was inadequate justification provided for the assumed 6-month period used to estimate the additional cost. It was unclear whether the estimated costs in the romosozumab arm appropriately value the residual treatment effects associated with teriparatide. The ESC considered that denosumab was the treatment most likely to be replaced in practice and as such an increase in the additional anti-resorptive costs may be appropriate. The PBAC noted that the additional cost is calculated as a weighted average of current anti-resorptive costs in Australia, with the weighting based on patient years of therapy received for each product in 2018. As denosumab (at a cost per day of \$1.49) accounted for █% of the weighting the PBAC considered the additional anti-resorptive costs proposed were acceptable.
- 6.56 In July 2019, the PBAC considered that it may be appropriate to include administration costs for romosozumab given the use of trial-based adherence associated with healthcare professional administration in the trials. Teriparatide was self-administered in the included trials (paragraph 6.51, romosozumab PSD, July 2019 PBAC meeting). The July 2019 PSCR revised the cost-minimisation analysis to include a total cost of \$█ for 10.8 doses (weighted average: 31% GP and 69% nurse administration) which was lower than calculated during the evaluation of \$406.08 (10.8 GP visits), claiming that 2 additional doctor visits were already included for monitoring of cardiovascular events and some patients will self-administer. At that time the ESC considered that while there may be some administration of romosozumab by nurses it was likely the administration costs will be in between the evaluation and PSCR estimates in practice (paragraph 6.51, romosozumab, PSD, July 2019 PBAC meeting).
- 6.57 The PBAC noted that the cost of administration in the resubmission was \$█, as the midpoint between \$█ and \$406.08 and was included in the July 2019 pre-PBAC response.
- 6.58 The resubmission also included costs for cardiovascular event monitoring (\$169.20 per 12 months of therapy, based on MBS item costs), cardiovascular event management (\$135.43 based on cardiovascular events in the ARCH trial, hospitalisation costs and out-of-hospital costs) and subsequent anti-resorptive therapy (\$193.93 based on estimated costs and PBS utilisation of denosumab, alendronate and risedronate for

139 days of therapy). These costs were unchanged from the cost-minimisation analysis presented in the July 2019 pre-PBAC response.

- 6.59 Table 8 shows a summary of the cost-minimisation analysis based on the published price of teriparatide. Changes in the resubmission compared to the revised base case in the July 2019 pre-PBAC response are underlined.

Table 8: Results of the cost-minimisation analysis

	Cost
Teriparatide 20 mcg once daily	
Drug costs (estimated AEMP)	\$329.18 ^a
Scripts per 504 days of therapy	14.22
Cost of 504 days of therapy	<u>\$4,680.87</u>
Romosozumab 210 mcg once monthly	
Cost of █ months anti-resorptive therapy in █% of patients who discontinue romosozumab prematurely	\$█
Cost of per 139 days of subsequent anti-resorptive therapy (DPMQ)	\$193.93
Cost of cardiovascular monitoring per 365 days of romosozumab therapy	\$169.20
Cost cardiovascular event management per 365 days of romosozumab therapy	\$█
Cost of administration	\$█
Cost of romosozumab for cost-minimisation	\$█
Scripts per 365 days of therapy	10.8
Drug acquisition costs (AEMP)	\$█

Source: Table 3.4-1 (p 90) of the resubmission. Underlining refers to changes in the resubmission compared to the revised base case in the July 2019 pre-PBAC response.

Abbreviations: AEMP, ex-manufacturer price; DPMQ, dispensed price maximum quantity

^a Estimated in the resubmission assuming 10% statutory price reduction for 10-year PBS anniversary (calculated as 0.9 x published AEMP \$365.75)

- 6.60 Based on the cost-minimisation analysis using the published price of teriparatide, the ex-manufacturer price of romosozumab was \$█ (DPMQ \$█).
- 6.61 The published cost per patient for treatment with teriparatide was \$4,681 (drug cost), which is the same as the cost per patient for treatment with romosozumab (drug cost, administration cost, cardiovascular event management and monitoring cost, subsequent anti-resorptive therapy cost, additional anti-resorptive therapy cost). Where these costs per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.
- 6.62 The resubmission noted that the price for romosozumab in this analysis was for illustrative purposes only and the requested published DPMQ was \$618.09. The resubmission claimed that a published DPMQ higher than the DPMQ derived from the cost-minimisation analysis would be required for the sponsor to be able to list romosozumab in Australia. The requested higher DPMQ for romosozumab compared with teriparatide was not justified in the resubmission. The ESC considered a higher published price may not be justified given the request for listing on a cost-minimisation basis to teriparatide.

Cost-utility analysis versus alendronate

6.63 The resubmission presented a stepped economic evaluation of the additive effects of using romosozumab followed by alendronate compared to alendronate alone for the treatment of severe osteoporosis. The economic evaluation was based on a direct randomised trial (ARCH) with additional modelled data. Table 9 shows a summary of the model structure, key inputs and rationale.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Romosozumab versus alendronate (both followed by alendronate)
Time horizon	26 years in the model base case versus median follow-up of 33 months in the ARCH trial
Outcomes	Patients without fractures; life years; quality adjusted life years
Methods used to generate results	Markov cohort model (with half-cycle correction)
Health states	Four health states: baseline severe osteoporosis health state, post-incident hip fracture, post-incident vertebral fracture and death
Cycle length	Annual
Transition probabilities/ Extrapolation method	<p>Transition probabilities for fracture were derived from the risk of fracture in the alendronate arm of the ARCH trial with adjustments using the Garvan risk calculator to account for the higher risk in the target PBS population. Probability of death was based on Australian life tables with mortality multipliers based on fracture history. The incidence of fatal and non-fatal cardiovascular events in the first year of the model was based on the first year of the ARCH trial.</p> <p>Treatment effect estimates were derived from the ARCH trial with additional extrapolation beyond the clinical data. Independent curves were derived for romosozumab followed by alendronate compared to alendronate alone. Parametric curves were used to extrapolate fracture risks over 5 years with linear convergence at 10 years.</p> <p>■% of incremental QALYs (and -147% of incremental costs) occur in the extrapolated period, where the trial duration is approximated by 3 years (median follow-up of 33 months in the trial).</p>
Health related quality of life	Osteoporosis baseline utility and disutility values for fracture were based on a systematic review of literature conducted for the denosumab March/July 2010 PBAC submission. Disutility values for cardiovascular events were based on data used in the PBS Statin Review (2012)

Source: 1.1-2 (p 2), 'Romo vs alen model write-up', Appendix 13 of the resubmission

6.64 The ESC reiterated the November 2018 advice of the PBAC that the economic model did not form a reliable basis for decision-making due to: overestimation of fracture risk; the assumption of continuing treatment effect (which relied on adherence and persistence rates unlikely to be achieved in the PBS population); and potentially unreliable fracture disutilities (paragraph 7.13, romosozumab, PSD, November 2018 PBAC meeting).

6.65 Table 10 summarises the main changes to the economic evaluation in the resubmission compared to the November 2018 submission.

Table 10: Main changes to the economic analysis

Variable	November 2018 submission	March 2020 submission
Drug costs	Romosozumab: \$6,671 for 1 year (proposed published DPMQ \$617.70 x 12 scripts per year x 90% adherence) Alendronate: \$176 per year (June 2018 DPMQ \$15.00 x 13 scripts per year x 90% adherence)	Romosozumab: \$ [redacted] for 1 year (placeholder DPMQ ^a \$ [redacted] x 12 scripts per year x 90% adherence) Alendronate: \$180 per year (Nov 2019 DPMQ \$15.39 x 13 scripts per year x 90% adherence)
Administration costs	None	Romosozumab: \$ [redacted] per year for 10.8 doses Alendronate: \$0
Cardiovascular event risks	Not included in base case but tested in sensitivity analyses: <u>Romosozumab</u> Non-fatal CV event (first year only): 1.7% Fatal CV event (first year only): 0.8% <u>Alendronate</u> Non-fatal CV event (first year only): 1.3% Fatal CV event (first year only): 0.6%	Same as sensitivity analysis in November 2018 submission (included in base case analysis of the resubmission)
Cardiovascular event and management costs	Not included in base case but tested in sensitivity analyses: Non-fatal CV event: \$9,969 Fatal CV event: \$3,423	Fatal and non-fatal CV event: \$17,843 CV monitoring: \$169.20
Cardiovascular event disutility	Not included in base case but tested in sensitivity analysis: -0.0626	Same as sensitivity analysis in the November 2018 submission (included in base case analysis of the resubmission)

Source: constructed during the evaluation based on the November 2018 and March 2020 submissions

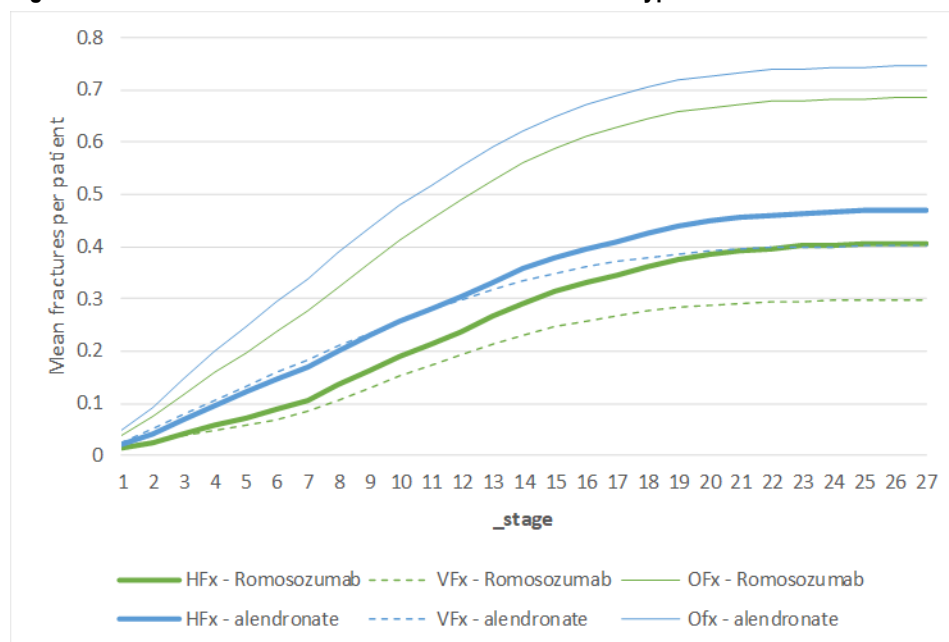
Abbreviation: CV, cardiovascular

^a Estimated in the cost-minimisation analysis versus teriparatide presented in the resubmission

- 6.66 A key change to the economic model in the current resubmission is the use of the cost-minimised price of romosozumab versus teriparatide (published price); compared with the use of the proposed published price of romosozumab in the November 2018 submission.
- 6.67 The ESC noted the resubmission estimated disutility values for cardiovascular events based on the same data sources used in the PBS Statin Review (2012). The ESC noted the availability of more recent cardiovascular event utility data and considered that the use of such data may be more reflective of current practice. However, the ESC acknowledged that the results from sensitivity analyses suggest that the model was not sensitive to cardiovascular event disutility inputs, nor to changes in romosozumab administration costs or cardiovascular event and management costs.
- 6.68 The ESC noted that there were no changes to the modelled population (based on predominantly treatment-naïve patients in the ARCH trial), model structure, fracture risks, treatment effect, circumstances of use, modelled survival, osteoporosis utility/disutility values and fracture costs.

6.69 Markov traces of the cumulative incidence of fractures over time are summarised in Figure 1. These estimates were largely unchanged from the previous November 2018 submission.

Figure 1: Markov traces of the cumulative incidence of each type of fracture



Source: Figure 1.7-2 (p 26), 'Romo vs alen model write-up', Appendix 13 of the resubmission
 Abbreviations: Hfx: Hip fractures, Vfx: Vertebral fractures; OFx: Other fractures

6.70 In November 2018, the ESC considered the submission’s estimation and adjustment of fracture risk using the Garvan risk calculator introduced considerable uncertainty as several adjustment inputs and assumptions were poorly justified (further outlined in paragraph 6.52, romosozumab, PSD, November 2018 PBAC meeting). Overall, in November 2018 the ESC considered that the methodology for adjustment of background fracture risk likely significantly overestimated the fracture risk in the PBS population (paragraph 6.53, romosozumab PSD, November 2018 PBAC meeting).

6.71 The ESC previously considered that the economic model substantially overestimated the fracture risk and incremental efficacy compared to the trial. In particular, the ESC considered that the cumulative incidence of hip fracture generated in the model was not plausible (5.7% in Years 1-4; 35.3% in Years 5-26). The ESC noted that the model estimated a 4% absolute reduction in the cumulative incidence of hip fracture between romosozumab and alendronate in Years 1-4, despite the difference not being statistically significant in the ARCH trial. Overall, the ESC considered the large difference in hip fracture generated in the model to be implausible (paragraph 6.61, romosozumab, PBAC PSD, November 2018).

6.72 In November 2018, the ESC noted that the model extrapolated 33 months (median follow-up) of trial data to ten years (using a parametric curve for 5 years with linear

convergence at 10 years). The ESC noted that the submission had assumed 100% persistence to subsequent therapy after discontinuation of romosozumab. The ESC considered that the persistence rates achieved in the trial were unlikely to reflect clinical practice outside the trial setting. Given the extent of treatment benefit is conditional on persistence to anti-resorptive therapy and there are no clinical data to support additional treatment effects of romosozumab beyond four years, the ESC considered the base case ICER was not reliable and likely significantly underestimated (paragraph 6.62, romosozumab, PBAC PSD, November 2018).

- 6.73 As in November 2018, the resubmission estimated mortality multipliers (used to inform mortality risk) that were based the Dubbo Osteoporosis Epidemiology Study. The results from the Dubbo Osteoporosis Epidemiology Study indicate an association between osteoporotic fracture and increased mortality but do not demonstrate causation. Additionally, the submission derived some multipliers using an approach that was inconsistent with the source data (paragraph 6.54, romosozumab PSD, November 2018 PBAC meeting).
- 6.74 In November 2018, the ESC noted the fracture disutility values were estimated from various published studies. Utility data from the ICUROS study indicated that the submission may have overestimated the disutility associated with incident vertebral fractures and prevalent hip fractures, particularly in Australian patients. At that time the ESC considered that fracture disutility values should have been estimated from the ICUROS study given these estimates are based on more recent data compared to that used in the submission (paragraph 6.55, romosozumab PSD, November 2018 PBAC meeting). The ESC noted that the economic model presented in the resubmission did not incorporate utility data from the ICUROS study.
- 6.75 The results of a stepped economic evaluation from the November 2018 submission to the current resubmission are summarised in Table 11.

Table 11: Results of the stepped analysis from the November 2018 submission to the current resubmission

Step and component	Romosozumab/alendronate	Alendronate/alendronate	Increment
November 2018: Modelled efficacy (parametric survival curves with romosozumab efficacy benefits to 5 years and convergence by 10 years), 26 year time horizon, drug and fracture costs, fracture risk adjusted using Garvan risk calculator, general population mortality with mortality multipliers for fracture, osteoporosis utility/disutility values, incremental cost per QALY gained			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
November 2018 cardiovascular sensitivity analyses: November 2018 base case with additional costs and disutility values associated with cardiovascular events^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 1: November 2018 cardiovascular sensitivity analyses with same event costs for both fatal and non-fatal cardiovascular events^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 2: November 2018 cardiovascular sensitivity analyses with same event costs for both fatal and non-fatal cardiovascular events and additional costs for cardiovascular monitoring^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 3: November 2018 cardiovascular sensitivity analyses with same event costs for both fatal and non-fatal cardiovascular events and additional costs for cardiovascular monitoring and romosozumab administration^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 4: November 2018 cardiovascular sensitivity analyses with same event costs for both fatal and non-fatal cardiovascular events and additional costs for cardiovascular monitoring and romosozumab administration. Increased alendronate drug costs due increased fees and markups^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 5: November 2018 cardiovascular sensitivity analyses with same event costs for both fatal and non-fatal cardiovascular events and additional costs for cardiovascular monitoring and romosozumab administration. Increased alendronate drug costs due to increased fees and markups and reduced romosozumab drug costs based on cost-minimised price versus teriparatide (estimated published price)^a			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Constructed during the evaluation based on “Evenity severe osteoporosis_Nov2019” TreeAge model and “Evenity severe osteoporosis model” Appendix 12 of the November 2018 submission

Abbreviations: QALY, quality adjusted life year

^a Estimates calculated during the evaluation

- 6.76 Based on the economic model using the cost-minimised price of romosozumab versus teriparatide (estimated published price), treatment with romosozumab followed by alendronate was associated with a cost per QALY gained of less than \$ [REDACTED]/QALY compared to alendronate alone for the treatment of severe osteoporosis.

Drug cost/patient

- 6.77 The estimated drug cost for romosozumab per patient per course was \$ [REDACTED] (based on 12 scripts using a DPMQ of \$ [REDACTED], calculated from cost minimisation analysis versus the estimated April 2020 published teriparatide price, for 2 x 105 mg monthly injections). The estimated drug cost used in the economic analyses and financial implications incorporated an adherence rate of 90%, resulting in a drug cost per patient per course of \$ [REDACTED].
- 6.78 The estimated drug cost for a full course of teriparatide therapy was \$6,687 (based on 18 scripts using the estimated DPMQ \$371.50 including the 10-year 10% statutory price reduction from April 2020 for 28 x 20 mcg daily injections). The estimated drug cost used in the economic analyses and financial implications incorporated an adherence rate of 79%, resulting in a drug cost per patient per course of \$5,282.

Estimated PBS usage & financial implications

- 6.79 This resubmission was not considered by DUSC. The resubmission used an epidemiological/market share approach to estimate the utilisation and financial impact for romosozumab summarised in Table 12.

Table 12: Estimation of number of treated patients

	Value	Year 6 ^a	Source and comment
Estimated eligible population			
Number of patients treated for osteoporosis	-	697,849	10% Medicare sample analysis of patients receiving osteoporosis treatments for the 12 months to June 2018 (552,227), extrapolated to 2020-2025 estimates based on growth rate of prevalent population (2014-2015) from the DUSC 2016 Osteoporosis report). May be underestimated as it only captures patients on active therapy. The DUSC 2016 report indicated there is an increasing number of patients who re-initiate therapy after a 2-year break.
Number of patients treated for ≥12 months	67.2%	469,057	10% Medicare sample analysis of patients who were on ≥12 months continuous therapy for 12 months to June 2018. It was difficult to interpret the analysis due to poor documentation. Estimates were lower than the November 2018 submission's estimates based on the DUSC 2016 Osteoporosis report (84.7%).
Patients with prior fracture	75%	351,793	Geelong Osteoporosis Study. The PBAC previously considered that the majority of treated osteoporosis patients have a prevalent fracture (November 2016 meeting, Consideration of the Report of DUSC). However, the magnitude of this proportion remains unclear as the data were based on a general population study (includes undiagnosed patients).
Treated patients with prior fracture and BMD ≤ -3	9.7%	34,089	Geelong Osteoporosis Study, 10% Medicare sample analysis, FREEDOM trial extension and multiple assumptions. Estimates from these sources may not be applicable to the treated population given the Geelong Osteoporosis Study population consists of diagnosed and undiagnosed participants. The applicability of the FREEDOM extension study population (primary osteoporosis) to the PBS population was unclear given limited detail provided in the resubmission. The resubmission appeared to misinterpret the data from the FREEDOM trial (use of relative reduction instead of proportion of patients below the BMD threshold).
Fracture while on anti-resorptive therapy	29.3%	9,974	Based on an assumed annual fracture rate derived from the Garvan Fracture risk calculator plus assumptions, multiplied by patient-years of exposure calculated from a 10% Medicare sample analysis. This estimate was uncertain due to concerns with the derived fracture rate (inappropriate application of risk synthesised from four individuals to estimate population risk, use of flat rate over time, unknown source for downward adjustment to treatment effects) and anomalous results from the 10% Medicare sample analysis.
Estimated use of romosozumab			
Romosozumab uptake calibration	█% ^b	less than 10,000	Single uptake assumption derived through calibration to match previous utilisation estimates in the July 2019 submission. The uptake rates for romosozumab in the July 2019 submission were based on an assumed increasing capture of the existing anabolic agent market share and a larger addition of patients from market growth (█-fold expansion). The new uptake rates do not differentiate between these markets, as they are applied directly to the eligible patient population, but maintain the previous assumption of increasing uptake over time.

Source: Section 4.1-4.2 (pp 94-97) of the resubmission

^a Number of treated patients estimated at each step in Year 6 of the financial estimates

^b Uptake rates, Yr 1: █%, Yr 2: █%, Yr 3: █%, Yr 4-6: █%

6.80 Overall, the approach and data sources used in the resubmission to estimate the financial impact of listing romosozumab remained largely unchanged from the July 2019 submission.

- 6.81 In July 2019 the ESC considered that the size of the eligible population was highly uncertain due to concerns with the overall approach (paragraph 6.64, romosozumab, PSD, July 2019 PBAC meeting). The following issues were not adequately addressed and remained as concerns in the resubmission:
- assuming that only patients receiving active treatment in the last 12 months will qualify for treatment;
 - assuming the qualifying BMD T-score must only be measured while the patient is on treatment;
 - the use of an incident fracture rate from an individual risk calculator (Garvan Fracture risk) based on assumed patient characteristics to estimate population-level risk;
 - the adjustment used to approximate a prevalent fracture rate from the incident fracture rate could not be validated due to inadequate documentation and appeared to have anomalous results; and
 - the use of a poorly documented 10% Medicare sample analysis to identify the actively treated population, with estimates that were lower than previous estimates based on the DUSC 2016 Osteoporosis report.
- 6.82 For the July 2019 submission, the PBAC considered that due to differences in administration frequency between romosozumab and teriparatide, substantial market expansion was plausible with the introduction of romosozumab despite a listing broadly consistent with the current PBS listing of teriparatide. In addition, the PBAC considered that romosozumab uptake from the existing market may be higher than estimated in the resubmission. The PBAC considered the utilisation estimates were very uncertain (paragraph 7.13, romosozumab, PSD, July 2019 PBAC meeting).
- 6.83 In July 2019, the PBAC noted that the net cost to the PBS was high in the context of a cost-minimisation analysis (less than \$10 million in Year 1, increasing to \$10 - \$20 million in Year 6) (paragraph 7.14, romosozumab, PSD, July 2019 PBAC meeting). The PBAC noted that the high net cost was due to the estimated additional growth in the use of anabolic agents that would occur with the availability of romosozumab and that █████% of costs in Year 1 and █████% in Year 6 were for additional romosozumab patients from net growth of the market (paragraph 7.15, romosozumab, PSD, July 2019 PBAC meeting).
- 6.84 The PBAC noted the consumer comments highlighting the potential dosing convenience of romosozumab compared with teriparatide (see paragraph 6.2) and reaffirmed its July 2019 advice that substantial market expansion was plausible.
- 6.85 The resubmission presented the estimated net cost of listing romosozumab over the first 6 years of listing using a romosozumab DPMQ of \$█████ (calculated from cost minimisation analysis versus the estimated April 2020 published teriparatide price) and a teriparatide DPMQ of \$412.19 (published, November 2019). During the evaluation, the estimates were recalculated using the estimated published price of

teriparatide from 1 April 2020 (DPMQ \$371.50 including 10-year 10% statutory price reduction) which was consistent with the cost-minimisation analysis in the resubmission (see Table 13). The PBAC noted that costs would be lower when incorporating effective prices.

Table 13: Estimated use and total cost of romosozumab to the PBS

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Estimated eligible population						
Number of patients treated for osteoporosis	590,417	610,491	631,248	652,710	674,902	697,849
Number of patients treated for ≥12 months (67.2%)	396,847	410,340	424,292	438,717	453,634	469,057
Patients with prior fracture (75%)	297,635	307,755	318,219	329,038	340,225	351,793
Treated patients with prior fracture and BMD ≤ -3 (9.7%)	28,841	29,821	30,835	31,884	32,968	34,089
Fracture while on anti-resorptive therapy (29.3%)	8,439	8,726	9,022	9,329	9,646	9,974
Romosozumab uptake calibration (derived using estimates from July 2019 submission)	█%	█%	█%	█%	█%	█%
Total romosozumab patients	█	█	█	█	█	█
Total romosozumab scripts (10.8 scripts/year)	█	█	█	█	█	█
Cost to PBS (DPMQ \$█)	\$█	\$█	\$█	\$█	\$█	\$█
Patient copayment	\$█	\$█	\$█	\$█	\$█	\$█
Net cost (less copay)	\$█	\$█	\$█	\$█	\$█	\$█
Cost offsets due to substitution						
Teriparatide cost (DPMQ ^a)*	\$█	\$█	\$█	\$█	\$█	\$█
Anti-resorptives cost (DPMQ)	\$█	\$█	\$█	\$█	\$█	\$█
Patient copay (combined)	\$█	\$█	\$█	\$█	\$█	\$█
Net cost offset (less copay)*	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to Government with romosozumab listing						
Net cost to PBS/RPBS including cost offset (less copay)*	\$█	\$█	\$█	\$█	\$█	\$█
MBS costs for treatment administration (\$300.80 per patient)	\$█	\$█	\$█	\$█	\$█	\$█
MBS costs for CV monitoring (\$144.00 per patient) ^{b,*}	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to Government*	\$█	\$█	\$█	\$█	\$█	\$█
Previous submission (July 2019 submission)						
Net cost to PBS less copay	\$█	\$█	\$█	\$█	\$█	\$█
Net cost including cost offset (less copay)	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to Government^c	\$█	\$█	\$█	\$█	\$█	\$█

Source: 'Romosozumab-utilisation-and-cost-model-v77' Excel workbook, Appendix 14 of the resubmission

Abbreviations: BMD, bone mineral density; DPMQ, dispensed price maximum quantity

^a Estimates were calculated during the evaluation

^a Calculated during the evaluation based on November 2019 published AEMP of teriparatide including 10-year 10% Statutory price reduction applicable from 1 April 2020 (\$365.75 x 0.9 plus dispensing fees and mark-ups)

^b MBS costs are different between the economic analyses (based on the MBS 100% benefit) and the budget impact analyses (based on the MBS 85% benefit)

^c Including MBS costs for cardiovascular monitoring of \$144 per patient

Note 1: MBS costs in the resubmission were based on the March 2019 Schedule. There were minor changes to these costs in the November 2019 Schedule that were not updated during the evaluation.

- 6.86 After cost offsets due to substitution of teriparatide and anti-resorptives, the estimated net cost to the PBS/RPBS for listing romosozumab was \$30 - \$60 million over 6 years. The PBAC noted these costs were based on the published price of teriparatide and the corresponding cost-minimised price for romosozumab. The PBAC noted that the net cost to the PBS will reduce once the effective price of teriparatide is applied.
- 6.87 Treatment with romosozumab is associated with additional administration costs and cardiovascular monitoring costs which results in a net cost to government of less than \$10 million (published price \$7.0 million) in Year 1, increasing to \$10 - \$20 million (published price \$20.0 million) in Year 6, a total cost of \$30 - \$60 million (published price \$91.9 million) over 6 years.
- 6.88 The ESC considered that, as the approach and data sources used in the resubmission remained largely unchanged from the July 2019 submission, the issues raised by the Committee at that time remained (see paragraph 6.81). As such, the ESC reiterated its July 2019 advice that the size of the potential eligible population was highly uncertain.
- 6.89 The PBAC noted the reduction in the estimated net cost to the PBS/RPBS as a result of the revised cost-minimised romosozumab price (\$10 - \$20 million in year 6 compared to \$10 - \$20 million in July 2019) and that the use of the effective price of the comparator would reduce these costs further. The PBAC noted that prescribing of romosozumab would be restricted to Specialists or Consultant Physicians and considered that with the revised cost-minimised romosozumab price it was now reasonable to accept the financial estimates as the basis of a risk sharing arrangement (RSA). The PBAC considered that a RSA remained appropriate to mitigate any residual uncertainties regarding the size of the eligible romosozumab population.

Quality Use of Medicines

- 6.90 In July 2019 the PBAC considered that the addition of anti-resorptive therapy following cessation of romosozumab was important to the consideration of effectiveness and subsequent cost-effectiveness. Whilst acknowledging that the use of anti-resorptive therapy may not be necessary to prevent rapid loss of bone after withdrawal of teriparatide treatment, the PBAC was concerned that the 10% Medicare sample analysis indicated approximately 30% of patients discontinue treatments for more than 6 months after stopping teriparatide. Therefore, in July 2019 the PBAC considered that a comprehensive and robust quality use of medicines implementation

strategy would be required to allay concerns regarding ensuring on-going use of anti-resorptive therapy following cessation of romosozumab if recommended for listing (paragraph 7.17, romosozumab, PSD, July 2019 PBAC meeting).

- 6.91 The resubmission acknowledged the importance of ensuring patients successfully transition back to anti-resorptive therapy on completion of romosozumab. The resubmission also noted a recently published position paper by Osteoporosis Australia, recommending the recommencement of anti-resorptives following teriparatide treatment in order to maintain the accrued benefits of anabolic therapy (Ebeling et al 2019).
- 6.92 The resubmission stated that the sponsor has a significant presence and reach in the osteoporosis setting, providing regular quality education to specialists and GPs. The planned education and patient support initiatives were detailed in the resubmission.
- 6.93 The resubmission also described a bespoke romosozumab patient support program available to all patients prescribed romosozumab. The program features planned contact between the specialist, patient and GP which involves alerts to transition to anti-resorptive therapy following completion of romosozumab treatment. Patients who transition to denosumab will be offered additional support via a denosumab patient support program.

Financial Management – Risk Sharing Arrangements

- 6.94 The PBAC previously considered that a RSA with ■■■% rebate for use beyond the utilisation caps was required to address the uncertainty in the uptake of romosozumab in eligible patients and the risk of use outside the proposed restriction (paragraph 7.16, romosozumab, PSD, July 2019 PBAC meeting).
- 6.95 Table 14 presents the proposed utilisation on which financial caps would be calculated. The resubmission noted that the RSA would include financial caps which would be based on the utilisation and the final agreed price.

Table 14: Proposed utilisation for informing the risk-share arrangement

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Total romosozumab scripts	■■■	■■■	■■■	■■■	■■■	■■■

Source: Table 4.6-2, p 100 of the resubmission

The redacted table shows that at Year 6, the estimated number of scripts for romosozumab was 10,000 – 50,000.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of romosozumab for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti-

resorptive therapy. The PBAC considered there is a clinical need for additional treatment options for severe osteoporosis in the later-line setting. The PBAC considered that the concerns raised at the July 2019 meeting regarding the non-inferiority claim were partially addressed by the more conservative cost-minimisation analysis presented in the resubmission. The PBAC considered that the remaining uncertainties could be managed by subsidisation caps through a risk sharing arrangement (RSA).

- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of romosozumab would be acceptable if were cost-minimised against teriparatide.
- 7.3 The PBAC noted comments from consumers, health care professionals and organisations highlighting the impact of fragility fractures on patient's quality of life and the Australian health care system more broadly. The PBAC reiterated its July 2019 advice that there is a clinical need for additional treatment options for severe osteoporosis in the later-line setting given there are limited alternative therapies available.
- 7.4 The PBAC considered that the nominated comparator, teriparatide, was appropriate for the restricted population proposed in the resubmission. The PBAC noted the evidence provided for alendronate and considered it was a reasonable proxy for anti-resorptive therapy but also agreed with the ESC that denosumab was the treatment most likely to be replaced in practice.
- 7.5 The PBAC noted there were no changes to the clinical trial evidence provided to support the claim of non-inferior effectiveness versus teriparatide. The PBAC recalled its July 2019 consideration that the claim was uncertain due to numerous issues with the comparison. The issues included, but were not limited to, the unknown clinical importance of BMD outcomes from the head-to-head STRUCTURE trial of romosozumab versus teriparatide and the exchangeability and applicability issues with the indirect comparison of fracture outcomes based on the FRAME, GHAC and ACTIVE trials. The PBAC considered that, while the comparison with teriparatide in the STRUCTURE trial remains suboptimal due to concerns with the 12 month treatment duration (see paragraph 6.15), results of the Bouxsein et al 2019 meta-regression reported in the PSCR support a correlation between increasing BMD at the total hip or femoral neck and reduced risk of hip and vertebral fracture. Acknowledging the limitations of the data the PBAC recalled that an increase in total hip, femoral neck and lumbar spine BMD was observed for romosozumab compared to teriparatide. The PBAC also recalled that the indirect comparison of fracture outcomes with romosozumab (12 months) and teriparatide (18 months) suggested there were no statistically significant differences in fracture outcomes between romosozumab and teriparatide. However, the PBAC remained of the view that the level of certainty around the indirect estimate of effects remained low given the wide confidence

intervals for fracture outcomes.

- 7.6 The PBAC recalled concerns that the long-term comparative efficacy of romosozumab was uncertain and that maintenance of the treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy. The PBAC considered that concerns regarding alerting patients to the need to transition to anti-resorptive therapy were reduced by restricting prescribing to Specialists or Consultant Physicians. However, the PBAC considered that the utilisation of anti-resorptive therapy following cessation of romosozumab should be reviewed after an appropriate period post listing to investigate the success of transitioning patients.
- 7.7 The PBAC considered that the claim of non-inferior comparative effectiveness versus teriparatide remained uncertain given the issues with the indirect comparison.
- 7.8 The PBAC reaffirmed its November 2018 advice that fracture outcomes data from the ARCH study supported a claim of superior efficacy of romosozumab followed by alendronate compared to alendronate alone. The PBAC considered that, in contrast to the proposed population, the ARCH study provided evidence for romosozumab use in patients who were predominantly naïve to anti-resorptive therapy.
- 7.9 The PBAC agreed with the ESC that the data from in the PSUR provided in the resubmission indicated that serious events of myocardial infarction and stroke remained an important potential risk with romosozumab and considered the claim of inferior comparative safety remained reasonable. The PBAC considered that the advice regarding the risk of myocardial infarction and stroke provided in the product information along with restricting prescribing to Specialists or Consultant Physicians would allow the risk to be managed in clinical practice.
- 7.10 The PBAC recalled its July 2019 advice that a cost-minimisation analysis would only be appropriate with a conservative base case given the uncertainty with the clinical claim of non-inferior efficacy for romosozumab versus teriparatide. The PBAC noted the changes to the base case for the cost-minimisation analysis compared to that presented in July 2019 (see paragraph 6.50). Specifically, the PBAC noted the teriparatide adherence rate used to estimate equi-effective doses was reduced from 87% to 79% and an additional cost for ■ months of anti-resorptive therapy in ■% of patients who do not transition to anti-resorptive therapy on completion of romosozumab was included. The PBAC considered that the concerns with the cost-minimisation analysis raised at the July 2019 meeting had been partially addressed by the revised base case presented in the resubmission. On balance, the PBAC advised that the cost-minimisation analysis may be sufficiently conservative to address the uncertainty regarding the non-inferiority claim for romosozumab versus teriparatide, if combined with an appropriate RSA (see paragraph 7.13).
- 7.11 The PBAC considered the equi-effective doses to be: 10.8 scripts of romosozumab 210 mg once monthly over 365 days of therapy and 14.22 scripts of teriparatide 20 mcg once daily over 504 days of therapy.

- 7.12 The PBAC recalled its concerns around the cost-effectiveness of romosozumab when used in a broader population than teriparatide. The PBAC noted the economic model presented in the resubmission, which was fundamentally unchanged from that included in the July 2019 submission, did not form a reliable basis for decision making (see paragraph 6.46) and hence could not be used to assess the cost-effectiveness of romosozumab in this broader population. However, the PBAC considered that romosozumab was likely to be cost-effective when used in the broader population as defined in the resubmission based on the BMD and fracture clinical evidence presented in the resubmission, the likely similar disease characteristics of the broader population versus the teriparatide treated population, and the price reduction for romosozumab due to the revisions to the cost-minimisation analysis.
- 7.13 The PBAC considered that the RSA proposed by the sponsor, with financial caps based on the utilisation estimated in the resubmission and the cost-minimised price of romosozumab together with a [REDACTED] % rebate for use exceeding the caps, was appropriate to mitigate the residual uncertainties regarding the size of the eligible romosozumab population.
- 7.14 The PBAC recommended that DUSC undertake a review of utilisation after an appropriate period post listing which includes an investigation of the success of transitioning patients from romosozumab to anti-resorptive therapy.
- 7.15 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* romosozumab should not be treated as interchangeable with any other drugs on an individual patient basis.
- 7.16 The PBAC advised that romosozumab is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Early Supply Rule should apply.
- 7.18 The PBAC noted the flow-on restriction changes to teriparatide's listing (Item 9411H) to prevent sequential use of romosozumab/teriparatide and considered that the treatment criteria should be consistent between the initial and continuing restriction.
- 7.19 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because romosozumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over teriparatide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new item as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Proprietary Name and Manufacturer	
ROMOSOZUMAB 105mg/1.17mL injection, 2 x 1.17mL pre-filled syringes	NEW	1	1	5	EVENTY®	Amgen Australia Pty Ltd

Initial treatment Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
Severity: Severe
Condition: Established osteoporosis
Indication: Severe established osteoporosis
Treatment Phase: Initial treatment
Clinical criteria: Patient must be at very high risk of fracture
AND Patient must have a bone mineral density (BMD) T-score of -3.0 or less
AND Patient must have had 2 or more fractures due to minimal trauma
AND Patient must have experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses
AND The treatment must be the sole PBS-subsidised agent for this condition.
AND The treatment must not exceed a lifetime maximum of 12 months therapy
AND Patient must not have received treatment with teriparatide; OR Patient must have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy
Treatment criteria: Must be treated by a specialist; or Must be treated by a consultant physician
Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

Public Summary Document – March 2020 PBAC Meeting

If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with this drug is initiated.
If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with this drug is initiated
Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
Administrative Advice: Details of accepted toxicities including severity can be found on the Services Australia website at www.servicesaustralia.gov.au
Applications for authorisation under this criterion may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

Continuing treatment Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required - Streamlined
Severity: Severe
Condition: Established osteoporosis
Indication: Severe established osteoporosis
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug,
AND
The treatment must not exceed a lifetime maximum of 12 months therapy
Treatment criteria: Must be treated by a specialist; or Must be treated by a consultant physician

Public Summary Document – March 2020 PBAC Meeting

Administrative Advice:
Applications for authorisation under this criterion may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

Flow on changes to teriparatide's listing to prevent sequential use of romosozumab/teriparatide and to ensure treatment criteria are consistent between the initial and continuing restriction are shown below:

Amend listing as follows:

Teriparatide initial treatment Restriction Summary 6305 / ToC: 6305: Authority Required

Indication: Severe established osteoporosis
Treatment Phase: Initial treatment
Treatment criteria:
Must be treated by a specialist; or
Must be treated by a consultant physician
AND
Clinical criteria:
Patient must be at very high risk of fracture
AND
Patient must have a bone mineral density (BMD) T-score of -3.0 or less
AND
Patient must have had 2 or more fractures due to minimal trauma
AND
Patient must have experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses
AND
The treatment must be the sole PBS-subsidised agent <i>for this condition</i>
AND
The treatment must not exceed a lifetime maximum of 18 months therapy
AND
<i>Patient must not have received treatment with romosozumab; OR</i>
<i>Patient must have developed intolerance to romosozumab of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy</i>
Prescribing Instructions:
A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with teriparatide is initiated.
If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with teriparatide is initiated.
Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.

Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
Administrative Advice: Details of accepted toxicities including severity can be found on the Services Australia website at www.servicesaustralia.gov.au .
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

Amend listing as follows:

Teriparatide continuing treatment Restriction Summary 4113 / Treatment of Concept: 4113: Authority Required

Indication: Severe established osteoporosis
Treatment Phase: Continuing treatment
Treatment criteria: <i>Must be treated by a specialist; or</i> <i>Must be treated by a consultant physician</i>
AND
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug,
AND
The treatment must not exceed a lifetime maximum of 18 months therapy
Administrative Advice: Up to a maximum of 18 pens will be reimbursed through the PBS
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
Special Pricing Arrangements apply.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor’s Comment

Amgen welcomes the positive recommendation for EVENITY and will now work with the PBAC on the next steps of the process.