

5.12 ROMOSUZUMAB, Injection 105 mg in 1.17 mL pre-filled pen Evenity®, Amgen

1 Purpose of Application

- 1.1 The submission requested a Section 85 (Authority Required) PBS listing for romosozumab for the treatment of severe osteoporosis. The PBAC has not previously considered romosozumab for any indication.
- 1.2 Listing was requested on a cost-minimisation basis compared to teriparatide and a cost-effectiveness basis compared to alendronate.

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

Component	Description
Population	Patients with severe osteoporosis (multiple minimal trauma fractures, at least one symptomatic fracture, and BMD T-score \leq -3.0).
Intervention	Romosozumab, 210 mg monthly subcutaneous injection for 12 months
Comparator	Teriparatide, 20 mg daily subcutaneous injection for 18 months Alendronate, 70 mg weekly oral tablet for long term therapy
Outcomes	Increased bone strength, prevention of osteoporosis-related fractures
Clinical claim	Romosozumab is similar in terms of efficacy and safety compared to teriparatide. Romosozumab is superior in terms of efficacy compared to alendronate. The submission did not specify a comparative safety claim for romosozumab compared to alendronate.

Source: Table 1.1.1.1 (p 14) of the submission

2 Requested listing

- 2.1 The listing requested in the submission is outlined below.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Romosozumab, 105mg/1.17mL injection, 1.17 mL syringe	4	2	5	\$617.70 (published price)	Evenity®
Romosozumab, 105mg/1.17mL injection, 1.17 mL injection device	1	2	5	\$ (published price)	Amgen

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
Condition:	Osteoporosis
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment phase	Initial treatment

Public Summary Document – November 2018 PBAC meeting

Treatment criteria	Must be treated by or in consultation with a Specialist; OR Must be treated by or in consultation with a Consultant Physician	
Clinical criteria	<p style="text-align: center;">Listing for later-line treatment</p> <p>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 minimal trauma fractures 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</p>	<p style="text-align: center;">Additional population (first-line)</p> <p>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 minimal trauma fractures AND Patient must have experienced at least 1 symptomatic fracture AND The treatment must be the sole PBS-subsidised agent</p>
<p>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.</p> <p>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 romosozumab is initiated.</p> <p>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 romosozumab is initiated.</p> <p>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.</p> <p>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.</p> <p><u>Note</u> Details of accepted toxicities including severity can be found on the Department of Human Services website at www.humanservices.gov.au.</p>		

- 2.2 The Pre-Sub-Committee Response (PSCR) stated that PBS-listing was no longer being sought for the syringe presentation (i.e. PBS-listing was only sought for the auto-injector).
- 2.3 The submission stated that teriparatide is currently subject to a special pricing arrangement (SPA) and noted that an SPA would also be required for romosozumab.

- 2.4 The submission requested listing in two population groups: a later-line population; and an “additional population”. The proposed PBS restriction for later-line treatment 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. The proposed “additional population” PBS restriction removes the requirement for patients to have prior anti-resorptive therapy and therefore allows treatment of a broader population and permits romosozumab to be used as an initial treatment option. The ESC noted that the proposed additional population restriction implicitly includes many of the patients who would be eligible for treatment with romosozumab under the requested later-line treatment restriction.
- 2.5 The pre-PBAC response requested the PBAC to focus on the proposal to list romosozumab as an option for severe osteoporosis patients who sustain a fracture whilst on anti-resorptive treatment i.e., the ‘later-line’ population. The sponsor considered the evidence presented supported a claim of non-inferiority versus the relevant comparator, teriparatide, in this patient population.
- 2.6 The submission did not propose a lifetime limit on the use of romosozumab on the PBS. This is inconsistent with the current listing for teriparatide which is limited to a lifetime maximum of 18 months therapy. This is also inconsistent with the available clinical data, economic evaluation and budget impact estimates which are all based on a single 12 month treatment course of romosozumab. The PSCR indicated that the sponsor was agreeable to limiting the PBS-subsidised use of romosozumab to a maximum of 12 months. The ESC and PBAC considered a maximum of 12 months per lifetime was appropriate given there is limited clinical data on use of romosozumab beyond 12 months.
- 2.7 The proposed restrictions do not prohibit the sequential use of romosozumab and teriparatide over a patient lifetime. The PSCR requested that the romosozumab restriction allow for use in patients who trial teriparatide but are intolerant (e.g. sequential use of romosozumab and teriparatide should be permitted in patients who need to discontinue one of the agents due to adverse events). The PBAC considered the financial implications of allowing sequential use to be uncertain.

3 Background

Registration status

- 3.1 Romosozumab was submitted under the TGA/PBAC parallel process with a proposed indication for the:
- treatment of primary osteoporosis in postmenopausal women at increased risk of fracture. Romosozumab reduces the risk of vertebral, clinical, and nonvertebral fractures.

- treatment of primary osteoporosis in men at increased risk of fracture. Romosozumab increases bone mass.
- 3.2 The TGA Delegate’s Overview was available at the time of the ESC meeting and the minutes from consideration by Advisory Committee on Medicines (ACM) were available at the time of the PBAC meeting.
- 3.3 The Delegate’s Overview stated [REDACTED]
- 3.4 The ACM considered romosozumab [REDACTED]
- 3.5 Subsequent to the ACM meeting, the TGA Delegate indicated [REDACTED]
- 3.6 An initial marketing application for romosozumab rejected by the FDA due to data becoming available during the assessment period indicating an imbalance in serious cardiovascular events associated with romosozumab treatment. The submission stated that the FDA application was lodged prior to the reporting of the ARCH trial.

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

4 Population and disease

- 4.1 Osteoporosis is a condition which 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 disability.

- 4.2 The ESC noted that romosozumab is an anti-sclerostin monoclonal antibody and increases bone formation that is an anabolic medication. Teriparatide is also anabolic in action but does so as a parathyroid hormone analogue which increases bone formation. Denosumab is an anti-receptor activator of nuclear factor kappa-B ligand (RANKL) and decreases bone resorption and the bisphosphonates (e.g. alendronate) decrease bone resorption.
- 4.3 The target population for romosozumab is patients with severe osteoporosis, which the submission defined as patients with multiple minimal trauma fractures, with at least one symptomatic fracture, and a bone mineral density (BMD) T-score \leq minus 3.0. The submission identified this population as a group with high clinical need given their high risk of additional fractures.
- 4.4 The submission positioned romosozumab as initial treatment for patients with severe osteoporosis prior to anti-resorptive therapy (referred to as the “additional population”). The submission also positioned romosozumab as an alternative to teriparatide for subsequent treatment of patients who develop severe osteoporosis while receiving anti-resorptive therapy (referred to as the “later-line” population). In both settings, the submission indicated that treatment with an anabolic agent should be followed-up with anti-resorptive therapy to maintain improvements in bone strength.

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

5 Comparator

- 5.1 The submission nominated teriparatide as the main comparator. This was appropriate for the later-line population.
- 5.2 The submission nominated alendronate (as a proxy for other anti-resorptive therapies) as a secondary comparator. Denosumab is currently the most widely used treatment for osteoporosis on the PBS and is the most likely anti-resorptive therapy to be replaced in practice. Denosumab was listed on a cost minimisation basis compared to zoledronic acid which in turn was listed on a cost minimisation basis compared to alendronate (PBS therapeutic relativity sheets, May 2018). Therefore, the evaluation considered that alendronate may be an appropriate comparator under these circumstances.
- 5.3 However, the ESC considered that comparative evidence against denosumab would also be informative given it is the therapy most likely to be replaced in clinical practice for the additional patient population.
- 5.4 The ESC recalled the PBAC’s July 2010 recommendation of denosumab, which was listed on a cost minimisation basis compared with zoledronic acid. The denosumab submission had claimed that denosumab was associated with a reduction in the incidence of vertebral fractures and an improvement in persistence relative to a mixed comparator comprised of alendronate, risedronate, zoledronic acid and strontium

ranelate; the July 2010 PBAC did not accept this claim. With regard to the analyses versus alendronate, the July 2010 PBAC noted that denosumab treatment was associated with a small but statistically significant increase in BMD compared to alendronate (approximately 1% in absolute terms at all measured locations) after 12 months of treatment. However, the PBAC considered that the clinical importance of this difference in BMD outcomes was unclear. Further, the submission noted that denosumab was associated with a numerically greater (but not statistically significant) reduction in clinical vertebral fractures in the total population analysis (RR 0.60, 95% CI 0.34, 1.04). (Denosumab Public summary Document, July 2010).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the trial data and indicated the benefits of romosozumab include better efficacy compared to alendronate and a different mechanism of action and reduced frequency of injections compared to teriparatide. The clinician would prefer to use romosozumab first-line in patients at high-risk of fracture because its mechanism of action promotes bone formation. The clinician noted studies were underway assessing the efficacy and safety of a second course of romosozumab.

Consumer comments

- 6.2 The PBAC noted and welcomed the input received from one health professional via the Consumer Comments facility on the PBS website. The health professional considered the benefits of romosozumab include its good evidence of efficacy and a different mechanism of action.
- 6.3 The PBAC noted the letters of support provided by Therapeutics Committee of the Australian and New Zealand Bone and Mineral Society (ANZBMS) and Osteoporosis Australia. Both groups consider romosozumab is an advance in the treatment of osteoporosis, providing clinicians and patients with an effective treatment option that has a different mechanism of action and reduced injection burden compared to teriparatide. The ANZBMS consider the cardiovascular adverse event profile to be a concern but are of the opinion that the risk can be managed in clinical practice.

Clinical trials

- 6.4 The submission was based on a series of direct and indirect comparisons between romosozumab and nominated comparators:
- A direct comparison of BMD outcomes with romosozumab versus teriparatide in postmenopausal women with osteoporosis who were previously treated with anti-resorptive therapy (STRUCTURE).

Public Summary Document – November 2018 PBAC meeting

- An 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.
 - A direct comparison of fracture outcomes with romosozumab versus alendronate in postmenopausal women with osteoporosis who were predominantly naïve to anti-resorptive therapy (ARCH).
- 6.5 The submission 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).
- 6.6 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, data on maintenance of treatment effect without ongoing anti-resorptive therapy and data on re-treatment with romosozumab after discontinuation.
- 6.7 Details of the trials presented in the submission are provided in the table below.

Public Summary Document – November 2018 PBAC meeting

Table 2: Trials and associated reports presented in the submission

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	<i>The Journal of Clinical Endocrinology & Metabolism</i> 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
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	Internal study report
	McClung M et al (2014). Romosozumab in Postmenopausal Women with Low Bone Mineral Density.	New England Journal of Medicine 370: 412-420
	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	Journal of Bone and Mineral Research 33: 1-10

Public Summary Document – November 2018 PBAC meeting

Trial ID	Protocol title/ Publication title	Publication citation
GHAC	Neer et al (2001). Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.	New England Journal of Medicine 344: 1434-1441
	Gallagher JC et al (2005). Teriparatide Reduces the Fracture Risk Associated with Increasing Number and Severity of Osteoporotic Fractures.	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

Source: Table 2.2-1 (p 26-27), Table 2.2-4 (p 29) of the submission

6.8 The key features of the included trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	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

Source: Table 2.3-1 (p 31), Table 2.3-2 (p 32), Table 2.4-1 (p 37), Table 2.4-2 (p 38), Table 2.4-3 (p 40-45), Table 2.4-4 (p 46-47) of the submission; p 1-6 Appendix 1 of the submission

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

6.9 The ESC noted that none of the populations in the key trials exactly matched the requested PBS populations. The trials had less severe disease both in terms of BMD T scores (BMD T score \leq minus 2.50 in the trials versus \leq minus 3.0 in the proposed PBS populations) and fracture history compared to the requested PBS populations.

Comparative effectiveness

Romosozumab versus teriparatide

6.10 Key BMD outcomes reported with romosozumab versus teriparatide in the STRUCTURE trial are summarised in the table below.

Table 4: BMD outcomes with romosozumab and teriparatide

Location	Romosozumab (N = 218)	Teriparatide (N = 218)	Difference
Baseline BMD T-score, mean (SD)			
Total hip	-2.27 (0.75)	-2.21 (0.72)	-
Femoral neck	-2.49 (0.67)	-2.43 (0.66)	-
Lumbar spine	-2.83 (1.10)	-2.87 (1.04)	-
Relative change from baseline to Month 12, LSM (95% CI)			
Total hip	2.6% (2.2, 3.0)	-0.6% (-1.0, -0.2)	3.2% (2.7, 3.8)
Femoral neck	3.2% (2.6, 3.8)	-0.2% (-0.8, 0.4)	3.4% (2.6, 4.2)
Lumbar spine	9.8% (9.0, 10.5)	5.4% (4.7, 6.1)	4.4% (3.4, 5.4)

Source: Table 2.5-1 (p 48), Table 2.5-2 (p 48-49) of the submission; Table 9-4 (p 54-55) of the STRUCTURE trial report
Abbreviations: BMD, bone mineral density; CI, confidence interval; LSM, least squares mean; SD, standard deviation

6.11 Treatment with romosozumab was associated with a statistically significant increase in total hip, femoral neck and lumbar spine BMD over one year compared to teriparatide. The evaluation and the ESC considered that the clinical importance of this difference is unclear as changes in BMD T-scores may not reflect changes in fracture risk with different therapies.

6.12 The indirect comparison of fracture outcomes with romosozumab versus teriparatide is summarised in the table below.

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 submission

^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

- 6.13 Based on the indirect analyses there were no statistically significant differences in fracture outcomes between romosozumab and teriparatide.
- 6.14 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. Overall, it was unclear whether the trials were sufficiently exchangeable to justify an indirect comparison. In particular, the ESC noted that the differences between trials may also be due to the >10 year gap between two of the trials, with the GHAC (teriparatide) trial concluded in 1998 and the FRAME (romosozumab) trial conducted from 2012-2015.
- 6.15 The evaluation and the ESC considered that the lack of a statistically significant difference between treatments may not adequately justify the claim of non-inferiority given the wide confidence intervals for fracture outcomes, which indicate substantial uncertainty around the indirect estimate of effects.
- 6.16 There were no data on fracture outcomes with romosozumab compared to teriparatide in patients who had received prior anti-resorptive treatment (which may be a treatment effect modifier).
- 6.17 Further, there were no data on the residual treatment effects of romosozumab compared to teriparatide in patients switching to anti-resorptive therapy or in patients discontinuing osteoporosis treatment.
- 6.18 Overall, the ESC considered the comparative efficacy of romosozumab versus teriparatide to be uncertain given the lack of fracture outcomes from the head-to-head STRUCTURE trial and the issues with exchangeability between the trials used in the indirect comparison.

Romosozumab versus alendronate

- 6.19 Key fracture outcomes reported with romosozumab versus alendronate (both followed by alendronate treatment) in the ARCH trial are summarised in the table below.

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 submission

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.

6.20 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.

6.21 The PBAC noted the ARCH trial excluded patients who: were on bisphosphonates at baseline; had more than three years of prior use of oral bisphosphonates; had

received any oral bisphosphonates in the previous six months; or who had received denosumab in the previous 18 months. As such, there were limited data on fracture outcomes with romosozumab compared to alendronate in patients with previous anti-resorptive treatment (which may be a treatment effect modifier).

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

Other data

- 6.23 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 submission noted that the BMD changes reported in males with romosozumab treatment were similar to those reported for postmenopausal women.
- 6.24 Treatment with the marketed formulation of romosozumab (90 mg/mL) was non-inferior compared to the trial formulation of romosozumab (70 mg/mL) and superior to placebo in terms of BMD outcomes over 6 months (Study 156).
- 6.25 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).
- 6.26 The results of Study 326 also indicated that the majority of BMD gains occurred in the first year but suggested that an additional year of treatment with romosozumab was associated with further incremental improvements in BMD outcomes. This study also demonstrated that BMD improvements associated with romosozumab are rapidly lost after discontinuation of osteoporosis treatment.
- 6.27 The results of Study 326 also indicated that patients re-treated with romosozumab after previously receiving placebo had improvements in BMD outcomes that were comparable to the initial treatment. However, the study also indicated that patients re-treated with romosozumab after previously receiving anti-resorptive therapy only had limited improvements in BMD outcomes.

Comparative harms

- 6.28 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.
- 6.29 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.

- 6.30 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 summarised in the table below).
- 6.31 The ESC noted that, in the ARCH trial (romosozumab versus alendronate for 12 months, followed by alendronate in both arms), the odds ratio for cardiac ischaemic events was 2.65 (95% CI: 1.03, 6.77) over the one year romosozumab treatment period, and the odds ratio for cerebrovascular events was 1.66 (95% CI: 1.03, 2.69) over the full trial period (median follow-up of 33 months).
- 6.32 The STRUCTURE trial (romosozumab versus teriparatide) did not report an analysis of adjudicated serious cardiovascular adverse events. The Clinical Study Report (Table 14-6.2.2) shows that the incidence of treatment-emergence serious cardiac adverse events was 0.9% (2/214) in the teriparatide arm, versus 2.3% (5/218) in the romosozumab arm.
- 6.33 The submission 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 was not observed in the FRAME trial.
- 6.34 This 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 did note 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. Finally, 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 epidemiology 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.
- 6.35 The ACM was of the view that [REDACTED]

Benefits/harms

- 6.36 A benefits/harms summary was not presented for romosozumab versus teriparatide due to the claim of non-inferiority.
- 6.37 On the basis of direct evidence presented in the submission (ARCH trial, as outlined in Tables 6 and 7), for every 1000 patients treated with romosozumab in comparison to alendronate over one year (primary treatment):
- Approximately 15 fewer patients would have a clinical fracture;
 - Approximately 6 additional patients would have a serious cardiovascular event.
- 6.38 On the basis of direct evidence presented in the submission (ARCH trial, as outlined in Tables 6 and 7), for every 1000 patients treated with romosozumab followed by alendronate in comparison to alendronate alone over a median of 33 months (primary and subsequent treatment):
- Approximately 33 fewer patients would have a clinical fracture;
 - Approximately 4 additional patients would have a serious cardiovascular event.

Clinical claim

- 6.39 The submission described romosozumab as similar in terms of efficacy and safety compared to teriparatide. The evaluation and the ESC considered that this claim was not adequately supported given the unknown clinical importance of BMD outcomes, the limited exchangeability, applicability and robustness of the indirect analysis of fracture outcomes, the lack of comparative data in patients with prior anti-resorptive therapy and lack of comparative data on residual effectiveness with and without subsequent anti-resorptive therapy. The ESC further considered that the claim of similar safety compared to teriparatide was not adequately supported given the higher rates of cardiovascular adverse events reported in the STRUCTURE trial in the context of the broader concerns about cardiovascular safety with romosozumab reported in other trials (discussed further below).

Public Summary Document – November 2018 PBAC meeting

Table 7: Summary of serious cardiovascular events reported in the key romosozumab trials

	Patients with serious events, n/N (%)						
	Any cardiovascular event	Cardiac ischaemic event	Heart failure	Non-coronary revascularisation	Cerebrovascular event	Peripheral vascular ischaemic event not requiring revascularisation	Cardiovascular death
Initial treatment period							
ARCH							
- Romosozumab (1 year)	50/2040 (2.5)	16/2040 (0.8)	4/2040 (0.2)	3/2040 (0.1)	16/2040 (0.8)	0/2040 (0.0)	17/2040 (0.8)
- Alendronate (1 year)	38/2014 (1.9)	6/2014 (0.3)	8/2014 (0.4)	5/2014 (0.2)	7/2014 (0.3)	2/2014 (<0.1)	12/2014 (0.6)
- Treatment difference; OR (95% CI)	1.31 (0.85, 2.00)	2.65 (1.03, 6.77)	0.49 (0.15, 1.64)	0.59 (0.14, 2.48)	2.27 (0.93, 5.52)	NE	1.40 (0.67, 2.94)
BRIDGE							
- Romosozumab (1 year)	8/163 (4.9)	3/163 (1.8)	1/163 (0.6)	NR	3/163 (1.8)	NR	1/163 (0.6)
- Placebo (1 year)	2/81 (2.5)	0/81 (0.0)	0/81 (0.0)	NR	1/81 (1.2)	NR	1/81 (1.2)
- Treatment difference; OR (95% CI)	NR	NR	NR	NR	NR	NR	NR
FRAME							
- Romosozumab (1 year)	44/3581 (1.2)	15/3581 (0.4)	7/3581 (0.2)	NR	10/3581 (0.3)	3/3581 (<0.1)	17/3581 (0.5)
- Placebo (1 year)	41/3576 (1.1)	14/3576 (0.4)	4/3576 (0.1)	NR	11/3576 (0.3)	1/3576 (<0.1)	15/3576 (0.4)
- Treatment difference; OR (95% CI)	1.07 (0.70, 1.65)	1.07 (0.52, 2.22)	1.75 (0.51, 5.98)	NR	0.91 (0.38, 2.14)	3.00 (0.31, 28.82)	1.13 (0.56, 2.27)
Full trial period							
ARCH							
- Romo/Ale (median 33 months)	133/2040 (6.5)	30/2040 (1.5)	12/2040 (0.6)	6/2040 (0.3)	45/2040 (2.2)	2/2040 (<0.1)	58/2040 (2.8)
- Ale/Ale (median 33 months)	122/2014 (6.1)	20/2014 (1.0)	23/2014 (1.1)	10/2014 (0.5)	27/2014 (1.3)	5/2014 (0.2)	55/2014 (2.7)
- Treatment difference; OR (95% CI)	1.08 (0.84, 1.39)	1.49 (0.84, 2.63)	0.51 (0.25, 1.03)	0.59 (0.21, 1.63)	1.66 (1.03, 2.69)	0.39 (0.08, 2.03)	1.04 (0.72, 1.52)
FRAME							
- Romo/Deno (3 years)	128/3581 (3.6)	36/3581 (1.0)	12/3581 (0.3)	2/3581 (<0.1)	43/3581 (1.2)	8/3581 (0.2)	43/3581 (1.2)
- Pbo/Deno (3 years)	124/3576 (3.5)	38/3576 (1.1)	15/3576 (0.4)	4/3576 (0.1)	36/3576 (1.0)	3/3576 (< 0.1)	50/3576 (1.4)
- Treatment difference; OR (95% CI)	1.03 (0.80, 1.33)	0.95 (0.60, 1.50)	0.80 (0.37, 1.71)	0.50 (0.09, 2.73)	1.20 (0.77, 1.87)	2.67 (0.71, 10.06)	0.86 (0.57, 1.29)

Source: Table 2.5-15 (p 64), Table 2.5-16 (p 65), Table 2.5-17 (p 66), Table 2.5-18 (p 67) of the submission; Table 7-14 (p 61) of the FRAME final analysis trial report; Table 14-6.8.1 (p 347) of the BRIDGE trial report
Abbreviations: Ale, alendronate; Deno, denosumab; NE, not estimable; NR, not reported; Pbo, placebo; Romo, romosozumab

- 6.40 The submission 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 submission noted a higher incidence of serious cardiovascular events with romosozumab compared to alendronate but argued that a causal relationship has not been established. The evaluation considered that the efficacy claim may be reasonable but the clinical data suggests that romosozumab is inferior in terms of safety compared to alendronate. The ESC considered that the data presented supported the claim of superior efficacy compared to alendronate for the duration of the ARCH trial. However, the ESC considered that the long term comparative efficacy of romosozumab was uncertain given the lack of long term data and that maintenance of the treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy. The ESC considered that based on the number of serious cardiovascular events reported in the romosozumab arm of the ARCH trial, romosozumab would likely have inferior safety compared with alendronate alone.
- 6.41 Further, the ESC considered that comparative evidence against denosumab would also be informative given it is the therapy most likely to be replaced in clinical practice under the requested additional population (first-line) listing.

Economic analysis

Cost minimisation analysis versus teriparatide

- 6.42 The submission presented a cost minimisation analysis of romosozumab compared to teriparatide. The ESC considered that a cost minimisation analysis may not be appropriate given the lack of reliable data on fracture outcomes with romosozumab compared to teriparatide and high incidence of cardiovascular events associated with romosozumab.
- 6.43 The equi-effective doses were based on the recommended dosing regimens outlined in the relevant product information documents and was consistent with trial protocols. The submission estimated that romosozumab 210 mg once monthly for 12 months was equivalent to teriparatide 20 mcg once daily for 18 months. The PBAC considered it may be more appropriate to base the equi-effective doses on the doses of romosozumab and teriparatide used by patients in the trials (e.g. taking into account compliance and discontinuations), rather than the doses stated in the product information documents.
- 6.44 The submission claimed no additional costs or cost-offsets. The evaluation considered there may have been increased costs associated with the administration of romosozumab as it was administered by healthcare professionals in the clinical trial while teriparatide was self-administered. The PSCR claimed that romosozumab would be self-administered which would reduce administration costs. The ESC and PBAC considered not including a cost for the administration of romosozumab was reasonable but noted it was administered by health care professionals in the trial, and

considered that self-administration may have an impact on the effectiveness in clinical practice due to reduced adherence.

- 6.45 The ESC and the PBAC considered that it may have been appropriate to include costs for monitoring and managing adverse events given the cardiovascular safety concerns with romosozumab.

Cost utility analysis versus alendronate

- 6.46 The submission 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 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Patients without fractures; life years; quality adjusted life years
Time horizon	26 years (lifetime)
Methods used to generate results	Markov cohort model (with half-cycle correction)
Treatments	Romosozumab followed by alendronate; alendronate followed by alendronate
Health states	Four health states: baseline severe osteoporosis health state, post-incident hip fracture, post-incident vertebral fracture and death
Cycle length	Annual
Transition probability	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. Treatment effect estimates were derived from the ARCH trial with additional extrapolation beyond the clinical data. Probability of death was based on Australian life tables with mortality multipliers based on fracture history.
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro 2018

Source: 3.1-1 (p 85) of the submission

- 6.47 All patients start in the baseline severe osteoporosis health state with an elevated mortality risk due to prior prevalent fracture. In each annual cycle, patients can have no event or experience a hip fracture, vertebral fracture, other fracture or death. Patients experiencing multiple fracture events accrue the acute costs and consequences of each event and have ongoing chronic costs and consequences based on the most severe event (hip fracture > vertebral fracture > severe osteoporosis with no fracture/other fracture). The model utilises tunnel states to adjust mortality risk based on the time since fracture. The model assumes that patients will receive romosozumab for one year followed by alendronate or alendronate only throughout the course of the model. Cardiovascular events were included as a fixed risk with the first year of romosozumab treatment rather than as a transition probability (sensitivity analysis).
- 6.48 The model structure does not allow patients to discontinue osteoporosis treatment. The ESC considered this was inappropriate and is unlikely to reflect clinical practice.

6.49 The model presented in the submission was broadly similar to other published economic evaluations. The main difference was the use of sequential therapy and the assumption of perfect persistence. In contrast to the current cohort model, many of the economic models previously considered by the PBAC for osteoporosis have used a microsimulation approach to track changing patient characteristics and disease histories over time.

6.50 Key drivers of the economic model are summarised in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of treatment effect	Extrapolation of treatment effect modelled using a parametric curve for 5 years with linear convergence at 10 years. Clinical data is limited to a median follow-up of 33 months. The long-term efficacy of romosozumab appears to be conditional on patients continuing to use anti-resorptive therapy. However, available epidemiology data suggest relatively poor persistence with osteoporosis treatments in clinical practice.	High, favours romosozumab
Magnitude of treatment effect	Treatment effects modelled based on data from the ARCH trial. The estimated cost effectiveness of romosozumab is sensitive to uncertainty around the point estimates used in the model	High, favours romosozumab
Circumstances of use	The economic analysis assumed patients would only receive a single 12 month treatment course of romosozumab. The cost-effectiveness of longer treatment courses or multiple treatment courses over a patient lifetime was unclear, although the Pre-Sub-Committee Response (PSCR) proposed that use of romosozumab should be restricted to a single 12 month course per patient. The PSCR proposed that patients would self-inject romosozumab; however in the clinical trial it was administered by health care professionals. The ESC considered that this may impact adherence and the incremental efficacy. Further, the model assumed levels of compliance to subsequent anti-resorptive therapies that were unlikely to be achieved in clinical practice.	High, favours romosozumab

Source: Constructed during the evaluation

6.51 The submission used a complex multi-step approach using the Garvan risk calculator to estimate the background risk of fracture in the target PBS population. Overall, the adjustment of fracture risk using the Garvan risk calculator was poorly justified (insufficient data available to reliably quantify risk factors, implausibly high hip fracture risks and lack of external validation) and may not be a reasonable estimate of fracture risk in the target PBS population.

6.52 The ESC considered that 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 including:

- Use of only female patient data from the Geelong osteoporosis Study to estimate the fracture and falls history of the target PBS population. Further, the ESC noted that the estimated fracture and falls histories were derived from

estimates approximately 25 years old which may not be representative of current clinical practice.

- The assumption that 50% of patients in the ARCH trial would have had a prior falls history.
 - Estimation of the distribution of prior fractures across patients in the ARCH trial were based on proportions of patients with prevalent vertebral and non-vertebral fractures. The ESC noted that this did not account for patients with multiple fractures at baseline.
 - Estimation of the difference in BMD T-scores was based on lumbar spine BMD T-scores whereas the Garvan risk calculator uses femoral neck BMD T-scores. The ESC noted that a comparison of femoral neck BMD scores indicated that the overall ARCH population has worse BMD scores than the target PBS population.
 - The Garvan risk calculator is used to estimate both a 5 and 10 year risk of hip fracture. The submission did not justify deriving fracture estimates based on 5-year risk only.
- 6.53 Overall, the ESC considered that the methodology for adjustment of background fracture risk was not sufficiently justified, and likely significantly overestimated the fracture risk in the PBS population (further discussed below).
- 6.54 The submission estimated mortality multipliers based on 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.
- 6.55 The submission estimated fracture disutility values from various published studies. Utility data from the ICUROS study (which was used for cost estimates in the submission) indicated that the submission may have overestimated the disutility associated with incident vertebral fractures and prevalent hip fractures, particularly in Australian patients. Estimates from the ICUROS study were based on more recent data than the disutility values used in the submission. The submission did not attempt to validate estimated utility values against utility data captured as part of the FRAME and ARCH trials. 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. Further, the ESC considered that the estimates derived in the submission may be confounded by other factors having been derived from several different sources. The ESC noted that incorporating the ICUROS utilities in the model increased the ICER of \$15,000/QALY - \$45,000/QALY by 20.6%.
- 6.56 The submission did not include cardiovascular events in the base case economic analysis. This was inconsistent with the available data from the ARCH trial.
- 6.57 The results of the stepped economic evaluation are summarised below.

Table 10: Stepped economic evaluation of romosozumab followed by alendronate compared to alendronate alone

Type of resource item	Romosozumab/ Alendronate	Alendronate/ alendronate	Incremental difference
Step 1a: Trial based efficacy (using time to event curve for clinical fracture), 12 month horizon, drug costs only, incremental cost per patient free of any clinical fracture			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patients without fracture	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per additional patient free of any incident fracture			\$ [REDACTED]
Step 1b: Trial based efficacy (using time to event curve for clinical fracture), 24 month horizon, drug costs only, incremental cost per patient free of any clinical fracture			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patients without fracture	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per additional patient free of any incident fracture			\$ [REDACTED]
Step 1c: Trial based efficacy (using time to event curve for clinical fracture), 36 month horizon, drug costs only, incremental cost per patient free of any clinical fracture			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patients without fracture	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per additional patient free of any incident fracture			\$ [REDACTED]
Step 1d: Trial based efficacy (using time to event curve for clinical fracture), 48 month horizon, drug costs only, incremental cost per patient free of any clinical fracture			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Patients without fracture	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per additional patient free of any incident fracture			\$ [REDACTED]
Step 2: Trial-based efficacy (using data from primary analysis period), 48 month horizon, drug costs only, general population mortality, osteoporosis utility/disutility values, incremental cost per QALY gained			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 3: Modelled efficacy (constant romosozumab efficacy benefits to 10 years), 26 year time horizon, drug costs only, general population mortality, osteoporosis utility/disutility values, incremental cost per QALY gained			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 4: Modelled efficacy (constant romosozumab efficacy benefits to 10 years), 26 year time horizon, drug costs only, fracture risk adjusted using Garvan risk calculator, general population mortality, osteoporosis utility/disutility values, incremental cost per QALY gained			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 5: Modelled efficacy (constant romosozumab efficacy benefits to 10 years), 26 year time horizon, drug and fracture costs, fracture risk adjusted using Garvan risk calculator, general population mortality, osteoporosis utility/disutility values, incremental cost per QALY gained			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]
Step 6: Modelled efficacy (constant romosozumab efficacy benefits to 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]
Step 7: Modelled efficacy (parametric survival curves with romosozumab efficacy benefits to 10 years), 26 year time horizon, drug and fracture costs, fracture risk adjusted using Garvan risk calculator, general population mortality			

Public Summary Document – November 2018 PBAC meeting

Type of resource item	Romosozumab/ Alendronate	Alendronate/ alendronate	Incremental difference
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]
Step 8: 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]

Source: Table 3.8-1 (p 113) of the submission

Abbreviations: QALYs, quality-adjusted life years.

The redacted table shows incremental costs per additional patient free of any incident fractures in the range of \$105,000 - \$200,000 to more than \$200,000. The redacted table also shows ICERs per QALY gained in the range of less than \$15,000/QALY - \$200,000/QALY.

6.58 Based on the economic model using published prices, treatment with romosozumab followed by alendronate was associated with a cost per QALY gained of \$15,000 - \$45,000 compared to alendronate alone for the treatment of severe osteoporosis.

6.59 The PSCR stated that the price of romosozumab used in the cost-effectiveness analysis versus alendronate was a proxy for the yet unknown effective price that would be derived from a cost-minimisation analysis using the effective price of teriparatide. Therefore, the modelled economic analysis does not incorporate any potential discounts which the PSCR stated may improve the overall cost-effectiveness of romosozumab.

6.60 The table below provides a comparison of trial-based versus model-based fracture estimates. The majority of fractures in the model occurred beyond the duration of the trial but the majority of the incremental difference between treatment arms occurred during the first four years.

Table 11: Cumulative incidence of hip and clinical fractures (hip, vertebral, other) generated in the model

	Romosozumab/ Alendronate	Alendronate/ alendronate	Incremental difference
Cumulative incidence of fracture in ARCH trial (Years 1-4)			
Clinical fractures	0.149	0.196	-0.037
Cumulative incidence of fracture in model (Years 1-4)			
Clinical fractures	[REDACTED]	[REDACTED]	[REDACTED]
- Hip fractures	[REDACTED]	[REDACTED]	[REDACTED]
Cumulative incidence of fracture in model (Years 5-26)			
Clinical fractures	[REDACTED]	[REDACTED]	[REDACTED]
- Hip fractures	[REDACTED]	[REDACTED]	[REDACTED]

Source: constructed during the evaluation using Evenity severe osteoporosis TreeAge model provided with the submission and additional data from Figure 2B of the Saag (2017) publication

6.61 The ESC 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 (■■■% in Years 1-4; ■■■% in Years 5-26). The ESC noted that the modelled proportion of all fractures that were hip fractures (■■■% in 70-74 years increasing to ■■■% in 95-99 years) is higher than both the clinical trial data (distribution of fracture types: hip fracture 20-22%, vertebral fracture 16-22%, other fracture 56-64%; based on incidence from ARCH trial) and the Dubbo osteoporosis study (hip fracture 17%, vertebral fracture 28-34%, other fractures 49-55%; Nguyen et al 2008). The ESC further noted that the model estimated a ■■■% 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.

- 6.62 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 adherence and persistence rates to subsequent therapy after discontinuation of romosozumab of ■■■% and ■■■%, respectively. While the evaluation had considered that persistence to anti-resorptives is generally poor in clinical practice, the PSCR argued this has improved in recent years, stating that a 10% PBS sample showed that, of initiating patients in 2017, 81% were on therapy at 12 months compared with 45% of patients who initiated in 2010. As noted in the commentary, these estimates could not be validated during the evaluation due to a lack of documentation. The ESC considered that while persistence may have increased with the availability of denosumab and zoledronic acid (which are 6- and 12-monthly injections, respectively, rather than daily tablets), 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 of \$15,000/QALY - \$45,000/QALY was not reliable and likely significantly underestimated.
- 6.63 Overall, the ESC considered that the economic model did not form a reliable basis for decision making due to the overestimation of fracture risk and treatment effect (including 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.
- 6.64 The results of the sensitivity analyses indicated that the model was most sensitive to the magnitude of treatment benefit and extrapolation of treatment benefits beyond the clinical trial data (summarised in the table below).

Table 12: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Treatment duration (base case: parametric extrapolation to 5 years, linear convergence to 10 years)			
Constant treatment to 4 years, linear convergence to 5 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Constant treatment to 4 years, linear convergence to 10 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Parametric extrapolation to 3 years, linear convergence by 3 years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Magnitude of treatment effect (base case: modelled estimates from ARCH trial)			
Decrease relative efficacy by 20% for hip, vertebral and other fracture	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Decrease relative efficacy by 40% for hip, vertebral and other fracture	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
No treatment effect on non-vertebral fractures	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 3.9-1 (p 118-119) of the submission

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Italicised analyses were conducted during the evaluation

The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY and \$45,000/QALY - \$75,000/QALY.

Drug cost/patient/year

- 6.65 The estimated drug cost for romosozumab per patient per year was \$7,412 (based on 12 scripts using the published DPMQ \$617.70 for 2 x 105 mg monthly injections).
- 6.66 The estimated drug cost for alendronate per patient per year was \$195 (based on 13 scripts using the June 2018 DPMQ \$15.00 for 4 x 70 mg weekly tablets).
- 6.67 The estimated drug cost for teriparatide per patient per year was \$5,353 (based on 13 scripts using the published DPMQ \$411.80 for 28 x 20 mcg daily injections). The estimated drug cost for a full course of teriparatide therapy was \$7,412 (based on 18 scripts using the published DPMQ \$411.80 for 28 x 20 mcg daily injections).

Estimated PBS usage & financial implications

- 6.68 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact for romosozumab in the two requested patient populations; patients with severe osteoporosis who experience a fracture while receiving anti-resorptive therapy (under the requested later-line listing) and patients with severe osteoporosis (under the requested additional population (first-line) listing).
- 6.69 The estimated eligible population and budget impact of the population under the requested later-line listing is summarised in the table below.

Public Summary Document – November 2018 PBAC meeting

Table 13: Estimated use and total cost of romosozumab to the PBS/RPBS in patients with severe osteoporosis who have experienced a prior symptomatic fracture while receiving anti-resorptive therapy (under the later-line listing)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated for osteoporosis	538,966	557,290	576,238	595,830	616,089	637,036
Eligible patient population	█	█	█	█	█	█
Romosozumab uptake from existing market	█	█	█	█	█	█%
Romosozumab uptake from market growth	█	█%	█	█	█	█
Total patients treated with romosozumab	█	█	█	█	█	█
Total romosozumab scripts (10.8 scripts/year)	█	█	█	█	█	█
Cost to PBS (DPMQ)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Patient copayment	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Total cost to PBS (less copay)	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost of teriparatide (DPMQ less copay)	-\$693,097	-\$1,433,325	-\$1,852,573	-\$2,298,673	-\$2,376,828	-\$2,457,640
Cost of anti-resorptives (DPMQ less copay)	-\$365,296	-\$566,573	-\$781,116	-\$807,674	-\$835,135	-\$863,529
Net cost of romosozumab	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: 'Financial analysis workbook' Excel workbook, Appendix 15 of the submission

Abbreviations: BMD, bone mineral density

Note: cost offsets due to substitution of other therapies was estimated using 1 June 2018 PBS prices. There was a slight increase in these prices due to mark-ups on 1 July 2018. The estimates used were not adjusted during the evaluation.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million per year.

6.70 The ESC noted that the estimated budget impact was large in the context of a cost-minimisation. The ESC noted that the net cost of romosozumab was largely due to the uptake rates for romosozumab from additional market growth. The submission claimed that reduced injection burden, shorter treatment duration and increased marketing activity by the sponsor will increase the number of patients treated with anabolic agents, all of which will be treated with romosozumab. The ESC considered this assumption was poorly justified. Further, the PBAC considered that it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently receive teriparatide.

6.71 The estimated eligible population and budget impact of the additional population (first-line) listing is summarised in the table below.

Table 14: Estimated use and total cost of romosozumab to the PBS/RPBS in patients with severe osteoporosis (additional population listing)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated for osteoporosis	538,966	557,290	576,238	595,830	616,089	637,036
Eligible patient population	█	█	█	█	█	█
Romosozumab uptake rates	█%	█%	█%	█%	█%	█%
Total patients treated with romosozumab	█	█	█	█	█	█
Total romosozumab scripts (10.8 scripts/year)	█	█	█	█	█	█
Cost to PBS (DPMQ)	\$█	\$█	\$█	\$█	\$█	\$█
Patient copayment	\$█	\$█	\$█	\$█	\$█	\$█
Total cost to PBS (less copay)	\$█	\$█	\$█	\$█	\$█	\$█
Cost of anti-resorptives (DPMQ less copay)	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net cost of romosozumab	\$█	\$█	\$█	\$█	\$█	\$█

Source: 'Financial analysis workbook' Excel workbook, Appendix 15 of the submission

Abbreviations: BMD, bone mineral density

Note: cost offsets due to substitution of other therapies was estimated using 1 June 2018 PBS prices. There was a slight increase in these prices due to mark-ups in 1 July 2018. The estimates used were not adjusted during the evaluation.

The redacted table shows that at Year 6 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

- 6.72 The approach used to estimate the eligible population failed to identify the pool of prevalent patients who would be eligible for treatment with romosozumab. This was because the submission only included: incident fracture populations for the later-line listing (i.e. patients with a fracture on prior anti-resorptive therapy); and patients with less than 12 months prior treatment for the additional population listing. Based on the estimates presented in the submission the severe osteoporosis population (additional population) eligible for romosozumab treatment represents <1% of the treated osteoporosis population.
- 6.73 The ESC noted that the additional population (first-line) listing would allow use in later-line settings. As such, the ESC considered that for clarity, the financial estimates for the additional population should incorporate relevant patients from the later-line listing in order to adequately estimate the financial impact. The ESC considered that over time, as incident patients use romosozumab first-line, there would be fewer patients eligible to use romosozumab later-line (if it is listed for once-in-a-lifetime use). The impacts of first-line use on later-line use would need to be incorporated into the additional population financial estimates.
- 6.74 The budget impact estimates are associated with significant uncertainties regarding the estimated cost of romosozumab (uptake rates were based on a static anabolic market) and cost offsets (there was a calculation error in substituted anti-resorptive scripts, substitution rates were based on a poorly documented 10% Medicare sample analysis, and the submission assumed no substitution of teriparatide beyond 1 year of therapy).

Quality Use of Medicines

- 6.75 The submission claimed that the availability of romosozumab will address an unmet need in the PBS population as it will provide access to another anabolic agent which has a lower treatment burden than teriparatide.
- 6.76 The submission stated that lifelong osteoporosis therapy is required in patients with severe disease. Based on the draft product information, romosozumab has a recommended duration of 12 months which must be followed-up with ongoing anti-resorptive therapy in order to retain treatment benefit. This is reliant on patient and clinician behaviour which was not addressed in the submission.
- 6.77 The submission did not propose a limit on the use of romosozumab on the PBS. There are limited clinical data on continuous use beyond 12 months, use of multiple courses of romosozumab or use in patients previously treated with other anabolic agents. Given the lack of clinical data for use beyond 12 months, the PBAC considered that PBS-subsidised use of romosozumab should be limited to a maximum of 12 months per lifetime.
- 6.78 The draft product information suggests that romosozumab can be administered by a trained individual. There were no clinical data on the self-administration of romosozumab by patients or carers. The PSCR indicated that only the auto-injector presentation of romosozumab would be marketed in Australia.

Financial Management – Risk Sharing Arrangements

- 6.79 The submission stated that teriparatide is currently subject to a special pricing arrangement and noted that a special pricing arrangement would also be required for romosozumab.
- 6.80 The submission did not propose a risk-sharing arrangement.

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

7 PBAC outcome

- 7.1 The PBAC did not recommend the listing of romosozumab for the treatment of severe osteoporosis due to uncertainties in the clinical claims and the financial estimates and concerns regarding the safety profile. For the comparison versus teriparatide, the PBAC considered that the cost-minimisation analysis and financial estimates were unreliable. For the comparison versus alendronate, the PBAC considered that the long-term comparative efficacy was uncertain, and the economic model was not a reliable basis for decision making. For both comparisons, the PBAC considered that romosozumab had inferior comparative safety (versus teriparatide or alendronate).
- 7.2 The PBAC noted the submission requested listing for two patient populations – a 'later line' population and an 'additional' population. The PBAC considered teriparatide was an appropriate comparator for the 'later line' population and alendronate was an appropriate comparator for the 'additional' population.

Analysis versus teriparatide (later-line population)

- 7.3 The PBAC noted there were numerous issues with the comparison versus teriparatide including the unknown clinical importance of BMD outcomes, the exchangeability and applicability issues with the indirect analysis of fracture outcomes, the lack of comparative data in patients with prior anti-resorptive therapy and lack of comparative data on residual effectiveness with and without subsequent anti-resorptive therapy. The PBAC considered the claim of non-inferior efficacy uncertain, however noted that further data may not be available to increase the certainty for this claim. In this context, the PBAC considered any economic evaluation versus teriparatide would need to be informed by conservative assumptions.
- 7.4 The PBAC considered that the claim of similar safety compared to teriparatide was not adequately supported given the higher rates of cardiovascular adverse events reported in the STRUCTURE trial in the context of the broader concerns about cardiovascular safety with romosozumab reported in other trials. The STRUCTURE trial (romosozumab versus teriparatide) reported that the incidence of treatment-emergent serious cardiac disorders adverse events was 0.9% (2/214) in the teriparatide arm, versus 2.3% (5/218) in the romosozumab arm.
- 7.5 The PBAC noted the cost-minimisation analysis of romosozumab compared to teriparatide was based on dosage regimens in the relevant product information documents. The PBAC considered a more appropriate methodology would be to apply trial-based equi-effective doses taking into account the mean dose administered to patients over the relevant treatment periods (12 months for romosozumab and 18 months for teriparatide). The economic evaluation should incorporate any costs associated with monitoring and managing the cardiovascular adverse events observed for romosozumab.
- 7.6 The PBAC considered the financial estimates for the 'later line' population were highly uncertain. The PBAC noted the approach to estimating the eligible population did not consider the pool of prevalent patients that may be appropriate for treatment with romosozumab which significantly underestimated the treated patient population.
- 7.7 The PBAC noted the net cost to the PBS/RPBS for the 'later line' population was high in the context of a cost-minimisation (less than \$10 million in Year 1, increasing to \$10 - \$20 million in Year 6). The high net cost was due to the additional growth in the use of anabolic agents that would occur with the availability of romosozumab. The PBAC considered the assumptions associated with the market growth and the uptake rates of romosozumab were poorly justified.
- 7.8 The PBAC noted that the financial estimates assumed that romosozumab would be used in patients other than those currently treated with teriparatide (i.e. due to the submission's assumptions around uptake due to market growth). The PBAC considered that it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently receive teriparatide.

The PBAC also considered there was a high potential for leakage into the broader first-line setting, where the cost-effectiveness of romosozumab was uncertain.

Analysis versus alendronate ('additional' population)

- 7.9 The PBAC considered alendronate was the appropriate comparator in this population but noted comparative evidence against denosumab would have been informative as it is the therapy most likely to be replaced in clinical practice for this patient population.
- 7.10 The PBAC considered the data presented supported a claim of superior efficacy compared to alendronate. The PBAC considered that 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. However, the PBAC considered 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.
- 7.11 The PBAC noted the submission did not specify a comparative safety claim for romosozumab compared to alendronate but considered it 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.
- 7.12 The PBAC noted an additional analysis of the ARCH, BRIDGE and FRAME trials was conducted to further investigate serious cardiovascular adverse events. The report concluded that a causal relationship between romosozumab and serious cardiovascular events could not be confirmed or refuted based on the available data.
- 7.13 For the cost-utility analysis versus alendronate, the PBAC noted the significant concerns regarding the economic model and agreed with the ESC that the economic model comparing romosozumab and alendronate 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.
- 7.14 The PBAC considered the financial estimates for the 'additional' population were highly uncertain. The PBAC considered the estimated total number of patients treated with romosozumab in the 'additional' population to be an underestimate with uptake in <1% of the treated osteoporosis population. The PBAC noted the approach to estimating the eligible population did not consider the pool of prevalent patients that may be appropriate for treatment with romosozumab which would significantly underestimate the treated patient population.

Overall comments

- 7.15 The PBAC considered there is a clinical need for additional options for the treatment of severe osteoporosis in later-line settings given the more limited alternative therapies available in this setting. The PBAC considered the risk of cardiac adverse events with romosozumab may be more manageable in a small population of patients with a higher level of fracture risk and more limited alternative treatment options.
- 7.16 The PBAC considered that any resubmission for romosozumab would need to be a major submission and should focus on the later-line population, should it be recommended by the TGA. The resubmission should address the following issues.
- The uncertainty with the clinical claim of non-inferior efficacy for romosozumab and teriparatide (to the extent possible). The PBAC considered that the economic analysis, including the use of trial-based equi-effective doses, should be based on conservative assumptions given the uncertainty in the clinical data.
 - The impact of the inferior safety profile for romosozumab versus teriparatide on the economic analysis. The analysis should include the costs associated with monitoring and managing the cardiovascular adverse events observed for romosozumab.
 - Revised financial estimates incorporating: prevalent patients to more appropriately identify the relevant treated patient population; and additional justification of the expected market growth should romosozumab be listed and uptake of romosozumab.
 - The risk of use outside the intended population. The PBAC considered that it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently receive teriparatide, and there is potential for leakage into the broader first-line setting.
 - Additional information regarding the self-administration of romosozumab and how this may impact on the effectiveness of the product.
 - Additional information to address the concerns regarding the use of on-going anti-resorptives after cessation of romosozumab.
 - A revised restriction criteria incorporating a 12 month treatment limit per lifetime, consistent with proposed TGA registration.
- 7.17 The PBAC noted that this submission is eligible for an Independent Review

Outcome:

Rejected

Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

Sponsor's Comment

Amgen is disappointed with this initial rejection but will continue to work with the PBAC to make romosozumab available on the PBS for osteoporosis patients at high risk of fracture. At the time the PBAC considered romosozumab, it was not registered anywhere in the world. As of July 2019, romosozumab has been approved for registration in the USA, Canada, Japan, South Korea and Australia.