7.10 ROMOSOZUMAB, 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.

1.2 Listing was requested on the basis of a cost-minimisation analysis versus teriparatide (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 ≤ -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
Comparator	Teriparatide, 20 mg daily subcutaneous injection for 18 months
Outcomes	Increased bone strength, prevention of osteoporosis-related fractures
Clinical claim	Romosozumab is similar (potentially superior) in terms of efficacy and potentially inferior in terms safety compared to teriparatide

Source: Table 1.1.1, p12 of the resubmission

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. An abridged version of the initial treatment restriction is presented, as the sponsor included the prescriber instructions in the clinical criteria. In its Pre-Sub-Committee Response (PSCR), the sponsor confirmed that the pre-filled syringe will be the only presentation available in Australia.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
ROMOSOZUMAB				Evenity Amgen
romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL syringes	1	5	$617.93 (published price)	
~~romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL injection devices~~	~~1~~	~~5~~		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	*Severe*
Condition:	*Established* osteoporosis
PBS Indication:	*Severe established osteoporosis*
Treatment phase:	Initial treatment
Restriction Level / Method:	☒Authority Required – Telephone/Electronic/Emergency
Treatment criteria:	Must be treated by a Specialist; OR Must be treated by a Consultant Physician.
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 ~~minimal trauma fractures~~ *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, 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.* ~~Patients who have received teriparatide are not eligible to receive PBS-subsidised romosozumab unless they have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.~~
Prescriber 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 romosozumab 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 romosozumab 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 Department of Human Services website at www.humanservices.gov.au.* *No increase in the maximum quantity or number of units may be authorised.* *No increase in maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
ROMOSOZUMAB				Evenity	Amgen
romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL syringes	1	5	$617.93 (published price)		
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Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	*Severe*
Condition:	*Established* osteoporosis
PBS Indication:	*Severe established osteoporosis*
Treatment phase:	Continuing treatment
Restriction Level / Method:	☒Authority Required – Telephone/Electronic/Emergency
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.*
Administrative Advice:	*No increase in the maximum quantity or number of units may be authorised.* *No increase in maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

2.2 The resubmission stated that teriparatide is currently subject to a special pricing arrangement (SPA) and noted that an 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.

2.3 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.

2.4 The resubmission proposed a lifetime limit of 12 months therapy with romosozumab, which was similar to the current listing for teriparatide, which is limited to 18 months. The PBAC previously considered a 12 month lifetime limit was appropriate given there are limited data on the use of romosozumab beyond 12 months (para 2.6, romosozumab PBAC minutes November 2018).

2.5 The PBAC considered that the due to safety concerns, the prescribing of romosozumab should be restricted to Consultant Physicians only.

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

3 Background

Registration status

3.1 TGA status at the time of PBAC consideration: Romosozumab was TGA registered on 1 July 2019 for:

- 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.

3.2 The PBAC noted that at the time of the evaluation the ACM considered romosozumab to have an overall positive benefit-risk profile but noted the cardiovascular safety concerns and were of the opinion that a long term cardiovascular safety study was necessary. The TGA delegate was of the opinion that romosozumab should be approved for registration, however it appears that the conduct of a cardiovascular study is dependent on registration in either Europe or the USA. The TGA delegate was reluctant to register romosozumab without a plan and firm commitment for active post market pharmacovigilance.

3.3 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 from 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.

3.4 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. Based on the product information, the FDA approval is for the syringe presentation of romosozumab which should be administered by a healthcare provider only.

3.5 The PBAC noted that a marketing application for romosozumab was submitted to the European Medicines Agency (EMA) for review. In June 2019, the EMA refused marketing authority for romosozumab due to concerns of an increased risk of serious effects on the heart or circulatory system, such as heart attacks or strokes.[1] In addition, the EMA reported that when all data were looked at together, there were more deaths in patients aged over 75 years given the medicine.[1]

Previous PBAC consideration

3.6 The outstanding matters of concern from the previous November 2018 PBAC meeting for severe osteoporosis (later-line therapy) are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

Matter of concern	How the resubmission addresses it
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 (November 2018 PBAC outcomes). The PBAC considered that any resubmission for romosozumab should focus on the later-line population, should it be recommended by the TGA (7.16 November 2018 PBAC minutes).	The resubmission requested a listing for the later-line population only. The resubmission was submitted to the PBAC under the TGA/PBAC parallel process.
The PBAC considered that a resubmission should include revised restriction criteria incorporating a 12 month treatment limit per lifetime, consistent with the proposed TGA registration (7.16 November 2018 PBAC minutes).	The restriction criteria in the resubmission was revised to include a 12 month lifetime limit of treatment with romosozumab.
The PBAC considered the clinical claim of non-inferior efficacy for romosozumab and teriparatide to be uncertain (7.3 November 2018 PBAC minutes) 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 (7.4 November 2018 PBAC minutes).	The resubmission described romosozumab as similar (potentially superior) in terms of efficacy and potentially inferior in terms of safety compared to teriparatide. No new data were presented in the resubmission in support of the clinical claim.

[1] Refusal of the marketing authorisation for Evenity (romosozumab). European Medicines Agency. 27 June 2019. Available at https://www.ema.europa.eu/en/medicines/human/summaries-opinion/evenity

Matter of concern	How the resubmission addresses it
The PBAC considered that a resubmission should include additional information regarding the self-administration of romosozumab and how this may impact on the effectiveness of the product (7.16 November 2018 PBAC minutes)	This was not addressed in the resubmission.
The PBAC considered that a resubmission should include additional information to address concerns regarding the use of ongoing anti-resorptives after cessation of romosozumab (7.16 November 2018 PBAC minutes)	The resubmission presented an analysis of anti-resorptive use after stopping teriparatide (as a proxy for anabolic agents) based on a 10% Medicare sample.
The PBAC considered that the economic analysis should be based on conservative assumptions given the uncertainty of the non-inferiority claim against teriparatide. The PBAC considered the use of trial-based equi-effective doses (compared to recommended dosage regimens) and the inclusion of costs associated with monitoring and managing cardiovascular adverse events observed with romosozumab would be more appropriate (7.16 November 2018 PBAC minutes).	The resubmission presented a cost-minimisation analysis using trial-based doses (with adjustments for compliance) with additional costs for anti-resorptive therapy, treatment and monitoring of cardiovascular adverse events.
The PBAC considered that a resubmission should include revised financial estimates incorporating: prevalent patients to more appropriately identify the relevant treated patient population; and additional justification of the expected market growth due to romosozumab and uptake of romosozumab (7.16 November 2018 PBAC minutes).	The resubmission provided adjustments to incident population estimates in order to approximate a prevalent population. There was no additional justification for the expected market growth due to romosozumab or uptake rates.
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 there was a high risk of use outside the intended population (in the broader first-line setting), where the cost-effectiveness of romosozumab was uncertain (7.8 and 7.16 November 2018 PBAC minutes).	The resubmission proposed a two-tiered utilisation cap with associated rebates on Government expenditure to address uncertainty in the uptake of romosozumab within the eligible population and the risk of use outside of the requested restriction.

Source: compiled during the evaluation

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 disability.

4.2 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 bone mineral density (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.

4.3 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 that teriparatide was an appropriate comparator for the 'later line' population (para 7.2, romosozumab PBAC minutes November 2018). The ESC considered the nominated comparator was appropriate.

5.2 The resubmission forecast an approximate [redacted]fold increase in the anabolic agent market with the introduction of romosozumab, with the majority of utilisation captured from patients not currently receiving teriparatide. As a consequence, anti-resorptives may also be a main comparator, with denosumab the most likely to be replaced in practice. The PBAC previously considered alendronate as an appropriate comparator for the broader population with severe osteoporosis, but noted comparative evidence against denosumab would have been informative (para 7.9, romosozumab PBAC minutes November 2018). The ESC considered that additional comparators would be informative.

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 an individual (1) via the Consumer Comments facility on the PBS website. The comment highlighted the physical, social and financial impact on the patient's quality of life of osteoporotic fractures.

6.3 The pre-PBAC response stated that the listing of romosozumab has support from the Osteoporosis Australia Medical and Scientific Committee and the Australian and New Zealand Bone and Mineral Society Therapeutic Committee, with letters of support provided for the November 2019 submission.

Clinical trials

6.4 The PBAC noted that there were no changes to the clinical evidence provided in the resubmission compared to the previous submission.

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 BMD 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 main comparisons and supportive analyses mentioned above were previously considered by the PBAC at the November 2018 meeting.

6.9 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, 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.

6.10 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 ongoing randomised controlled trial assessing the efficacy and safety of romosozumab when administered by a patient rather than a healthcare professional (NCT03432533). The expected completion date is July 2019.

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	Internal study report

Trial ID	Protocol title/ Publication title	Publication citation
	Concentration Compared With a 70 mg/mL Concentration in Postmenopausal Women With Osteoporosis	
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
	Ishibashi H et al (2017). Romosozumab increases bone mineral density in postmenopausal Japanese women with osteoporosis: A phase 2 study.	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.	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
VERO[a]	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.	Lancet 391:230-40
	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.	Journal of Bone and Mineral Research 33 (5):783-794

Source: Table 2.2-1, p25-26, Table 2.2-4, p28 of the resubmission

[a] The VERO trial was included during the evaluation

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
Romosozumab vs. teriparatide					
STRUCTURE	436	MC, R, OL, AC 12 months	Unclear	PMO with prior treatment	BMD
Romosozumab 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
Romosozumab 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
Teriparatide vs. placebo					
GHAC	1,637	MC, R, DB, PC Median 19 months[a]	Unclear	PMO with prevalent fracture	Fractures
ACTIVE	2,463	MC, R, PC, AC Aba vs Pbo: DB Teri: OL 18 months	Unclear	PMO	Fractures
Meta-analysis	2,724	Included vertebral fractures and non-vertebral fractures from the teriparatide 20mcg and placebo arms of the GHAC and ACTIVE trials			
Teriparatide vs. risedronate					
VERO	1,360	MC, R, AC, DB 24 months	Low	PMO with prevalent fracture	Fractures

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 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

6.13 Results based on BMD outcomes from the STRUCTURE trial suggest that 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 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, romosozumab PBAC minutes November 2018).

6.14 The indirect comparison of fracture outcomes with romosozumab versus teriparatide is summarised in Table 5.

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 70) 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

6.15 The indirect analyses suggest there were no statistically significant differences in fracture outcomes between romosozumab and teriparatide.

6.16 The resubmission also provided an additional 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.

6.17 The PBAC previously noted issues of exchangeability and applicability with the indirect analyses of fracture outcomes (para 7.3, romosozumab PBAC minutes November 2018). 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.

6.18 The resubmission did not nominate a non-inferiority margin. The ESC agreed with the evaluation that the lack of a statistically significant difference between treatments is

not 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.

6.19 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.

6.20 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.

Impact of prior anti-resorptive therapy

6.21 The PBAC previously noted a lack of comparative data in patients with prior anti-resorptive therapy (para 7.3, romosozumab PBAC minutes November 2018) as there were no data on fracture outcomes with romosozumab compared to teriparatide in patients who had received prior anti-resorptive treatment. No data to support the efficacy of romosozumab in patients with prior anti-resorptive therapy was provided in the resubmission.

Impact of subsequent anti-resorptive therapy

6.22 The PBAC previously noted a lack of comparative data on residual treatment effects with or without subsequent anti-resorptive therapy (para 7.3, romosozumab PBAC minutes November 2018).

6.23 No further clinical evidence was provided in the resubmission. The ESC noted that the limited available data from Study 326 suggested that treatment effects associated with romosozumab are rapidly lost after discontinuation of treatment. The ESC noted that the FRAME trial intervention was 1 year of romosozumab followed by 2 years of denosumab.

6.24 The product information for teriparatide includes data from a post-teriparatide follow-up study of patients from the GHAC parent trial (GHBJ study). During a median of 18 months following discontinuation of teriparatide, there was a 40% relative risk reduction for vertebral fractures in patients previously treated with teriparatide compared to placebo. The relative risk reduction was similar for women with and without post-teriparatide osteoporosis treatment, 41% and 37% respectively. During the same observation period, there was a 42% risk reduction for non-vertebral fractures in patients previously on teriparatide compared to placebo. The ESC noted

that the exploratory data suggest that treatment benefits associated with teriparatide were maintained regardless of follow-up osteoporosis treatment.

Comparative harms

6.25 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.

6.26 The most frequently reported adverse events in the romosozumab trials were musculoskeletal disorders (osteoarthritis, arthralgia, back pain, musculoskeletal pain, and pain in the extremity), infections (nasopharyngitis, upper respiratory tract infection), injury (falls), vascular disorders (hypertension), nervous system disorders (headache) and metabolism disorders (hypocalcaemia). Individual serious adverse events and adverse events leading to discontinuation were generally low in all treatment arms.

6.27 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 6 is a summary of serious cardiovascular events reported in the ARCH trial.

Table 6: 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 65) and Table 2.5-16 (p 66) of the resubmission

6.28 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.

6.29 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 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. The ESC considered that the cardiovascular safety signal remained a consideration for comparative safety analysis.

Benefits/harms

6.30 The resubmission described romosozumab as similar in terms of efficacy to teriparatide (see clinical claim below).

6.31 On the basis of direct evidence presented in the resubmission (ARCH trial, as outlined in Table 6), for every 1,000 patients treated with romosozumab in comparison to alendronate:

- Approximately 6 additional patients would have a serious cardiovascular event over one year (primary treatment);
- Approximately 4 additional patients would have a serious cardiovascular event over a median of 33 months (primary and subsequent treatment).

Clinical claim

6.32 There were no changes to the clinical evidence provided in the resubmission compared to the previous submission. The PBAC considered the previous claim of non-inferior efficacy was uncertain due to numerous issues with the comparison versus teriparatide including unknown clinical importance of BMD outcomes, exchangeability and applicability issues with the indirect comparison of fracture outcomes, lack of comparative data in patients with prior anti-resorptive therapy and lack of comparative data on residual efficacy with or without subsequent anti-resorptive therapy. The PBAC also considered that romosozumab was inferior in terms of safety

compared with teriparatide due to potential cardiovascular safety concerns (para 7.3 and 7.4, romosozumab PBAC minutes November 2018).

6.33 The resubmission described romosozumab as similar (potentially superior) in terms of efficacy compared to teriparatide.

6.34 The ESC noted that no new evidence was provided in the resubmission to support the clinical efficacy claim. Hence, the ESC considered that the clinical efficacy claim of similar (potentially superior) efficacy remained unsubstantiated.

6.35 The resubmission described romosozumab as potentially inferior in terms of safety compared to teriparatide due to cardiovascular safety signals observed with romosozumab. The ESC considered that this claim appeared reasonable based on available data.

6.36 As there were no changes to the clinical evidence provided in the resubmission compared to the previous submission, the PBAC reiterated its November 2018 consideration that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.37 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.38 The PBAC previously considered that the economic analysis should be based on conservative assumptions given the uncertainty with the clinical claim of non-inferior efficacy (para 7.16, romosozumab PBAC minutes November 2018).

6.39 The resubmission presented a cost-minimisation analysis of romosozumab versus teriparatide. The ESC questioned whether a cost-minimisation analysis was appropriate in view of the failure to demonstrate non-inferiority in efficacy and the likelihood of inferior safety for romosozumab versus teriparatide. The ESC agreed with the November 2018 PBAC recommendation that, in view of the limited clinical data, if such an analysis was used, conservative estimates would be required.

6.40 The ESC noted that key changes to the cost-minimisation analysis presented in the resubmission compared to the previous submission included the use of trial-based doses (with adjustments for adherence) with additional costs for anti-resorptive therapy, treatment and monitoring of cardiovascular adverse events. The ESC considered that the assumptions used to inform the key changes to the cost-minimisation analysis were not appropriately conservative in the context of the limited clinical data.

6.41 The equi-effective doses 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 = 15.66 scripts of teriparatide 20 mcg once daily over 504 days of therapy

6.42 The average number of scripts of romosozumab was based on the mean number of doses administered in the FRAME trial (10.8 doses over 12 months). The average number of scripts and days of therapy for teriparatide were based on adherence estimates from the GHAC (adherence rate of 79% to 83% over mean duration of 18 months; 3-year trial stopped prematurely) and ACTIVE (adherence rate greater than 90% over 18 months) trials, applied to the maximum PBS quantity for teriparatide (a weighted average adherence rate of 87% was assumed for teriparatide over a treatment duration of 504 days).

6.43 During the evaluation it was considered the equi-effective doses may not be reliable given concerns with the robustness of the indirect comparison between romosozumab and teriparatide. There were additional concerns with adherence estimates used in the resubmission due to: potential differences in administration between the FRAME trial and clinical practice (self-administration versus healthcare provider administration), uncertainty with adherence data from the GHAC trial that was stopped prematurely, potential risk of bias from the open-label ACTIVE trial; and not accounting for treatment persistence.

6.44 The resubmission provided a sensitivity analysis using the higher adherence estimate for teriparatide from the ACTIVE trial only. During the evaluation, alternative estimates from the GHAC trial were included in sensitivity analyses (see Table 8 below).

6.45 The resubmission did not provide sensitivity analyses using alternative adherence estimates for romosozumab. The average number of doses of romosozumab administered in the first 12 months of the ARCH trial was similar to the FRAME trial (10.8 doses).

6.46 There was some difference in the number of doses administered in the STRUCTURE trial of BMD outcomes for romosozumab versus teriparatide although the data were limited to the 12-month trial period. Alternative compliance estimates were calculated during the evaluation for romosozumab (11.1/12 x 100% = 93%) and teriparatide (302.6/365 x 100% = 83%). These estimates were included in sensitivity analyses during the evaluation (see Table 8 below). The PSCR argued that it was inappropriate to use adherence data from the STRUCTURE trial for the purposes of a cost-minimisation analysis as the trial demonstrated superiority for romosozumab compared with teriparatide. The ESC disagreed with the PSCR noting that in November 2018 the PBAC had considered that the clinical importance of the significant difference in BMD outcomes reported in the STRUCTURE trial was unclear (see paragraph 6.13).

6.47 The ESC considered that the trial-based equi-effective doses used in the cost-minimisation analysis base case were not conservative given the variation in the adherence estimates reported across included trials.

6.48 The resubmission estimated additional costs for cardiovascular event monitoring associated with romosozumab treatment ($[redacted] per 12 months of therapy) based

on MBS item costs for 2 blood tests, 2 electrocardiographs and 2 specialist visits. During the evaluation it was noted that the estimated costs appeared reasonable.

6.49 The resubmission also included estimated costs of $[redacted] due to an increased incidence of cardiovascular events associated with romosozumab based on public hospital costs of a myocardial infarction with or without a coronary procedure ($[redacted] using Australian Refined Diagnosis Related Groups codes and Round 20 public hospital costs for 2015-2016) and the incidence of serious cardiovascular events reported in the ARCH trial ([redacted]%). The resubmission did not consider ongoing costs associated with subsequent care following a cardiovascular event.

6.50 The resubmission included the cost of subsequent anti-resorptive therapy (after romosozumab) to account for the difference in days of therapy between romosozumab and teriparatide (i.e. 365 days of romosozumab and 504 days of teriparatide). The cost of 139 days of anti-resorptive therapy was included in the romosozumab arm based on estimated costs of denosumab, alendronate and risedronate and their utilisation on the PBS. The ESC noted that the limited data available suggested that after romosozumab, ongoing anti-resorptive therapy was required to maintain efficacy, but this was not the case for teriparatide (see paragraphs 6.23 and 6.24). The ESC noted it is unclear how long the duration of the anti-resorptive treatment should be, however, anti-resorptive therapy was continued for 24 months after romosozumab in the FRAME trial and in the ARCH trial it was continued until the end of the trial. The ESC considered that the estimated cost of subsequent anti-resorptive therapy after romosozumab was not conservative and that a longer duration of treatment would be required in practice.

6.51 No administration costs were initially included for either treatment. It may be appropriate to consider 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. The PSCR revised the cost-minimisation analysis to include an allowance for administration costs with romosozumab as the marketed presentation will be a pre-filled syringe. The PSCR argued that it was unreasonable for the most conservative cost assumptions to be applied as suggested in the evaluation (i.e. 10.8 visits x $[redacted] resulting in an administration cost of $[redacted]). Instead the PSCR proposed the analysis use a lower administration cost of $[redacted] per visit (31% by GP at $[redacted], MBS item 23 level B consultation; 69% by nurse at $[redacted], MBS item 82200 nurse practitioner attendance), which resulted in an administration cost of $[redacted] per patient. The PSCR claimed that the lower costs are conservative as the cost of two additional doctor visits are already included in the cost-minimisation analysis (for monitoring of cardiovascular events) and some patients will have administration at home. The ESC noted that self-administration of romosozumab at home is inconsistent with the FDA approved product information, which indicated the administration of romosozumab should be performed by a health care provider only, and that self-administration could impact

on adherence and efficacy. The ESC noted that MBS item 82200 is for nurse practitioners (not GP practice nurses) and is rarely used. 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. However, the ESC maintained the view that a conservative base case was appropriate given the lack of the clinical data supporting the clinical claim.

6.52 Drug costs were estimated using the published DPMQ for teriparatide on the PBS. The resubmission noted that the PBS listing of teriparatide is subject to a SPA and that romosozumab would also require an SPA. The resubmission did not propose an effective price but stated that the purpose of the cost-minimisation analysis was to propose a framework from which the cost-minimised price for romosozumab can be estimated once the effective price of teriparatide is known.

6.53 During the evaluation it was noted that the cost-minimisation analysis should have been conducted using ex-manufacturer prices due to differences in fees and mark-ups associated with the different total script numbers between treatments. The analysis was recalculated during the evaluation based on ex-manufacturer prices (Table 7). The PSCR argued that the resubmission correctly applied the DPMQ in the cost-minimisation analysis based on the Guidelines for preparing submissions to the PBAC, Version 5.0. The ESC noted that pricing agreements are made by Government under the National Health Act 1953 at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. The ESC considered that the inclusion of DPMQ in the cost-minimisation analysis was not conservative given the differences in total script numbers between treatments and therefore it supported the analysis based on ex-manufacturer prices.

Table 7: Results of the cost-minimisation analysis (based on ex-manufacturer prices)

	Cost
Teriparatide 20 mcg once daily	
Drug acquisition costs (DPMQ)	$ [redacted]
Drug acquisition costs (AEMP)	$ [redacted]
Scripts per 504 days of therapy	[redacted]
Cost of 504 days of therapy	$ [redacted]
Romosozumab 210 mcg once monthly	
Cost of 139 days of subsequent anti-resorptive therapy (DPMQ)	$ [redacted]
Cost of cardiovascular monitoring per 365 days of romosozumab therapy [b]	$ [redacted]
Cost cardiovascular event management per 365 days of romosozumab therapy [c]	$ [redacted]
Cost of romosozumab for cost-minimisation	$ [redacted]
Scripts per 365 days of therapy	[redacted]
Drug acquisition costs (AEMP)	$ [redacted]
Drug acquisition costs (DPMQ)[a]	$ [redacted]

Source: Table 3.4-1 (p 94) of the resubmission

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

[a] Wholesale mark-up $36.85; administration, handling and infrastructure mark-up $16.18; dispensing fee $7.29

[b] Assumed each patient would require 2 blood tests (MBS item 66500, $9.70), 2 electrocardiographs (MBS item 11700, $31.25) and 2 specialist visits (MBS item 115, $43.65) over 12 months of treatment.
[c] Assumed a 0.76% increase in the risk of serious (fatal or life-threatening) cardiovascular events (based on the ARCH trial) and a hospitalisation cost of $9,457 based on weighted AR-DRGs for myocardial infarction with or without a coronary procedure
[d] Values calculated during the evaluation

6.54 Based on the cost-minimisation analysis, the published DPMQ for romosozumab was calculated to be $[redacted] (the estimate in the resubmission was $[redacted] using dispensed prices rather than ex-manufacturer prices). The resubmission noted that the DPMQ for romosozumab in this analysis was for illustrative purposes only and the requested published DPMQ was $617.93. No justification was provided for the requested DPMQ that was higher than the DPMQ calculated from the cost-minimisation analysis.

6.55 Table 8 is a summary of sensitivity analyses conducted during the evaluation using alternative compliance/adherence rates and administration costs.

Table 8: Results of sensitivity analyses

	AEMP of romosozumab
Base case[a]	**$[redacted]**
Romosozumab adherence: 90%, teriparatide adherence: 90%; based on FRAME and ACTIVE trials	$[redacted]
Romosozumab adherence: 90%, teriparatide adherence: 83%; based on FRAME and GHAC trials	$[redacted]
Romosozumab adherence: 90%, teriparatide adherence: 79%; based on FRAME and GHAC trials	$[redacted]
Romosozumab adherence: 93%, teriparatide adherence: 83%; based on the STRUCTURE trial	$[redacted]
Romosozumab administration cost $406.08[b]	$[redacted]

Source: compiled during the evaluation based on 'Romosozumab cost minimisation workbook', Appendix 12 of the resubmission; Table 14-5.1.1 (p 221) of the STRUCTURE trial report
Abbreviation: AEMP, ex-manufacturer price
[a] Calculated during the evaluation using ex-manufacturer prices. Based on adherence rates of 90% for romosozumab and 87% for teriparatide and no administration costs for either treatment arm.
[b] Based on MBS item 23 (level B GP visit, $37.60) for 10.8 visits

6.56 The results were sensitive to adherence rates, which were associated with significant uncertainties, and the inclusion of administration costs for romosozumab (consistent with trial-based administration and adherence estimates).

6.57 The pre-PBAC response revised the cost-minimisation analysis to include increased cardiovascular adverse event management costs (from $[redacted] to $[redacted]) to account for long-term follow up costs and included administration costs of $[redacted] (10.8 administrations at $[redacted]) for romosozumab. The pre-PBAC response stated that the cost of administration has been increased to be midway between what was proposed in the PSCR (i.e. [redacted] administrations at $[redacted]) and the highest cost noted in the ESC advice (i.e. [redacted] administrations at $[redacted]). In addition, the revised cost-minimisation analysis assumed [redacted] teriparatide scripts per [redacted] days of therapy and undertook the analysis using drug costs at the ex-manufacturer level. Based on the revised cost-minimisation analysis, the pre-PBAC response stated the ex-manufacturer price for romosozumab was $[redacted].

6.58 The PBAC considered that conservative assumptions in the following key areas were important in providing a reliable cost-minimisation base case for romosozumab versus teriparatide: trial-based equi-effective doses (with appropriate conservative adjustments for adherence for romosozumab and teriparatide); the costs associated with monitoring for and treatment of cardiovascular events associated with romosozumab; the additional costs for anti-resorptive therapy following cessation of romosozumab; and the inclusion of administration costs for romosozumab. The PBAC considered that while the revised base case proposed in the pre-PBAC response addressed some of these key areas, concerns remained around the trial-based equi-effective doses, the additional costs for anti-resorptive therapy following cessation of romosozumab and administration costs.

Drug cost/patient

6.59 The drug cost per patient for romosozumab and teriparatide is summarised in Table 9.

Table 9: Drug cost per patient for romosozumab and teriparatide

	Romosozumab			Teriparatide			
	FRAME	**Economic analysis**	**Financial estimates**	**GHAC**	**ACTIVE**	**Economic analysis**	**Financial estimates**
Treatment regimen	210 mg/ month for 12 months	210 mg/ month for 12 months	210 mg/ month for 12 months	20 mcg/day planned for 3 years[a]	20 mcg/day for 18 months	20 mcg/day for 18 months	20 mcg/day for 1 year[b]
Mean duration of exposure	NR[c]	12 months	-	18 months	18 months	504 days[d]	-
Adherence	90%[e]	90%	90%	79-83%[f]	>90%[f]	87%[g]	90%[h]
Average number of scripts per course	10.8	10.8	10.8	14.58[i]	16.2[j]	15.66[k]	-
Average number of scripts per year	10.8	10.8	10.8	-	-	-	11.7[l]
Cost/patient/script	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Cost/patient/course	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	-
Cost/patient/year	$ [redacted]	$ [redacted]	$ [redacted]	-	-	-	$ [redacted]

Source: Table 12-1 (p 192) of the FRAME trial report; Miller et al 2016 publication; Neer et al 2001 publication; 'Romosozumab cost minimisation workbook', Appendix 12 of the resubmission; Romosozumab financial analysis workbook' Excel workbook, Appendix 13 of the resubmission

[a] Study was prematurely terminated after a median of 19 months treatment due to potential risk of osteosarcoma detected in animal studies
[b] The resubmission did not estimate cost offsets for teriparatide beyond 1 year of treatment
[c] Drug exposure was reported as cumulative number of doses received only
[d] Based on days of therapy covered by the maximum PBS quantity of 18 pens (28 doses)
[e] Based on mean number doses administered (10.8) and expected doses for 12 months of treatment in the FRAME trial
[f] Average adherence rate reported across all arms in the trial
[g] Weighted adherence rate based on the relative size of populations in the GHAC and ACTIVE trials
[h] Assumed to be the same as the adherence rate for romosozumab
[i] Based on the mid-point of the GHAC trial adherence rate (81%) and the maximum PBS script quantity (18)
[j] Based on an assumed adherence rate of 90% and the maximum PBS script quantity (18)
[k] Based on the weighted adherence rate from the GHAC and ACTIVE trials (87%) and the maximum PBS script quantity (18)
[l] Based on 90% adherence and 12 scripts per year
[m] Requested published DPMQ for romosozumab
[n] Results from the cost-minimisation analysis based on the published ex-manufacturer price for teriparatide
[o] Published DPMQ for teriparatide

Estimated PBS usage & financial implications

6.60 This resubmission was not considered by DUSC. The resubmission used a market share approach to estimate the utilisation and financial impact for romosozumab.

6.61 The PBAC previously considered that the financial estimates should incorporate prevalent patients to more appropriately identify the relevant treated patient population; and additional justification of the expected market growth due to romosozumab and uptake of romosozumab (para 7.16, romosozumab PBAC minutes November 2018).

6.62 Key changes in the resubmission include the use of a 10% Medicare sample analysis to identify patients who were on at least 12 months of active treatment, a downward adjustment to the proportion of patients who have BMD T-score of ≤ -3 to account for treatment effects and an upward adjustment to the fracture rate while on anti-resorptive therapy (as an adjustment to the incident population estimate in order to approximate a prevalent population). The estimated eligible population and budget impact is summarised in Table 10.

Table 10: 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
Anabolic agent market size estimates						
Existing market (15% uptake)	1266	1309	1353	1399	1447	1496
Market expansion due to romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net growth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated use of romosozumab						
Romosozumab uptake from existing market	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients on romosozumab from existing market	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional romosozumab patients from net growth (100% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated with romosozumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total romosozumab scripts (10.8 scripts/year)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS (DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Patient copayment	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost (less copay)	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Cost of teriparatide (DPMQ less copay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of anti-resorptives (DPMQ less copay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net PBS cost including cost offset (less copay)	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
MBS costs for CV monitoring ($144 per patient)[a]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to government	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: 'Romosozumab financial analysis workbook' Excel workbook, Appendix 13 of the resubmission
Abbreviations: BMD, bone mineral density; CV, cardiovascular; DPMQ, dispensed price maximum quantity
[a] MBS costs for CV monitoring include two of each of the following MBS items per patient: specialist visit (MBS item 105, 85% benefit), electrocardiogram (MBS 11700, 85% benefit) and blood test (MBS item 6650, 85% benefit).

6.63 At year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be $10-$20 million. The PBAC noted these costs were based on the

published price of the comparator, and corresponding price for romosozumab. The net cost to the PBS will reduce once the effective price of the comparator is flowed on to the romosozumab price.

6.64 The ESC considered that the size of the eligible population was highly uncertain due to concerns with the overall approach:

- 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 patients 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.

6.65 The resubmission did not provide further justification for romosozumab uptake rates (up to [redacted]% from existing market and [redacted]% from net growth market) and the forecast expansion of the anabolic agent market (approximate [redacted]fold expansion by Year 4 of listing). The resubmission reiterated that this was due to increased patient preference, lower treatment burden and increased promotional activity. The magnitude of market expansion appears substantial and remains unclear. The PBAC considered that due to differences in administration frequency between romosozumab and teriparatide substantial market expansion was plausible. However, the PBAC considered the utilisation estimates remained very uncertain.

6.66 The PBAC also considered that MBS costs for administration of romosozumab would also be incurred in addition to the MBS costs for monitoring of cardiovascular adverse events presented in Table 10.

Quality Use of Medicines

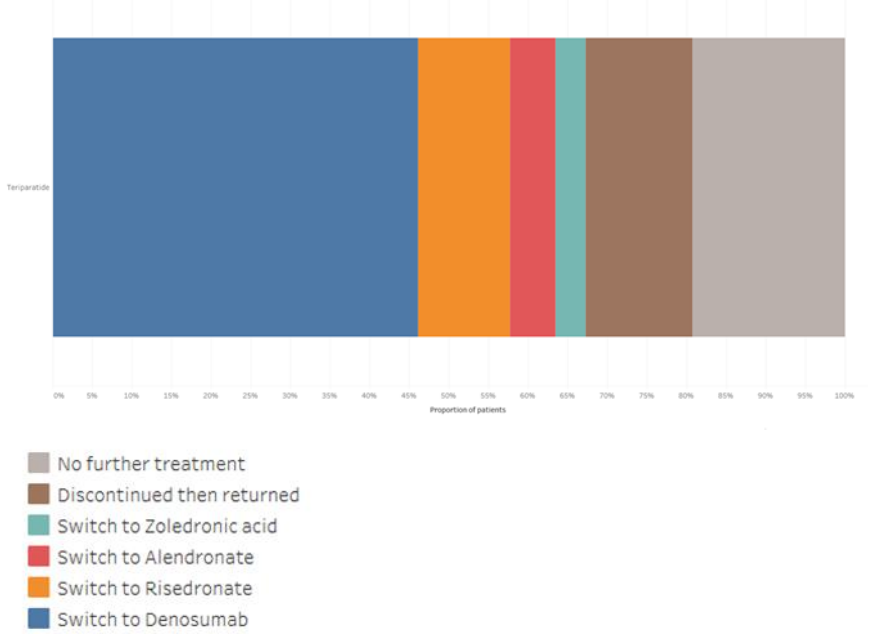
6.67 The PBAC requested additional information regarding the self-administration of romosozumab and how this may impact on the effectiveness of the product (paragraph 7.16, romosozumab PBAC minutes November 2018). The draft Australian product information suggests that romosozumab can be administered by a trained individual, however, the FDA approved product information for romosozumab (in the syringe presentation) suggests administration by a health care provider only. The updated proposed product information, provided as part of the PSCR, indicated that the romosozumab pre-filled syringe may be administered by anyone "adequately trained in injection techniques". The ESC noted that the PSCR did not comment on

how self-administration may impact on the effectiveness of the treatment. The PBAC considered that self-administration of subcutaneous injections is common with other conditions (e.g. rheumatoid arthritis) and considered the likelihood that a proportion of patients would self-administer romosozumab was high.

6.68 The resubmission acknowledged a potential identified risk of cardiovascular events associated with romosozumab but considered the overall risk-benefit profile to be favourable in patients with severe osteoporosis and that the risk may be minimised with the lifetime treatment limit of one year. The FDA approved product information contains a black boxed warning for cardiovascular events, recommending 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. The proposed product information for romosozumab states that the relative benefits and risks of treatment should be considered in patients at high cardiovascular risk and that treatment should be discontinued if a patient experiences a myocardial infarction or stroke during therapy.

6.69 The PBAC requested additional information to address concerns regarding the use of on-going anti-resorptives following cessation of romosozumab (para 7.16, romosozumab PBAC minutes November 2018). Based on the proposed product information, romosozumab has a recommended treatment duration of 12 months that must be followed-up with ongoing anti-resorptive therapy in order to retain treatment benefit. The resubmission claimed that this is also a concern for teriparatide and provided a 10% Medicare sample analysis to describe the use of anti-resorptives following treatment with teriparatide (Figure 1). The ESC considered that while the use of anti-resorptive therapy may occur frequently after treatment with teriparatide, unlike romosozumab, this therapy may not be necessary to prevent rapid loss of bone after withdrawal of treatment. The ESC also considered that the addition of anti-resorptive therapy following cessation of romosozumab treatment is important to the claim of similar comparative efficacy with teriparatide.

Figure 1: Treatment utilisation following teriparatide in 12 months to September 2018



Source: Figure 4.7-1, p103 of the resubmission

6.70 The analysis captured patients who filled a teriparatide script between 1 April 2017 and 31 March 2018. The allowed treatment gap was 6 months and 1 script was enough to transition a patient to another therapy. The definitions used appeared generous and may not adequately account for differences in duration of script coverage between treatments that can vary from 1 to 12 months. The resubmission assumed that 1 script of any treatment following teriparatide would sufficiently define treatment switching, which is likely to overestimate the number of patients who are on continuous anti-resorptive therapy following teriparatide treatment.

6.71 The resubmission claimed that approximately 19% of patients do not appear to transition to anti-resorptive treatment following cessation of treatment with teriparatide. A further 12% of patients appear to discontinue and then return to treatment. The results suggest a reasonable proportion of patients (approximately 30%) discontinue treatments for more than 6 months after stopping teriparatide. This proportion is likely to be higher should tighter definitions for treatment gaps be used for the analysis (e.g. higher number of scripts following cessation of teriparatide to determine ongoing anti-resorptive therapy).

6.72 The resubmission claimed that the inclusion of stronger recommendations for ongoing anti-resorptive therapy in the product information, a patient support program and greater marketing potential of the sponsor may result in improved use of anti-resorptives following romosozumab compared with teriparatide. No data were provided in support of this claim. The ESC considered that evidence of a comprehensive and robust quality use of medicines implementation strategy was

required to allay concerns regarding ensuring on-going use of anti-resorptive therapy following cessation of romosozumab.

Financial Management – Risk Sharing Arrangements

6.73 Table 11 presents utilisation caps proposed in the resubmission to address the uncertainty in the uptake of romosozumab in eligible patients and the risk of use outside the proposed restriction. The resubmission stated that the script numbers were for illustrative purposes only, and the final deed of agreement will have utilisation caps based on the net agreed price (with potential adjustments for time of listing).

Table 11: Proposed utilisation caps (script numbers) for the risk-share arrangement

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Tier 1 (% rebate)						
Tier 2 (% rebate)[a]						

Source: Table 4.6-2, p102 of the resubmission

[a] The resubmission assumed an additional % of patients from the eligible population are treated with romosozumab (approximately less than 10,000 additional patients in each year)

6.74 The resubmission proposed a two-tier rebate on Government expenditure based on utilisation caps (script numbers):

- An initial Tier 1 rebate of % on Government expenditure for utilisation above the base case; and
- A Tier 2 rebate of % on Government expenditure for utilisation exceeding estimates assuming an additional absolute % uptake for romosozumab from the estimated eligible patient population.

6.75 The nominated caps were highly uncertain as they were associated with significant uncertainties regarding the eligible population, and assumptions regarding the size of the anabolic agent market (plus romosozumab-driven growth) and uptake rates. The ESC considered that the nominated two tier rebate may not be an appropriate mechanism to address the uncertainties in the clinical data and utilisation estimates and advised that a hard cap may be a more reasonable way forward.

For more detail on 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 in patients who have experienced a prior fracture while on anti-resorptive therapy (later-line setting) due to concerns regarding the claim of comparative clinical effectiveness, the cardiovascular safety profile of the treatment and the uncertain size of the eligible patient population. The PBAC also considered the

estimated financial implications were unacceptably high for a cost-minimisation analysis given it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently use teriparatide.

7.2 The PBAC noted the consumer comment received for this item and recalled the support from professional organisations provided for the November 2018 romosozumab submission. The PBAC considered there is a clinical need for additional treatment options for severe osteoporosis in the later-line setting given there are limited alternative therapies available.

7.3 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 by the resubmission (i.e. an approximate [redacted]-fold increase in the market size with the introduction of romosozumab), a comparison with anti-resorptives is relevant.

7.4 The PBAC noted that there were no changes to the clinical evidence provided in the resubmission. The PBAC recalled its November 2018 advice that the claim of non-inferior efficacy was uncertain due to numerous issues with the comparison versus teriparatide. The issues included, but were not limited to, exchangeability and applicability concerns with the indirect comparison of fracture outcomes based on the FRAME, GHAC and ACTIVE trials. The PBAC noted the indirect analysis suggested there were no statistically significant differences in fracture outcomes between romosozumab and teriparatide. However, the PBAC noted the resubmission did not nominate a non-inferiority margin and agreed with the ESC that the level of certainty around the indirect estimate of effects was low given the wide confidence intervals for fracture outcomes.

7.5 In addition, the PBAC considered 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 available data suggest the treatment benefits associated with teriparatide were maintained regardless of follow-up osteoporosis treatment. The PBAC agreed with the ESC 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.

7.6 The PBAC considered that the claim of non-inferior comparative effectiveness remained inadequately justified given the issues with the indirect comparison versus teriparatide and the uncertainty in the benefits of romosozumab following cessation of treatment.

7.7 The PBAC noted that both the FDA and TGA have recently approved the registration of romosozumab with a requirement for active post-market surveillance of cardiovascular safety. However, the PBAC also noted that the EMA did not

recommend the marketing of the romosozumab due to concerns regarding the risk of serious cardiovascular events. The PBAC remained concerned regarding the cardiovascular safety signals observed with romosozumab and considered the claim of inferior comparative safety was reasonable.

7.8 The PBAC noted that the cost-minimisation analysis presented in the resubmission was based on the claims of non-inferior efficacy and the inferior safety for romosozumab versus teriparatide. The PBAC reiterated its November 2018 advice that a cost-minimisation analysis would only be appropriate with a conservative base case.

7.9 The PBAC noted that the sponsor provided updates to the cost-minimisation analysis in both the PSCR and Pre-PBAC response. The PBAC considered that the revised base case proposed in the pre-PBAC response addressed some of the key areas considered important in providing a reliable base case for romosozumab versus teriparatide. However, 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.

7.10 The PBAC noted that the proposed equi-effective doses were adjusted using trial-based adherence estimates for teriparatide, and agreed with ESC's concerns regarding the variation in the adherence estimates reported across included trials. The resubmission assumed a weighted average adherence rate of 87% for teriparatide over a treatment duration of 504 days based on the trial-based estimates, which was reduced to 85% in the pre-PBAC response. Given the administration method and frequency of administration required for teriparatide, the PBAC considered that adherence in clinical practice would be likely lower than reported in trials. The PBAC also considered that, given the potential option of self-administration in clinical practice, there is uncertainty in the adherence rates for romosozumab. As such, the PBAC agreed with the ESC that the trial-based equi-effective doses used in the cost-minimisation analysis base case were not conservative.

7.11 As outlined in paragraph 7.5, the PBAC considered that addition of anti-resorptive therapy following cessation of romosozumab treatment was important to the claim of similar comparative efficacy with teriparatide. The PBAC noted that anti-resorptive therapy was continued for 24 months after romosozumab in the FRAME trial and in the ARCH trial it was continued until the end of the trial. As such, the PBAC agreed with the ESC that the estimated cost of subsequent anti-resorptive therapy after romosozumab (139 days at $1.40 per day) was not conservative and that a longer duration of treatment would be required in practice.

7.12 The PBAC noted that the revised cost-minimisation analysis presented in the pre-PBAC response included an administration cost of $[redacted] ([redacted] administrations at $[redacted]) per course for romosozumab. The PBAC agreed with the ESC that in clinical practice there may be some administration of romosozumab by nurses but considered that the administration cost proposed may be underestimated.

7.13 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 restrictive proposed restriction. In addition, the PBAC considered that romosozumab uptake from the existing market may be higher than estimated in the resubmission. As such, the PBAC considered that the level of certainty about the size of the eligible population and utilisation estimates was low.

7.14 The PBAC noted that the net cost to the PBS 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 PBAC noted these costs were based on the published price of the comparator, and corresponding price for romosozumab. The PBAC noted that the net cost to the PBS will reduce once the effective price of the comparator is flowed on to the romosozumab price. However, the PBAC considered that the net cost to the government for romosozumab would also include the addition of MBS costs for administration and monitoring of cardiovascular adverse events.

7.15 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. The PBAC noted that [redacted]% of costs in Year 1 and [redacted]% in Year 6 were for additional romosozumab patients from net growth of the market. The PBAC reiterated its November 2018 advice that it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently use teriparatide. The PBAC considered that it would be appropriate for the sponsor to demonstrate the additional benefits that would be anticipated with such use to ensure cost-effectiveness.

7.16 The PBAC considered that a Risk Sharing Arrangement was required to address the uncertainty in the uptake of romosozumab in eligible patients and the risk of use outside the proposed restriction. However, as the certainty about the size of the eligible population and utilisation estimates was low the PBAC considered that the nominated two tier rebate caps were unlikely to be appropriate. The PBAC agreed with the ESC that a hard cap may be required to address the uncertainties in the clinical data and utilisation estimates.

7.17 The PBAC considered that, as outlined in paragraph 7.11, 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, the PBAC agreed with the ESC 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.

7.18 The PBAC advised that any resubmission for romosozumab would need to:

- address the uncertainty with the claim of non-inferior comparative effectiveness given the issues with the indirect comparison versus teriparatide, including the impact of the requirement for continued anti-resportive therapy following cessation of romosozumab;
- provide any additional information regarding the cardiovasular safety profile of romosozumab;
- address the remaining areas of concern for the cost-minimisation analysis for romosozumab versus teriparatide (see paragraph 7.9);
- address concerns regarding the cost-effectiveness of romosozumab use in a much broader population than teriparatide;
- provide revised financial estimates and include a Risk Sharing Arragement which addresses concerns regarding use in a larger population compared to teriparatide;
- 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.

7.19 The PBAC noted that this submission is eligible for an Independent Review

Outcome:
Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.