6.10 ROMOSOZUMAB
Injection 105 mg in 1.17 mL single use pre-filled syringe,
Evenity®,
AMGEN AUSTRALIA PTY LIMITED.

1 Purpose of submission

1.1 The Category 2 submission requested the PBAC consider its previous recommendation to list romosozumab as a General Schedule Authority Required (Telephone/Online) listing for the treatment of severe osteoporosis in the first-line setting.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus alendronate.

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

Component	Description
Population	Patients with severe osteoporosis who are at very high risk of fracture defined as those with a BMD T-score of ≤-2.5 and have either: a recent hip or symptomatic vertebral fracture, or multiple fractures (including 1 recent symptomatic fracture).
Intervention	Romosozumab 210 mg monthly subcutaneous injection for 12 months followed by ongoing anti-resorptive therapy.
Comparator	Alendronate 70 mg weekly oral tablet, ongoing.
Outcomes	Prevention of osteoporosis-related fractures that lead to reduced morbidity and mortality.
Clinical claim	In terms of fracture risk reduction, the efficacy achieved with romosozumab (12-month treatment course) followed by alendronate is superior to that achieved with alendronate alone. Romosozumab could have an inferior safety profile compared with alendronate due to the potential identified risk of CV events with romosozumab.

Source: Table 1, Romosozumab Public Summary Document, March 2023 PBAC meeting.
Blue highlighting represents values from the previous submission.
BMD = bone mineral density; CV = cardiovascular

2 Background

Registration status

2.1 Romosozumab was registered by the TGA on 21 June 2019 for the following indications:

- Treatment of osteoporosis in postmenopausal women at high risk of fracture.
- Treatment to increase bone mass in men with osteoporosis at high risk of fracture.

2.2 On 7 December 2023, the TGA provided a safety update regarding romosozumab treatment. The TGA noted its investigation into the risk of myocardial infarction and stroke in patients taking romosozumab found that stronger warnings regarding these risks were needed in the Product Information and Consumer Medicine Information. Romosozumab use is now also contraindicated in patients with a history of myocardial infarction or stroke. The Pre-Sub-Committee Response (PSCR) outlined that the update aligns the Australian Product Information with the European Summary of

Product Characteristics and stated that there has been no change in the cardiovascular benefit/risk profile of romosozumab nor upward trend in myocardial infarction or stroke identified since the marketing approval of romosozumab globally.

Previous PBAC consideration

2.3 The submission stated that the sponsor was unable to proceed with listing romosozumab in the first-line setting because the model assumptions and incremental cost-effectiveness ratio (ICER) recommended by the PBAC in March 2023 resulted in a price that was too low. The submission stated that the sponsor could accept all other aspects of the recommendation including the restriction and Risk Sharing Arrangement (RSA) with % rebates for expenditure above the caps.

2.4 The submission proposed an ex-manufacturer price (EMP) of $ in the first-line setting, which is 13% higher than the EMP required for the scenario advised by the PBAC in March 2023 (EMP of $).

2.5 The submission proposed an overall weighted EMP of $, as outlined in Paragraph 4.40 based on:

- 75% of use in the first-line setting (EMP of $); and
- 25% of use in the existing second-line setting (EMP of $).

2.6 The weighted price is unchanged from the previous submission, which also proposed a weighted price of $ across the first- and second-line settings. However, the previous submission applied the weighted price in the economic model (as it sought a line-agnostic listing with an expanded second-line population) while the current submission correctly applied the indication-specific price in the model.

2.7 To achieve an ICER of $35,000 to < $45,000per QALY (consistent with the ICER advised by the PBAC in March 2023) at the price proposed by the sponsor, the submission presented two revised economic model "scenarios" with the following assumptions:

- Scenario 1: the annual baseline fracture risk was increased from 5.02% (as in the ARCH trial) to 5.16%, and the model assumed that 50% of patients in the alendronate arm who experience a fracture would receive second-line romosozumab (versus 0% in the model submitted in March 2023); or
- Scenario 2: the annual baseline fracture risk was increased from 5.02% (as in the ARCH trial) to 5.40% (and no second-line romosozumab use assumed in the model).

2.8 Table 2 outlines the key changes versus the scenario recommended by the PBAC in March 2023.

Table 2: Changes in the submission versus scenario recommended by PBAC in March 2023

Component	Scenario recommended by PBAC in March 2023	Submission proposal
Population	The PBAC considered the clinical and cost-effectiveness evidence for romosozumab was adequate to support listing in the first-line setting but not an expansion to the current second-line listing. (Para 7.1, romosozumab PSD, March 23 PBAC meeting.)	As requested, the submission proposed listing in the first-line setting (i.e. removed the request for the expanded second-line setting).
ICER and price	The PBAC advised that romosozumab would be considered cost-effective in the first-line setting if the price of romosozumab was reduced such that the ICER was no higher than $[redacted][1] per QALY gained. The PBAC considered it would be reasonable for this ICER to be achieved through a reduction in the price of romosozumab for the first-line setting and/or the existing second-line setting (as was proposed in the resubmission)(Para 7.7, romosozumab PSD, March 23 PBAC meeting). <u>PBAC recommendation:</u> ICER recommended by PBAC: $[redacted][1] /QALY (versus $[redacted][2]/QALY in resubmission base case) EMP required for PBAC recommendation: $[redacted] <u>March 2023 resubmission</u> EMP proposed by sponsor: $[redacted] for line agnostic listing	EMP proposed in 1L: $[redacted] which would result in an ICER of $[redacted][2]/QALY using the base case recommended by the PBAC in March 2023. The submission proposed revised model inputs to achieve an ICER of $[redacted][1] /QALY.
Price	EMP proposed by sponsor: $[redacted] for line agnostic listing	1L EMP: $[redacted] Weighted price (EMP): $[redacted]
Economic model inputs	The PBAC accepted the scenario proposed in the resubmission … could be used to assess the cost-effectiveness of romosozumab in the first-line setting with an ICER no higher than $[redacted][1] per QALY gained (Para 7.7, romosozumab PSD, March 23 PBAC meeting).	The following changes were made to the economic model: - EMP in 1L $[redacted] - Updates to MBS costs, PBS dispensing fees and fracture costs <u>Scenario 1:</u> increase annual baseline fracture risk from 5.02% (as in the ARCH trial) to 5.16%; and 50% of patients in the alendronate arm who experience a fracture receive 2nd-line romosozumab. ICER $[redacted][1] /QALY <u>Scenario 2:</u> increase annual baseline fracture risk from 5.02% (as in the ARCH trial) to 5.40%. ICER $[redacted][1] /QALY.
Financial estimates	The PBAC advised that the second-line population should be removed from the financial estimates." "The PBAC considered that it was reasonable to accept the first-line population numbers presented as the maximum number of first-line patients to be treated per annum. (Para 7.9, romosozumab PSD, March 23 PBAC meeting).	As requested, the second-line population was removed from the financial estimates. The patient numbers in first-line were unchanged from the March 2023 resubmission. Minor updates were made to the financial estimates: the price of romosozumab was reduced to an EMP of $[redacted]; and the PBS costs for offsets (displaced anti-resorptives) were updated.

Component	Scenario recommended by PBAC in March 2023	Submission proposal
Weighted price		Weighted price: $[redacted] based on: - 75% of use in 1st-line (at $[redacted]) - 25% of use in 2nd-line (at $[redacted], which is the current price)
RSA	The PBAC noted that the sponsor proposed a [redacted]% rebate for any expenditure above the caps and considered this was appropriate. (paragraph 7.10, romosozumab PSD, March 2023 PBAC meeting).	As requested, a [redacted]% rebate for expenditure above the caps was proposed. Updated estimates of RSA expenditure caps were not provided.

Source: compiled during the evaluation
EMP = ex-manufacturer price; ICER = incremental cost-effectiveness ratio; PSD = Public Summary Document; QALY = quality adjusted life year*; RSA = Risk Sharing Agreement*
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$45,000 to < $55,000*

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The restriction recommended by the PBAC at the March 2023 meeting is outlined below (Section 8, romosozumab Public Summary Document (PSD), March 2023 PBAC meeting).

Add new item:

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ROMOSOZUMAB						
romosozumab, 105mg/1.17mL injection, 2 x 1.17mL syringes		NEW	1	2	5	Evenity
Restriction Summary new / Treatment of Concept: new						
Concept ID	**Category / Program:** GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
	Indication: Severe established osteoporosis					
	Treatment Phase: Initial treatment					
	Clinical criteria:					
	Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab					
	AND					

	Clinical criteria:
	Patient must be at a very high risk of fracture
	AND
	Clinical criteria:
	Patient must have a bone mineral density (BMD) T-score of -2.5 or less
	AND
	Clinical criteria:
	Patient must have had a symptomatic fracture due to minimal trauma
	AND
	Clinical criteria:
	Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months; or
	Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS subsidised therapy
	Treatment criteria:
	Must be treated by a consultant physician
	Prescribing Instructions: Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.
Restriction Summary New / Treatment of Concept: New	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
	Indication: Severe established osteoporosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy
	Treatment criteria:

	Must be treated by a medical practitioner identifying as either: (i) a Consultant Physician, (ii) a General Practitioner.
Restriction Summary [new] / Treatment of Concept [New]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
	Indication: Severe established osteoporosis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this PBS indication prior to [insert listing date],
	AND
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of the following prior to initiating non-PBS-subsidised treatment with this drug for this condition: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab,
	AND
	Clinical criteria:
	Patient must be at a very high risk of fracture,
	AND
	Clinical criteria:
	Patient must have had a bone mineral density (BMD) T-score of -2.5 or less prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must have had a symptomatic fracture due to minimal trauma prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must have had at least 1 hip or symptomatic vertebral fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition, OR
	Patient must have had at least 2 fractures including 1 symptomatic new fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition,
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy,
	Treatment criteria:
	Must be treated by a consultant physician
	Prescribing Instructions: Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application.

	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted and welcomed the input from an individual, a health care professional and from an organisation via the Consumer Comments facility on the PBS website. The comments emphasised the efficacy of romosozumab in the first-line setting in terms of improving outcomes and preventing fractures. The comments also described the unmet need in the first-line setting and the benefits of romosozumab as a first-line treatment, rather than after anti-resorptive therapy. One comment outlined that fewer fractures would mean greater independence and less need for assistance from family members or carers.

4.3 The PBAC noted the advice received from Healthy Bones Australia which outlined the need for treatment options with both an anabolic and anti-resorptive effect, the efficacy in terms of fracture reduction and the advantages of romosozumab in terms of being administered monthly for 12 months (while teriparatide requires a daily injection over 18 months). Healthy Bones Australia also outlined that, while romosozumab is contraindicated in patients with a history of myocardial infarction or stroke, prescribers are aware of this risk and are careful with patient selection. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical claim

4.4 At its March 2023 meeting, the PBAC noted that the comparative effectiveness evidence presented was unchanged from the July 2022 resubmission. Hence, the resubmission was based on a direct comparison of romosozumab versus alendronate in the ARCH trial which was conducted in patients predominantly naïve to anti-

resorptive therapy. The PBAC noted that treatment with romosozumab versus alendronate was associated with statistically significant decreases in vertebral fractures, clinical fractures and non-vertebral fractures over a median of 33 months compared to alendronate alone. In March 2023, the PBAC reiterated its July 2022 advice that the claim of superior comparative effectiveness was reasonable for the first-line setting in treatment naïve patients, however the magnitude of effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab (para 7.4, romosozumab PSD, March 2023 PBAC meeting).

4.5 The PBAC reiterated its March 2023 advice that the claim of superior comparative effectiveness was reasonable in the first-line setting, however the magnitude of effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab.

4.6 The PBAC reiterated its March 2023 advice that the claim of inferior comparative safety was reasonable (para 7.6, romosozumab PSD, March 2023 PBAC meeting).

Economic analysis

4.7 The submission presented a cost-utility analysis of romosozumab versus alendronate in patients with severe osteoporosis. Compared with the inputs that the PBAC advised would be reasonable in its March 2023 consideration, the submission proposed changes to two parameters: baseline fracture risk; and the proportion of patients in the alendronate arm who are assumed to use romosozumab in the second-line setting.

Baseline fracture risk:

4.8 In the previous economic model (March 2023), the baseline fracture risk (annual risk of a clinical fracture) was 5.02% per year, based on the alendronate arm of the ARCH trial. The submission claimed that the PBS restriction defines a population with a higher average fracture risk than the ARCH trial population, as outlined in Table 3.

Table 3: Comparison of the proposed PBS population versus the patients enrolled in the ARCH trial

PBS criteria	ARCH	
	Eligibility criteria	Enrolled population
No gender restriction	Postmenopausal woman	0% of patients were men
BMD T-score ≤ -2.5	BMD T-score ≤ -2.5 or > -2 depending on fracture number and severity	31% of patients had BMD > -2.5
At least one symptomatic/clinical fracture	No requirement for symptomatic/clinical fracture	33% of patients had a morphometric fracture(s) only
Symptomatic fracture in last 24 months	No requirement on timing of fracture unless other BMD/fracture entry criteria not met [a]	37% of patients had their most recent fracture > 24 months prior
Mix of patients with a single hip or clinical vertebral fracture or multiple fractures	Mix of patients with single or multiple fractures [b]	Mix of patients with single or multiple fractures

Source: Table 1 of the submission
BMD = bone mineral density
[a] Fracture of the proximal femur that occurred within 3 to 24 months prior to randomisation required for BMD > - 2.5 patients with a history of < 2 fractures.

[b.] Entry criteria: BMD T-score ≤ -2.5 at the total hip or femoral neck AND EITHER at least one moderate (SQ2) or severe (SQ3) vertebral fracture OR at least 2 mild (SQ1) vertebral fractures; BMD T-score ≤ -2.0 at the total hip or femoral neck AND EITHER at least 2 moderate (SQ2) or severe (SQ3) vertebral fractures OR a fracture of the proximal femur that occurred within 3 to 24 months prior to randomisation

4.9 The submission discussed key differences between the two populations that may affect baseline fracture risk.

- Gender. The submission argued that the ARCH trial excluded male patients, who have a higher fracture risk than females of the same age, fracture history and bone mineral density (BMD). The submission presented results from the Garvan Fracture Risk Calculator which demonstrated that, based on a 74 year old with a BMD of -2.9, a male would have a 3.7% to 35.1% relative increase in fracture risk compared with a female (depending on number of prior falls). The submission stated that application of an increase in the midpoint of this range to the ARCH trial average would lead to an annual fracture risk of 5.99% [1] and, accounting for only 20% of the PBS population being male, this would result in an annual risk of 5.21% across the whole PBS population.
- BMD. In the ARCH trial, 31% of patients had a BMD T-score > -2.5 whereas the proposed PBS restriction requires patients to have a BMD T-score ≤ -2.5. The submission argued that, based on the Garvan Fracture Risk Calculator, a 74 year old female with a BMD T-score of -3.1 instead of -2.9 (the average in ARCH), would have a relative increase in fracture risk of 5.7% to 8.7%. Application of an increase in the midpoint of this range to the ARCH trial average would lead to an annual fracture risk of 5.38%.[2]
- Fracture severity. The proposed PBS restriction requires patients to have a clinical fracture whereas one-third of the ARCH trial population had only morphometric fracture(s).
- Recency of fracture. The proposed PBS restriction requires patients to have had a symptomatic fracture in the last 24 months whereas 37% of the ARCH trial population had experienced their most recent fracture more than 2 years ago. The submission argued that the relative risk of a second fracture is highest within the first 2 years after the index fracture, and 40% to 60% of all recurrent fractures will occur within those 2 years (Kanis et al., 2018).

4.10 The submission proposed a baseline fracture risk of either 5.16% and 5.40% per annum (rather than 5.02% from the ARCH trial, as applied in the previous submission) and stated these were likely to be conservative. The PSCR also noted the average baseline risk applied in the two new scenarios was only marginally higher than the March 2023 base case. The ESC noted the values were in line with the increase in fracture risk associated with including males and those with a lower BMD T-score (5.21% and 5.38%, respectively as outlined in Paragraph 4.9), but considered that it

[1] Based on: 5.02% x 1.194. The value 1.194 was based on 19.4% higher risk, which is the midpoint of 3.7% to 35.1%.
[2] Based on: 5.02% x 1.071. The value 1.071 was based on a 7.1% increase, which was the midpoint of 5.7% to 8.7%.

was unclear why the specific values of 5.16% and 5.40% were selected. The ESC considered that while it was plausible for the baseline fracture risk to be higher than 5.02%, the precise baseline fracture risk in the proposed PBS population was unknown.

4.11 The submission applied the relative treatment efficacy from the ARCH trial; however the evaluation considered that it was unclear if the relative efficacy of romosozumab versus alendronate would be the same in a higher risk population. The application of the same relative efficacy to the higher underlying fracture risk population resulted in larger reductions in absolute fracture risk in the PBS population compared to the trial population. The PSCR stated that subgroup analyses from the ARCH trial demonstrated a consistent treatment effect across subgroups that included higher versus lower risk populations. Thus, the PSCR argued that it was reasonable to apply the same relative treatment effect to a higher risk population.

Second-line romosozumab use

4.12 The previous economic model (March 2023) did not include the impact (cost or efficacy) of the use of second-line romosozumab or teriparatide (anabolic agents) in the comparator arm, despite such use being permitted in clinical practice in those patients who meet the other eligibility criteria for the existing second-line listing.

4.13 The submission acknowledged that the extent of use and the clinical outcomes associated with anabolic treatment in this setting was uncertain. Thus, the submission applied the same romosozumab treatment effect in the second-line setting for the comparator arm as was applied in the first-line setting for the intervention arm. The submission and the PSCR argued this was conservative as romosozumab is likely to be less effective in the second-line setting. The submission quoted the commentary from the PBAC's March 2023 consideration, which stated "recently published results from post-hoc analyses of BMD outcomes in romosozumab trials suggest the relative efficacy of romosozumab used after anti-resorptives is smaller than when romosozumab is used before anti-resorptives" (7.05.COM.91).

4.14 However, the analysis also assumed that patients treated with second-line romosozumab would have the same baseline fracture risks as estimated for first-line use of romosozumab, which may not be conservative given the second-line population are older with multiple fractures compared to the first-line population, some of whom were treated after a single fracture. Thus, the absolute fracture reductions associated with the second-line romosozumab in this specific setting is difficult to quantify.

4.15 The submission assumed that 50% of patients who experience a fracture while treated with alendronate would receive an anabolic agent in the second-line setting. The submission claimed this was likely to be an underestimate. However, the evaluation and the ESC considered it was unclear if this was an underestimate as the proportion of patients who would meet the eligibility criteria for second-line romosozumab is unknown as it is dependent on patient characteristics (BMD and multiple fractures) which is not captured in the model.

4.16 This had been included as a sensitivity analysis in the submission considered by the PBAC in July 2022 and the Public Summary Document (PSD) stated "The impact of second line use of romosozumab under the existing listing could not be adequately assessed due to lack of data informing the proportion of patients who would progress to second line romosozumab, underlying fracture risk and fracture outcomes associated with romosozumab in patients previously treated with anti-resorptive therapy" (paragraph 6.85, romosozumab PSD, July 2022 PBAC meeting). While the submission argued that the relative treatment efficacy that was applied was likely conservative, the overall impact was difficult to quantify given the lack of data informing: the proportion of patients who would progress to second line romosozumab: and the underlying fracture risk of this specific population.

4.17 Overall, the submission stated that the economic model estimated that 12% of patients in the alendronate arm would receive 2nd-line romosozumab (after considering the annual fracture rate, along with the rate of discontinuation and death).

Model results

4.18 The results of each step of the changes to the economic model are presented in Table 4.

Table 4: Revised modelled analyses

Analysis	ICER per QALY
March 2023 recommended base case with EMP proposed at that time ($[redacted])	[redacted][1]
Changes made in March 2024 submission	
Revised 1st-line effective price (EMP: $[redacted])	[redacted][2]
Updated unit costs and revised 1st-line effective price	[redacted][2]
Proposed base case options	
Scenario 1:	
a. Increase baseline fracture risk from 5.02% to 5.16% per annum	[redacted][2]
b. 50% of patients who fracture in the alendronate arm receive 2nd-line romosozumab	[redacted][2]
Both a and b	[redacted][2]
Scenario 2:	
Increase baseline fracture risk from 5.02% to 5.40% per annum	[redacted][2]
March 2023 PBAC recommendation	
March 2023 recommended base case (EMP of $[redacted])	[redacted][2]

Source: Table 4, p5 of the submission

Blue highlighting represents values from the previous submission.

During evaluation, minor discrepancies were noted between the updated PBS and MBS costs applied in the economic model, versus those that applied at the time of evaluation (likely due to changes in dispensing fees and indexation from when the submission was prepared). The differences were minor and increased the ICER by around $0 to < $5,000/QALY in most scenarios.

The redacted values correspond to the following ranges

[1] *$45,000 to < $55,000*

[2] *$35,000 to < $45,000*

4.19 Results of the economic evaluation, including the cumulative costs and QALYs in each arm, are outlined in Table 5.

Table 5: Results of the economic evaluation

Step and component	Romosozumab/alendronate	Alendronate/alendronate	Increment
Romosozumab (EMP $[redacted])			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	7.7083	7.6752	0.0331
March 2023 base case: Incremental cost/QALY gained			**$[redacted][1]**
Revised March 2024 model (EMP $[redacted])			
Scenario 1 Increase baseline fracture risk from 5.02% to 5.16% per annum AND 50% of patients who fracture in the alendronate arm receive 2nd-line romosozumab			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	7.6997	7.6671	0.0325
Incremental cost/QALY gained (submission base case)			**$[redacted][2]**
Scenario 2 Increase baseline fracture risk from 5.02% to 5.40% per annum			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	7.6859	7.6504	0.0354
Incremental cost/QALY gained (submission base case)			**$[redacted]2**

Source: Constructed during evaluation using 'Evenity_CEA_PBAC_Nov23.xlsx'
Blue highlighting represents values from the previous submission.
EMP = ex-manufacturer price; QALY = quality adjusted life year
The redacted values correspond to the following ranges
[1] *$45,000 to < $55,000*
[2] *$35,000 to < $45,000*

4.20 In the two scenarios proposed in the submission, the ICER would be $35,000 to < $45,000 per QALY, consistent with the ICER requested by the PBAC in March 2023.

4.21 While the March 2023 model may have applied potentially conservative assumptions around baseline fracture risk and the use of romosozumab in the second-line setting, this was in the context of a model that included other assumptions that were likely non-conservative (e.g. assumptions around treatment adherence and persistence, and the extrapolation of treatment effect). Further, the evaluation and the ESC considered that the magnitude of any changes to these two parameters was difficult to quantify. The ESC considered that, while changes to these two parameters may be plausible, there was insufficient information available to determine the precise baseline fracture risk in the proposed PBS population and the precise proportion of patients in the alendronate arm who would receive an anabolic agent in the second-line setting (along with the magnitude of efficacy in the second-line setting in this population). The ESC noted that the values appeared to have been selected in order to achieve an ICER of $35,000 to < $45,000/QALY, consistent with the March 2023 PBAC Minutes, rather than on the basis of any clear clinical rationale. The pre-PBAC response confirmed that the rationale for selecting the revised input values was to achieve an ICER of $35,000 to < $45,000/QALY, and acknowledged the magnitude of any changes to these two parameters was difficult to quantify but argued that the proposed increases to the baseline fracture risk were relatively small (2.8-7.6%) compared with the 5.02% fracture risk in the ARCH trial.

4.22 The ESC noted that, in order for the ICER to be less than $35,000 to < $45,000/QALY, the PBAC would need to consider that it is plausible for the proposed PBS population

to have a baseline fracture risk that is at least 4% higher than the ARCH trial population i.e. a baseline fracture risk of 5.22% rather than 5.02%, or a 0.20% percentage point increase (with no changes to the proportion of patients in the alendronate arm who would receive an anabolic agent in the second-line setting).

Drug cost/patient/year

Table 6: Drug cost per patient for romosozumab

	ARCH trial	Economic model	Financial estimates
Treatment adherence	Not reported [a]	90%[b]	90% [b]
Treatment persistence	Not reported; approximately 90% of patients remained in the study at 1 year	80%[c]	Not included
Romosozumab doses/scripts	Mean 10.8 doses over 1 year	8.64 doses in Year 1[d]	10.8 scripts over a year [e]
Follow-up alendronate	Not reported	11.7 scripts per year in patients remaining on treatment in subsequent years[f]	Not included
Romosozumab drug cost per patient	-	$ in Year 1 [g] March 2023: $	$ over a year [h] March 2023: $
Follow-up alendronate drug cost per patient	-	$ per year in patients remaining on treatment in subsequent years [i]	Not included

Source: Table 12, romosozumab PSD, March 2023 PBAC meeting, updated during evaluation
Blue highlighting represents values from the previous submission.
[a] Drug exposure data (i.e. reported as mean doses administered) did not differentiate between adherence and persistence
[b] Calculated using drug exposure data from the ARCH trial, mean 10.8 doses divided by expected number of doses at full adherence and persistence (12 doses)
[c] Assumption based on PBAC advice
[d] Assuming 90% adherence and 80% persistence, applied to 12 doses
[e] Assuming 90% adherence, applied to 12 doses
[f] Assuming 90% adherence, applied to 13 doses
[g] $ (proposed effective DPMQ) x 8.64 scripts
[h] $ (proposed effective DPMQ) x 10.8 scripts/year
[i] $ x 11.7 scripts/year

Estimated PBS usage & financial implications

4.23 This submission was not considered by DUSC.

4.24 Compared with the March 2023 resubmission, the only changes to the financial estimates were: the price of romosozumab was reduced to an EMP of $ (from $); the proposed expanded second-line population was removed; and the PBS costs for offsets (displaced anti-resorptives) were updated (based on the prices at the time the submission was prepared). These changes were appropriate as the PBAC previously considered that it was reasonable to accept the first-line population numbers presented as the maximum number of first-line patients to be treated per annum (paragraph 7.9, romosozumab PSD, March 2023 PBAC meeting).

4.25 Table 7 presents the estimated use and financial impact to the PBS/RPBS of listing romosozumab in the proposed first-line setting.

Table 7: Estimated use and financial implications (first-line setting)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated osteoporosis patients	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]
First-line population						
Initiate osteoporosis therapy (19.8%)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]
Patients with prior fracture (75%)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
BMD ≤-2.5 (32.5%)	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]
Multiple clinical fractures or single hip/clinical vertebral fracture (57%)	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Uptake	16.50%	25.90%	34.70%	40%	40%	40%
Patients initiating romosozumab	[redacted][11]	[redacted][12]	[redacted][12]	[redacted][13]	[redacted][13]	[redacted][13]
Grandfather patients [b]	[redacted][14]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients initiating romosozumab	[redacted][11]	[redacted][12]	[redacted][12]	[redacted][13]	[redacted][13]	[redacted][13]
Total scripts (10.8 scripts/year)	[redacted][7]	[redacted][15]	[redacted][16]	[redacted][17]	[redacted][17]	[redacted][17]
Estimated financial implications						
PBS/RPBS cost of romosozumab	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][20]	[redacted][20]	[redacted][20]
PBS/RPBS cost offsets from displaced anti-resorptives	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]
Net PBS/RPBS cost	[redacted][18]	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][19]
Total MBS costs [a]	[redacted][18]	[redacted][18]	[redacted][18]	[redacted][18]	[redacted][18]	[redacted][18]
Net cost to PBS/RPBS/MBS	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][20]
March 2023 resubmission – 1st line population only at EMP proposed by sponsor of $[redacted]						
PBS/RPBS cost of romosozumab	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][20]	[redacted][20]	[redacted][20]
PBS/RPBS cost offsets	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]
Net PBS/RPBS cost	[redacted][18]	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][19]
March 2023 resubmission – 1st line population only at EMP per PBAC advice of $[redacted]						
PBS/RPBS cost of romosozumab	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][20]
PBS/RPBS cost offsets (updated)	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]	[redacted][21]
Net PBS/RPBS cost	[redacted][18]	[redacted][18]	[redacted][19]	[redacted][19]	[redacted][19]	[redacted][19]

Source: Table 15, romosozumab Public Summary Document, March 2023 PBAC meeting; Table 5, p6 of the submission.
Blue highlighting represents values from the previous submission.
BMD = bone mineral density; Blue highlighting represents values from the previous submission.
Note: The estimates were not updated to include further changes to PBS fees and mark-ups (subsequent to the fees in place at the time the submission was prepared) and updated MBS fees.
[a] Includes additional costs due to increased specialist visits, electrocardiography and blood tests over 1 year of romosozumab treatment
[b] In March 2023, the PBAC "noted that grandfathered patients were assumed to meet the proposed PBS eligibility criteria as first-line patients and considered their inclusion in the estimates as additional patients appropriate" (Para 7.9, romosozumab Public Summary Document, March 2023 PBAC meeting). In the financial estimates, grandfathered patients were assumed to receive 6 months of treatment at 90% adherence (i.e. 5.4 scripts per grandfathered patient).
The redacted values correspond to the following ranges:
[1] *700,000 to < 800,000*
[2] *800,000 to < 900,000*
[3] *900,000 to < 1,000,000*
[4] *1,000,000 to < 2,000,000*
[5] *100,000 to < 200,000*
[6] *200,000 to < 300,000*
[7] *30,000 to < 40,000*
[8] *40,000 to < 50,000*
[9] *50,000 to < 60,000*
[10] *20,000 to < 30,000*
[11] *500 to < 5,000*
[12] *5,000 to < 10,000*
[13] *10,000 to < 20,000*
[14] *<500*
[15] *60,000 to < 70,000*
[16] *90,000 to < 100,000*
[17] *100,000 to < 200,000*

[18] $0 to <$10 million
[19] $10 million to <$20 million
[20] 20 million to <$30 million
[21] net cost saving

4.26 The cost to the PBS/RPBS of the proposed first-line listing of romosozumab was estimated to be $20 million to < $30 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing (excluding offsets). The net cost to the PBS/RPBS and MBS, including PBS/RPBS offsets for reduced use of anti-resorptives, was estimated to be $20 million to < $30 million in Year 6 and $90 million to < $100 million in the first 6 years of listing.

4.27 At the EMP advised by the PBAC in March 2023 (i.e. EMP of $[redacted]), the submission estimated that the cost to the PBS/RPBS would be $80 million to < $90 million over 6 years (excluding PBS offsets). As such, the total cost to the PBS/RPBS was estimated to be $10 million to < $20 million higher in the submission (with an EMP of $[redacted]) compared with the scenario advised by the PBAC in March 2023.

4.28 The submission did not update the financial estimates for an additional year of population growth (i.e. Year 1 in the submission's financial estimates was based on population projections for 2023 and was not updated to account for an additional year of population growth, noting an annual growth rate of 6.9% was applied in other years, which was based on a 10% PBS sample analysis of patients receiving osteoporosis treatments). However, this was likely conservative in the context of estimating financial expenditure caps for the RSA.

Financial Management – Risk Sharing Arrangements

4.29 In March 2023, the PBAC considered that a RSA was appropriate to mitigate any residual uncertainties regarding the size of the eligible first-line population and any remaining concerns regarding the cost-effectiveness of romosozumab use in the first-line setting. The PBAC considered that the overall financial caps proposed in the pre-PBAC response would need to be adjusted for the removal of the second-line expanded listing population from the resubmission financial estimates and for the price reduction [to achieve the ICER advised by the PBAC]. The PBAC noted that the sponsor proposed a [redacted]% rebate for any expenditure above the caps and considered this was appropriate (paragraph 7.10, romosozumab PSD, March 2023 PBAC meeting).

4.30 The submission stated the sponsor can accept all other aspects of the recommendation including the restriction and risk sharing arrangement (caps + [redacted]% rebate).

4.31 Updated estimates of the financial caps for the RSA were not provided in the submission. The previous submission proposed a combined financial cap across the first- and second-line settings based on the sum of the existing second-line caps plus the financial estimates for the additional populations. This approach was re-iterated by the PSCR and pre-PBAC response, which stated "Our caps proposal, as effectively agreed by PBAC in March 2023, remains the sum of the established second-line caps

plus the financial estimates for the first-line listing". Table 8 outlines the expenditure caps based on that method. Per the March 2023 resubmission, an adjustment to the contribution from the current second-line caps was made in acknowledgement that initial romosozumab uptake under the current listing has been slower than anticipated (Year 2 caps for April 2022 – March 2023 have been shifted to 2024 for the proposed new overall caps).

Table 8: Overall financial caps based on method used in March 2023 resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5
Current caps with time shift adjustment	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Commonwealth payment for expanded listing [b]	[redacted]1	[redacted]2	[redacted]2	[redacted]3	[redacted]3
New overall caps	[redacted]2	[redacted]2	[redacted]3	[redacted]3	[redacted]3
March 2023 resubmission Proposed new overall caps	[redacted]2	[redacted]2	[redacted]3	[redacted]4	[redacted]4

Source: Compiled during evaluation based on Table 17, romosozumab PSD, March 2023 PBAC meeting
Note: Caps are based on calendar years and, if the submission is recommended, would require adjustment depending on the actual listing date.
Blue highlighting represents values from the previous submission.
[a] Additional year forecast based on immediately prior year-on-year growth.
[b] Based on the submission's estimates, refer to Table 7.
The redacted values correspond to the following ranges:
[1] $0 to <$10 million
[2] $10 million to <$20 million
[3] 20 million to <$30 million
[4] 30 million to <$40 million

Utilisation in the second-line setting

4.32 As outlined in Table 9, expenditure in the existing second-line setting has been lower than estimated.

Table 9: Current RSA for romosozumab in severe established osteoporosis (deed started 1st April 2021)

Romosozumab	Cap Threshold ($)	Total Commonwealth Payment (%)	% of Cap Reached
1 Year	[redacted]	[redacted]	[redacted]
2 Year	[redacted]	[redacted]	[redacted]
3 Year	[redacted]	[redacted]	[redacted]
4 Year	[redacted]	-	-
5 Year	[redacted]	-	-

Source: Constructing during the evaluation
*based on 9 months' data (Apr-2023 – Dec-2023)

4.33 The ESC noted that in February 2024, DUSC considered a 24 month predicted versus actual analysis of romosozumab in the existing second-line setting. Table 10 shows the results of the analysis of actual versus predicted utilisation.

Table 10: Predicted versus actual utilisation of romosozumab in the existing second-line setting

		Year 1	Year 2
		April 2021- March 2022	April 2022-March 2023
Patients	**Predicted**	[1]	[1]
	Actual	705	1,516
	Difference		
Prescriptions	**Predicted**	[2]	[3]
	Actual	3,977	8,739
	Difference		

Source: Table 8, p23 of DUSC Report titled 'Romosozumab for severe established osteoporosis: 24 month predicted versus actual analysis'
The redacted values correspond to the following ranges:
[10] 20,000 to < 30,000
[1] 500 to < 5,000
[2] 10,000 to < 20,000
[3] 20,000 to < 30,000

4.34 The DUSC report noted that in the first year of listing, the number of patients treated was [redacted]% lower than estimated and the number of prescriptions supplied was [redacted]% lower than estimated. In the second year of listing, the number of patients treated with romosozumab was [redacted]% lower than estimated and the number of prescriptions was [redacted]% lower than estimated. The ESC considered it was unclear as yet whether uptake was slower than anticipated or whether the data reflected overall reduced uptake. However, the PBAC considered this likely reflected: fewer prescriptions per patient; and overall reduced uptake, which was likely to continue should romosozumab become available in the first-line setting (given it is proposed as a once in a lifetime treatment) and given the recent TGA safety update (noting that patients in the second-line setting may be more likely to have comorbidities). Further, the PBAC noted that Table 9 indicated that romosozumab utilisation in Year 3 was likely to result in around [redacted]% of the cap being reached i.e. around $[redacted] million of expenditure (based on a linear extrapolation of the nine months of available data). As such, the PBAC considered that the estimated utilisation in the second-line setting had been substantially overestimated, and utilisation in the second-line setting was likely to remain at the most recent levels. That is the PBAC considered that expenditure in the second-line setting was likely to remain at around $[redacted] million per year over the forward estimates period.

4.35 The evaluation considered that it was unclear whether a combined cap remained appropriate given there is no longer any overlap between the two patient populations (as the proposed expanded second-line listing is no longer relevant), however the pre-PBAC response stated a combined cap was requested given miscoding is known to occur. The evaluation considered that, should a combined cap be used, further adjustment of the existing second-line expenditure cap (i.e. in addition to the 'time shift adjustment') may be required given uptake to date has been less than anticipated, in order to sufficiently manage the risk of the uncertain size of the eligible first-line population.

Reduction in second-line use due to use in the first-line setting instead

4.36 The evaluation considered that use of romosozumab in the first-line setting will reduce its use in the second-line setting over time given romosozumab is proposed as a once in a lifetime treatment (noting that the existing second-line romosozumab restriction states: The treatment must not exceed a lifetime maximum of 12 months therapy). The evaluation considered that the financial expenditure caps and weighted price should be adjusted to account for this reduction in expenditure in the second-line setting.

4.37 In Scenario 2 of the economic model (which assumed that 50% of patients in the comparator arm would receive romosozumab in the second-line setting), the submission stated that the economic model estimated that 12% of patients in the alendronate arm would receive second-line romosozumab (after taking into account the annual fracture rate, along with the rate of discontinuation and death). Thus, for every 100 patients treated with romosozumab instead of alendronate, 12 fewer patients would require second-line romosozumab. Potential reductions in overall expenditure caps and the weighted price, reflecting this estimate, are outlined in Table 11. This table does not take into account any potential revisions to the second-line financial caps to account for lower than anticipated utilisation in this setting.

Table 11: Estimation of the percent reduction in 2L romosozumab use due to it being used in the 1L setting (Note – this table does not include the impact of lower than estimated use in the second-line setting)

		Year of first-line listing				
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
A	Estimated number of 1L romosozumab patients [b]	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]
B	Percent of 1L patients who will no longer require romosozumab in 2L	12%				
C	Fewer 2L romosozumab patients (A*B)	- [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
D	Estimated number of 2L romosozumab patients – existing estimate (Table 12) [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
E	Estimated number of 2L romosozumab patients – revised estimate (D-C)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
	Reduction in use in 2L setting	0%	21%	29%	34%	35%
	Revised weighting across 1L and 2L settings					
F	Total number of romosozumab patients in 1L and 2L (A+E)	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
	% of patients in 2L setting (for weighted price) (E/F)	44%	32%	23%	19%	**18%**

Source: Compiled during evaluation

1L = first-line; 2L = second-line

[a] Assumes that the reduction in use in the second-line setting would not commence until Year 2 of listing in the first-line setting.[b] Based on the patient numbers stated on page 8 of the submission, noting that the 'listing years' may not line up.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 5,000 to < 10,000

[3] 10,000 to < 20,000

4.38 Adjusting the existing second-line romosozumab estimates to account for a reduction in use due to the first-line listing, would lead to up to a 35% reduction in the number of patients using romosozumab in the second line setting by Year 5. It may also affect the weighted price, as outlined in Paragraph 4.41.

Weighted price

4.39 The submission proposed a weighted price (EMP) across the existing second-line listing and the proposed first-line listing. As outlined in Table 12, the weightings were proposed to be based on the original agreed financial estimates for the established second-line listing and the estimates for the first-line setting.

Table 12: Patient numbers and derived weightings, proposed in submission

	2023	2024	2025	2026	2027	2028
Patient numbers						
1st-line	[redacted]1a	[redacted]2	[redacted]2	[redacted]3	[redacted]3	[redacted]3
2nd-line	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1	[redacted]1
Total	[redacted]2	[redacted]2	[redacted]3	[redacted]3	[redacted]3	[redacted]3
Weighting						
1st-line ($[redacted])	56%	63%	70%	74%	75%	75%
2nd-line ($[redacted])	44%	37%	30%	26%	25%	25%

Source: page 8 of the submission

[a] Updated during evaluation to include grandfathered patients. As the financial estimates assume each grandfather patient will receive an average of 6 months of treatment, the number of grandfathered patients was halved.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 5,000 to < 10,000

[3] 10,000 to < 20,000

4.40 The submission used the steady state weighting of 25% use in second-line, and 75% use in first-line to calculate the proposed overall effective price of $[redacted] (i.e. 0.25 x $[redacted] + 0.75 x $[redacted]), which was unchanged from the weighted price proposed in the previous submission. The submission's use of percentages at steady state was appropriate.

4.41 The evaluation considered the proportion of romosozumab use in the second-line setting may have been overestimated (see paragraphs 4.32 to 4.34) and thus the weighted price may not be conservative. The evaluation considered that, in order to achieve a weighting that reflects use in clinical practice (at steady state), it may be appropriate to adjust the second-line utilisation estimates to: (a) account for lower than expected prescription utilisation in the second-line setting; and (b) reflect a reduction in use in the second-line setting due to romosozumab being used in the first-line setting instead. However, the weighted price is not overly sensitive to changes in the proportion of use in each setting, for example even with 90% use in the first-line setting and 10% use in the second-line setting, the weighted price would be $[redacted], which is 1.6% lower than proposed by the submission.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the Authority Required (Telephone/electronic) listing of romosozumab for the treatment of severe osteoporosis in the first-line setting. The PBAC considered that romosozumab provides, for some patients, a significant improvement in efficacy over alendronate. The PBAC considered that the submission's proposed changes to the economic model inputs resulted in the cost-effectiveness estimate being uncertain, but considered that this could be mitigated through a combined Risk Sharing Arrangement (RSA) across the first- and second-line settings with the first-line expenditure caps based on the price at which it had previously considered romosozumab to be cost-effective. The PBAC further advised that the caps for the second-line setting should be revised to reflect no further growth in this setting (i.e. utilisation remaining at the most recent levels). The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of romosozumab would be acceptable in the first-line setting at the indication-specific price proposed in the submission and with the RSA outlined in paragraph 5.10.

5.2 The PBAC reiterated its July 2022 advice that there is likely a clinical need for earlier use of romosozumab in patients at very high risk of fracture (para 7.2, romosozumab Public Summary Document (PSD), July 2022 PBAC meeting) and noted the consumer comments outlining the benefits of romosozumab as a first-line treatment, rather than after anti-resorptive therapy.

5.3 The PBAC reiterated its July 2022 advice that alendronate, as a proxy for anti-resorptive therapy, was the appropriate comparator (para 7.4, romosozumab PSD, July 2022 PBAC meeting).

5.4 The PBAC noted that no new evidence was provided regarding the comparative effectiveness or safety of romosozumab. The PBAC reiterated its previous advice that the claim of superior comparative effectiveness was reasonable for the first-line setting, however the magnitude of effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab (para 7.8, romosozumab PSD, July 2022 PBAC meeting).

5.5 The PBAC noted that, in December 2023, the TGA had updated the safety information for romosozumab by: including stronger warnings regarding the risk of myocardial infarction and stroke in the Product Information and Consumer Medicine Information; and advising that romosozumab is contraindicated in patients with a history of myocardial infarction or stroke. The PBAC noted that the Pre-Sub-Committee Response had stated that there has been no change in the cardiovascular benefit/risk profile of romosozumab nor upward trend in myocardial infarction or stroke identified since the marketing approval of romosozumab globally. Overall, the PBAC reiterated its previous advice that the claim of inferior comparative safety versus alendronate was reasonable (para 7.6, romosozumab PSD, March 2023 PBAC meeting).

5.6 The PBAC recalled its previous advice that romosozumab would be considered cost-effective in the first-line setting if the price was reduced such that the ICER was no higher than $35,000 to < $45,000/QALY gained, using the model parameters provided in the March 2023 submission. The PBAC noted that the submission had proposed changing one or two model inputs (under two different scenarios) so as to maintain the ICER at $35,000 to < $45,000/QALY, but with a 13% higher EMP (in the first-line setting) compared with the scenario recommended by the PBAC in March 2023. The changes proposed by the submission were to:

- increase the baseline fracture risk from 5.02% (based on the alendronate arm of the ARCH trial) to either 5.16% or 5.40% per annum, with the submission arguing that the PBS criteria will identify a higher risk population than the ARCH trial.
- assume 50% of patients who experience a fracture while treated with alendronate would receive an anabolic agent (romosozumab or teriparatide) in the second-line setting, versus 0% in the March 2023 model (this was applied in one of the submission's two proposed scenarios).

5.7 The PBAC noted that the values were selected in order to achieve an ICER of $35,000 to < $45,000/QALY, rather than on the basis of any clear clinical rationale. The PBAC agreed with the submission that the proposed PBS population was intended to be at a higher baseline fracture risk than the ARCH trial and considered the proposed increase to the baseline fracture risk, while poorly quantified, was small in magnitude. Further, while the PBAC considered it was reasonable to include the impact of second-line romosozumab use in the comparator arm of the model, the submission had not adequately quantified the proportion of such use or the overall treatment effect in this specific setting.

5.8 Overall, the PBAC agreed with the ESC that, while changes to these two parameters may be plausible, the precise magnitude of the changes was poorly justified and thus imparted a high degree of uncertainty in the estimated ICER. However, the PBAC also considered that while the March 2023 model may have applied potentially conservative assumptions around baseline fracture risk and romosozumab use in the second-line setting, this was in the context of a model that included other assumptions that were likely non-conservative (e.g. assumptions around treatment adherence and persistence, and the extrapolation of treatment effect). Overall, the PBAC considered romosozumab would be cost-effective in the first-line setting at the indication-specific price proposed in the current submission and with the RSA outlined in paragraph 5.10.

5.9 The PBAC noted the submission had updated the financial estimates as advised in the March 2023 Minutes and recalled its previous advice that it was reasonable to accept the first-line population numbers presented as the maximum number of first-line patients to be treated per annum (para 7.9, romosozumab PSD, March 2023 PBAC meeting).

5.10 The PBAC noted that the submission had proposed a combined cap across the first and second-line populations based on the sum of the financial estimates for the first-

line listing plus the established second-line caps (with a time-shift adjustment for lower than anticipated initial uptake). The PBAC advised that, to mitigate the remaining concerns regarding the cost-effectiveness of romosozumab use in the first-line setting and to ensure a high degree of confidence in the financial estimates, a combined RSA (across both the first and second line settings) would be required with expenditure caps based on the following:

- First-line setting: The PBAC considered the first-line RSA expenditure caps should be based on the levels of utilisation estimated in the submission, but using the price at which it had previously considered romosozumab to be cost-effective (i.e. the March 2023 model with an ICER of $35,000 to < $45,000/QALY, as previously recommended, para 7.7 romosozumab PSD, March 2023 PBAC Meeting).
- Second-line setting: The PBAC considered that utilisation in the second-line setting was likely to remain at the most recent levels (i.e. the PBAC considered that expenditure in the second-line setting was likely to remain at around $[redacted] million per year over the forward estimates period) given that: the trend of lower-than-estimated levels of expenditure over the first three years of the deed; the availability of romosozumab in the first-line setting would reduce its use in the second-line setting (given it is proposed as a once in a lifetime treatment); and the recent TGA safety update (noting that patients in the second-line setting may be more likely to have comorbidities).

5.11 The PBAC reiterated its previous advice that a [redacted]% rebate for any expenditure above the caps was appropriate.

5.12 The PBAC noted that a weighted price was requested (with the indication-specific price being slightly higher in the second-line setting) and noted that weightings are usually based on the latest actual utilisation for the established listing and the final predicted utilisation for the new listing.

5.13 The PBAC reaffirmed that the restriction recommended in March 2023 (as outlined in Section 3, Requested listing) was appropriate.

5.14 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for romosozumab:

a) The treatment is expected to provide a clinically relevant improvement in efficacy, over alternative therapies, on the basis of the fracture outcomes reported in the ARCH trial, however the magnitude of the benefit was likely overestimated compared to the clinical effectiveness in the Australian treatment setting;

b) The treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative treatments.

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

5.15 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Add new item:

MEDICINAL PRODUCT **medicinal product pack**		**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ROMOSOZUMAB						
romosozumab, 105mg/1.17mL injection, 2 x 1.17mL syringes		NEW	1	2	5	Evenity
Restriction Summary new / Treatment of Concept: new						
Concept ID	**Category / Program:** GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)					
Prescribing rule level	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.					
	Administrative Advice: No increase in the maximum number of repeats may be authorised.					
	Administrative Advice: Special Pricing Arrangements apply.					
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
	Indication: Severe established osteoporosis					
	Treatment Phase: Initial treatment					
	Clinical criteria:					
	Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab					
	AND					
	Clinical criteria:					
	Patient must be at a very high risk of fracture					
	AND					
	Clinical criteria:					
	Patient must have a bone mineral density (BMD) T-score of -2.5 or less					
	AND					
	Clinical criteria:					
	Patient must have had a symptomatic fracture due to minimal trauma					

	AND
	Clinical criteria:
	Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months; or
	Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS subsidised therapy
	Treatment criteria:
	Must be treated by a consultant physician
	Prescribing Instructions: Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.
Restriction Summary New / Treatment of Concept: New	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
	Indication: Severe established osteoporosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy
	Treatment criteria:
	Must be treated by a medical practitioner identifying as either: (i) a Consultant Physician, (ii) a General Practitioner.
Restriction Summary [new] / Treatment of Concept [New]	
Concept ID)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
	Indication: Severe established osteoporosis

	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements
	Clinical criteria:
	Patient must have received non-PBS subsidised treatment with this drug for this PBS indication prior to [insert listing date],
	AND
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with any of the following prior to initiating non-PBS-subsidised treatment with this drug for this condition: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab,
	AND
	Clinical criteria:
	Patient must be at a very high risk of fracture,
	AND
	Clinical criteria:
	Patient must have had a bone mineral density (BMD) T-score of -2.5 or less prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must have had a symptomatic fracture due to minimal trauma prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must have had at least 1 hip or symptomatic vertebral fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition, OR
	Patient must have had at least 2 fractures including 1 symptomatic new fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition,
	AND
	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy,
	Treatment criteria:
	Must be treated by a consultant physician
	Prescribing Instructions: Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.

	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

6.2 Flow on changes to current romosozumab listing (PBS item code: 12301K) for consistency as follows:

From:

	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months therapy

To:

	Clinical criteria:
	The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy

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

7 Context for Decision

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

8 Sponsor's Comment

The sponsor had no comment.