7.04 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 standard re-entry submission requested a Section 85 (Authority Required) listing for romosozumab for the treatment of severe osteoporosis in the first line setting, and an expanded listing in the second line setting. The PBAC previously considered romosozumab for severe osteoporosis in November 2018 (first- and second-line settings), July 2019 (second line setting) and March 2020 (second line setting). Romosozumab is currently listed on the PBS for severe osteoporosis under a restricted second 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 resubmission

Component	Description
Population	(First line) 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 clinical vertebral fracture, or multiple clinical fractures (including 1 recent), OR At least 1 symptomatic new fracture after 12 months anti-resorptive therapy
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	Romosozumab is superior in terms of efficacy and inferior in terms of safety compared to alendronate.

Source: Table 1.1-1, p15 of the resubmission

2 Background

Registration status

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

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

2.2 The product information includes special warnings and precautions for use due to the potential risk of serious events of myocardial infarction and stroke.

Previous PBAC consideration

2.3 The table below summarises key matters of concern from previous romosozumab submissions (November 2018, July 2019 and March 2020) that are relevant to the current resubmission for a first line and expanded second line listing. Some of the key matters of concern from the original November 2018 submission are outstanding as subsequent submissions focussed on a restricted second line listing.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
First line setting	
The PBAC considered alendronate was the appropriate comparator but noted comparative evidence against denosumab would have been informative as it is the therapy most likely to be replaced in clinical practice for this patient population (para 7.9, romosozumab PSD, November 2018 PBAC meeting).	The resubmission used results from an indirect comparison of fracture outcomes between denosumab (FREEDOM trial) and alendronate (FIT-VFA, FIT-CFA trials) using placebo as a common reference, to inform a sensitivity analysis with denosumab as an alternative comparator in the economic model.
The PBAC considered the long-term comparative efficacy of romosozumab versus alendronate was uncertain and that maintenance of treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy (para 7.10, romosozumab PSD, November 2018 PBAC meeting).	The resubmission claimed that data from the ARCH trial show sustained treatment benefit for up to 2 years after discontinuation of 12 months of romosozumab. Therefore, the resubmission assumed that treatment benefit would not immediately diminish to zero after the 3-year trial period. In the economic model, the resubmission assumed that treatment efficacy was fixed for 3 years then declined linearly to zero by Year 6. The resubmission assumed treatment persistence of 95% per year to all treatments.
The PBAC considered that the economic model comparing romosozumab and alendronate did not form a reliable basis for decision making due to overestimation of fracture risk and treatment effect, the assumption of continuing treatment effect (which relied on adherence and persistence rates unlikely to be achieved in the PBS population), and potentially unreliable fracture disutilities (para 7.13, romosozumab PSD, November 2018 PBAC meeting).	Multiple revisions were made to model inputs including the extrapolation of treatment effect, fracture risks, mortality, utility values and cardiovascular events. There were additional changes to the model structure with the inclusion of off-treatment health states, and all cost inputs have been revised.
The PBAC considered the financial estimates were highly uncertain. The PBAC considered the estimated number of patients treated with romosozumab was underestimated with uptake of < [redacted]% of the total treated osteoporosis population. The PBAC noted the approach to estimating the eligible population did not consider the pool of prevalent patients that may be appropriate for treatment with romosozumab, which would significantly underestimate the treated patient population (para 7.14, romosozumab PSD, November 2018 PBAC meeting).	The resubmission's financial estimates remain based on treated osteoporosis patients with a prevalent fracture, with changes to accommodate the newly proposed clinical criteria in the PBS restriction relating to fracture history (number, location, severity, recency) and BMD T-scores.
Second line setting	

Matter of concern	How the resubmission addresses it
The PBAC noted that alendronate was a reasonable proxy for anti-resorptive therapy but considered that denosumab would be the therapy most likely to be replaced in practice (para 7.4, romosozumab PSD, March 2020 PBAC meeting).	The resubmission nominated alendronate as the main comparator, as a proxy for anti-resorptive therapies. The resubmission acknowledged that denosumab is the therapy most likely to be replaced, however, a robust comparison with romosozumab was not feasible due to a lack of direct comparative trial data.
The PBAC considered that fracture outcomes data from the ARCH study supported a claim of superior efficacy of romosozumab followed by alendronate compared to alendronate alone. The PBAC considered that, in contrast to the proposed population, the ARCH study provided evidence for romosozumab use in patients who were predominantly naïve to anti-resorptive therapy (para 7.8, romosozumab PSD, March 2020 PBAC meeting).	The resubmission assumed that the comparative efficacy of romosozumab versus alendronate (as a proxy for anti-resorptives) in the first line setting would apply to the second line setting.
The PBAC recalled concerns that the long-term comparative efficacy of romosozumab was uncertain and that maintenance of treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy (para 7.6, romosozumab PSD, March 2020 PBAC meeting).	Assumptions regarding long-term comparative efficacy and persistence were applied in the economic model of the resubmission (see above, first line setting model changes).
The PBAC considered that concerns regarding alerting patients to the need to transition to anti-resorptive therapy were reduced by restricting prescribing to Specialists or Consultant Physicians (para 7.6, romosozumab PSD, March 2020 PBAC meeting). The PBAC considered that the advice regarding cardiovascular risk in the product information along with restricted prescribing to Specialists or Consultant Physicians would allow the risk to be managed in clinical practice (para 7.9, romosozumab PSD, March 2020 PBAC meeting).	The resubmission requested Specialist/Consultant Physician prescribing for initial scripts and GP prescribing for continuing scripts.
The PBAC considered that the economic model could not be used to assess the cost-effectiveness of romosozumab when used in a broader population than those treated with teriparatide, based on the economic model that was fundamentally unchanged from the November 2018 and July 2019 submissions. However, the PBAC considered that romosozumab was likely to be cost-effective when used in the broader population as defined in the March 2020 submission based on the BMD and fracture clinical evidence presented in the resubmission, the likely similar disease characteristics of the broader population versus the teriparatide treated population, and the price reduction for romosozumab due to the revisions to the cost-minimisation analysis (para 7.12, romosozumab PSD, March 2020 PBAC meeting).	The resubmission acknowledged that the cost-effectiveness of romosozumab in the expanded second line setting was uncertain, however, the resubmission claimed that there was historical PBAC precedence of recommending second line use of osteoporosis medications based on evidence in the first line setting. The resubmission argued that the cost-effectiveness of romosozumab in the second line setting can be assumed to be equivalent to the first line setting.
The ESC previously considered that the size of the eligible population was highly uncertain due to multiple concerns with the approach and data sources used that were largely unchanged from the July 2019 submission (para 6.88, romosozumab PSD, March 2020 PBAC meeting).	The resubmission used the same approach presented in the March 2020 submission to derive the size of the eligible population. Additional data sources and assumptions were used to determine the number of patients meeting newly proposed fracture and BMD criteria.

Matter of concern	How the resubmission addresses it
The PBAC noted that it was reasonable to accept the financial estimates as the basis of a risk sharing arrangement (RSA) given the revised cost-minimised romosozumab price and restricting prescribing of romosozumab to Specialists/ Consultant Physicians (para 6.89, romosozumab PSD, March 2020 PBAC meeting). The PBAC considered that an RSA with [redacted]% rebate for use exceeding the caps was appropriate to mitigate any residual uncertainties regarding the size of the eligible romosozumab population (para 7.13, romosozumab PBAC PSD, March 2020 PBAC meeting).	The resubmission claimed the sponsor is willing to agree to a revised deed for romosozumab, extending the current risk-sharing arrangement for a further 5 years. The resubmission proposed that the new financial caps be the sum of the existing caps with the addition of financial estimates presented for the additional first- and second-line populations. The sponsor proposed a [redacted]% rebate on any expenditure above the caps in place of the current hard caps.
The PBAC recommended that DUSC undertake a review of utilisation after an appropriate period post listing which includes an investigation of the success of transitioning patients from romosozumab to anti-resorptive therapy. (para 7.14, romosozumab PSD, March 2020 PBAC meeting).	The length of time post listing was inadequate at the time of evaluation to undertake this review given romosozumab has a recommended 12-month treatment course and it was only listed on 1 April 2021.

Source: romosozumab November 2018, July 2019 and March 2020 Public Summary Documents

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

3 Requested listing

3.1 Separate restrictions were proposed for initial treatment in the first line and expanded second line settings. The resubmission also requested amendments to the current continuing treatment restriction. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Proposed 1L restrictions

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed price for maximum quantity	Available brands
ROMOSOZUMAB						
romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL syringes	NEW	1	2	5	$404.75 (published price) $[redacted] (effective price)	evenity

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)
Prescribing		**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.
		Episodicity:
		Severity: Severe
		Condition: Established osteoporosis

	Indication: Severe established osteoporosis
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must be at very high risk of fracture.
	AND
	Clinical criteria:
	Patient must have a bone mineral density (BMD) T-score of -2.5 or less.
	AND
	Clinical criteria:
	~~Patient must have received less than 12 months of treatment with an anti-resorptive agent;~~
	AND
	Clinical criteria:
	Patient must have had at least 1 hip or clinical vertebral fracture in the previous 24 months, OR Patient must have had *multiple symptomatic*~~at least 2 clinical~~ fractures including 1 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 *PBS and non-PBS subsidised* therapy.
	Treatment criteria:
	Must be treated by a Specialist; OR 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.*
	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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED)
	Episodicity:
	Severity: Severe
	Condition: Established osteoporosis
	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 *PBS and non-PBS subsidised* therapy
	Treatment criteria:
	Must be treated by a Specialist; OR Must be treated by a Consultant Physician.
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)
	Episodicity:
	Severity: Severe
	Condition: Established osteoporosis
	Indication: Severe established osteoporosis
	Treatment Phase: Grandfathered
	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 be at very high risk of fracture.
	AND
	Clinical criteria:
	Patient must have 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 received less than 12 months of treatment with an anti-resorptive agent 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 clinical vertebral fracture in the previous 24 months prior to starting non-PBS subsidised treatment with this drug for this condition, OR Patient must have had *multiple symptomatic*~~at least 2 clinical~~ fractures including 1 in the previous 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 *PBS and non-PBS subsidised* therapy
	Treatment criteria:
	Must be treated by a Specialist; OR 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.

	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.
	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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*

Proposed 2L restrictions

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed price for maximum quantity	Available brands
ROMOSOZUMAB						
romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL syringes	NEW	1	2	5	$404.75 (published price) $[redacted] (effective price)	evenity

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)
Prescribing		**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.
		Episodicity:
		Severity: Severe
		Condition: Established osteoporosis
		Indication: Severe established osteoporosis
		Treatment Phase: Initial treatment
		Clinical criteria:
		Patient must be at very high risk of fracture.
		AND
		Clinical criteria:
		Patient must have a bone mineral density (BMD) T-score of -2.5 or less.
		AND
		Clinical criteria:
		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
		Clinical criteria:
		The treatment must be the sole PBS-subsidised ~~agent~~ *therapy for this condition.*
		AND
		Clinical criteria:
		The treatment must not exceed a lifetime maximum of 12 months *PBS and non-PBS subsidised* therapy

	AND
	Clinical criteria:
	Patient must not have received treatment with PBS-subsidised teriparatide; or
	Patient must have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.
	Treatment criteria:
	Must be treated by a Specialist; OR Must be treated by a Consultant Physician.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with *this drug* ~~romosozumab~~ is initiated.
	Prescribing Instructions: If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with *this drug*~~romosozumab~~ is initiated.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
	Prescribing Instructions: Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
	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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*
Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (STREAMLINED)
	Episodicity:
	Severity: Severe
	Condition: Established osteoporosis
	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 *PBS and non-PBS subsidised* therapy
	Treatment criteria:

	Must be treated by a Specialist; OR Must be treated by a Consultant Physician.
	~~**Administrative Advice:** Details of accepted toxicities including severity can be found on the Department of Human Services website at www.humanservices.gov.au.~~
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)
	Episodicity:
	Severity: Severe
	Condition: Established osteoporosis
	Indication: Severe established osteoporosis
	Treatment Phase: Grandfathered
	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 be at very high risk of fracture.
	AND
	Clinical criteria:
	Patient must have 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 experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses 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 *PBS and non-PBS subsidised* therapy
	AND
	Clinical criteria:
	Patient must not have received treatment with PBS-subsidised teriparatide prior to starting non-PBS subsidised treatment with this drug for this condition; or
	Patient must have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy prior to starting non-PBS subsidised treatment with this drug for this condition.
	Treatment criteria:
	Must be treated by a Specialist; OR Must be treated by a Consultant Physician.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

	Prescribing Instructions: If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with this drug romosozumab is initiated.
	Prescribing Instructions: If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with *this drug* ~~romosozumab~~ is initiated.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
	Prescribing Instructions: Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
	~~**Administrative Advice:** Details of accepted toxicities including severity can be found on the Department of Human Services website at www.humanservices.gov.au.~~
	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.*
	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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).*

3.2 The proposed published and effective prices are the same as the current prices of romosozumab on the PBS for the treatment of severe osteoporosis in the second line setting.

3.3 The requested restrictions are narrower than the TGA indication (patients with osteoporosis at high risk of fracture) as they are limited to secondary prevention, in a subset of patients with severe osteoporosis at very high risk of fracture who meet specific clinical criteria relating to fracture history (number, location, severity, recency), BMD T-scores and prior therapies.

3.4 The proposed first line restriction limits the patient population to patients who have received less than 12 months of anti-resorptive therapy. The intent of this criterion was uncertain given the proposed algorithm positioned romosozumab as initial treatment prior to the use of anti-resorptives (i.e. in treatment naïve patients). The Pre-Sub Committee Response (PSCR) clarified that the intent of the first line restriction wording was to allow access to romosozumab in the complementary population of patients who have either not yet started osteoporosis therapy or have received an anti-resorptive agent for a very short time (<12 months) in addition to the fracture and BMD requirements. The ESC noted that the financial estimates of the resubmission were based on treated patients only, stratified by duration of treatment of less than 12 months (first line) and 12 months or more (second line).

3.5 The PBAC secretariat suggested it may be reasonable to consider a combined single restriction for secondary prevention that identifies the various very high-risk groups proposed as separate first- and second-line restrictions. This approach may reduce the complexities associated with overlapping populations. The pre-PBAC response provided a combined single restriction for romosozumab which encompassed both first- and second-line use. The suggested clinical criteria are outlined below:

Proposed combined single restriction encompassing first- and second-line use

Clinical criteria:
Patient must be at very high risk of fracture.
AND
Patient must have a bone mineral density (BMD) T-score of -2.5 or less.
AND
Patient must have had at least 1 symptomatic minimal trauma fracture
AND
• Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months, OR • Patient must have had multiple symptomatic fractures including 1 in the previous 24 months, OR • 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 therapy for this condition.
AND
The treatment must not exceed a lifetime maximum of 12 months PBS subsidised therapy.

Source: Pg 1. Romosozumab pre-PBAC response

3.6 The resubmission claimed that updated international guidelines support the earlier use of anabolic agents in patients with very high and/or imminent risk. The characterisation of very high risk varied between guidelines and was generally based on fracture history, BMD and fracture probability calculated using risk algorithms that incorporate a variety of clinical factors. Treatment thresholds were country-specific and likely reflect broader factors such as willingness to pay, health care resources, reimbursement policies and geographical variations in fracture incidence.

3.7 Traditionally, guidelines have classified fracture risk as high or very high based on fracture history, age and BMD T-scores. However, there is increasing recognition of the time-dependent nature of fracture risk and that patients with a recent major osteoporotic fracture are at "imminent risk" with an increased risk of fracture immediately after the incident fracture. The resubmission cited emerging evidence based on observational data suggesting the risk of a subsequent fracture was highest in the immediate post-fracture interval (1-2 years) and decreased markedly over a 10-year period (Kanis 2018). The resubmission claimed that anabolic agents provide the greatest probability of rapidly normalising BMD and reducing the risk of subsequent fractures in patients with imminent risk. The resubmission claimed that this proposition is supported by data from head-to-head trials demonstrating the superiority of anabolic agents compared to anti-resorptive therapy. The ESC

considered these claims were inadequately supported in the resubmission, with no data presented supporting the treatment benefit of romosozumab in patients at imminent fracture risk.

3.8 The rationale for the proposed clinical criteria in first line was unclear but appeared to be based on a synthesis of factors incorporating fracture location, number of fractures, clinical symptoms, recency of fracture and BMD T-score. The clinical criteria did not appear consistent with the wide range of very high risk groups identified in published guidelines.

3.9 It was difficult to reconcile the proposed clinical criteria for first line therapy with the inclusion criteria of the ARCH trial (see Table 3 below).

3.10 The requested first line restriction was also inconsistent with responses to a survey of the sponsor's advisory board, with the majority of respondents indicating the most important very high-risk factor was multiple minimal trauma fractures. This was followed by low BMD T-score (≤-3.0) and fracture site (e.g. hip or vertebral). Other definitions included various combinations of multiple fractures, high falls risk, fracture site, low BMD and microarchitectural decay. The concept of 'imminent risk' was not included in the survey.

3.11 The PSCR acknowledged that the proposed restriction is not precisely consistent with the varied definitions of very high fracture risk in published guidelines. However, the PSCR claimed the proposed restriction defines a very high fracture risk population, where the risk-benefit profile of romosozumab is clearly favourable. The ESC noted there were inconsistencies in the subpopulation definitions of very high risk between the restriction, clinical evidence, economic model and financial estimates (see Table 3). In the combined restriction proposed in the pre-PBAC response the clinical criterion terminology referring to 'at least 2 clinical fractures' was replaced with 'multiple symptomatic fractures'.

3.12 The proposed changes to the current second line listing of romosozumab include the removal of the requirement for patients to have multiple minimal trauma fractures and changing the BMD T-score threshold from ≤ -3.0 to ≤ -2.5. The resubmission's claim that these changes were recommended by the sponsor's advisory board appeared to be a misrepresentation of responses to a sponsor-commissioned survey which asked which PBS requirements stopped the prescribing of anabolic agents most often but did not determine whether the current requirements were appropriately identifying patients with severe osteoporosis who would benefit from treatment with anabolic agents.

3.13 The resubmission stated that the sponsor's advisory board had highlighted that access to second line anabolic treatment was inequitable for patients without multiple minimal trauma fractures. The resubmission claimed that when qualifying for initial treatment (first line), the primary and secondary prevention populations were of similar fracture risk and therefore both populations remain at an equivalent, albeit higher fracture risk when experiencing an on-treatment fracture. The combined

restriction proposed in the pre-PBAC response required that all patients must have had at least 1 symptomatic minimal trauma fracture.

3.14 The resubmission claimed that eligibility for osteoporosis treatments was historically limited to secondary prevention of fracture and that age and BMD thresholds were subsequently introduced to define a primary prevention population of similar fracture risk to the secondary prevention population (citing the alendronate PSD, July 2006 PBAC meeting). The resubmission's claim did not appear consistent with PBAC's historical considerations of submissions to extend the listing of anti-resorptives to include primary prevention. Subsequent PBAC recommendations to include the primary prevention population were based on acceptable cost-effectiveness, originally based on a BMD threshold of ≤ -3 then extended to BMD ≤ -2.5. Patients with multiple fractures are likely to be at a higher fracture risk than patients with a single fracture.

3.15 The PBAC previously noted numerous issues with the data presented to support the restricted second line listing of romosozumab including the lack of comparative data in patients with prior anti-resorptive therapy and lack of comparative data on residual effectiveness with and without subsequent anti-resorptive therapy (para 7.3, romosozumab PSD, November 2018 PBAC meeting). The ESC noted that no new data were presented in the current resubmission to address these concerns or support the expanded use of romosozumab in the second line setting.

3.16 For continuing treatment, the resubmission proposed allowing general practitioner prescribing. The PBAC previously raised concerns regarding the need to transition to anti-resorptive therapies after romosozumab, the cardiovascular risk associated with romosozumab, and uncertainties regarding the size of the eligible population and potentially substantial market expansion (in the second line setting). In March 2020, the PBAC considered that restricting prescribing to Specialists/Consultant Physicians would reduce concerns regarding these risks. At that meeting the PBAC also considered that the utilisation of anti-resorptive therapy following cessation of romosozumab should be reviewed to investigate the success of treatment transition (para 7.6, 7.9 and 7.13, romosozumab PSD, March 2020 PBAC meeting). The ESC considered the effectiveness of ongoing monitoring of the cardiovascular risk associated with romosozumab would not be reduced by general practitioner prescribing. However, the ESC noted no new data were presented in the resubmission in support of successful patient transitions to anti-resorptives after romosozumab treatment.

3.17 For continuing treatment, the resubmission also proposed changing the restriction level to Streamlined Authority. The ESC considered an Authority Required (telephone/online PBS Authorities system) listing may be more appropriate for both initial and continuing treatment restrictions to allow compliance with the requirement for a lifetime maximum of 12 months therapy to be checked by Services Australia.

3.18 The resubmission requested grandfathering provisions for patients meeting the proposed clinical criteria for the first line and expanded second line listings. The pre-PBAC response estimated that around < 500 patients are currently privately funding romosozumab and anticipated the number would increase to approximately 500 to < 5,000 patients by 2023 with the introduction of a shared cost program by the sponsor.

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 consequent increase in fracture risk. Loss of bone strength occurs gradually over many years and is usually symptom-free. 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 Four mutually exclusive subgroups are being targeted in the resubmission in addition to the population eligible under the current PBS restriction. The definition of each subgroup informing the clinical evidence, economic model and financial estimates in the resubmission are compared in the table below.

Table 3: Subgroup definitions used in the resubmission

Restriction	Clinical	Economic model	Budget impact
First line setting			
≥1 hip or clinical vertebral fracture in the previous 24 months, AND BMD T-score ≤ -2.5, AND Received <12 months anti-resorptive therapy	Based on ARCH trial ITT population with single/multiple fractures at varying BMD thresholds (defined below) who were predominantly treatment naïve <u>At least one fracture</u> BMD T-score ≤ -2.5, and ≥1 moderate or severe vertebral fracture OR BMD T-score ≤ -2.0, and ≥1 fracture of the proximal femur that occurred within 3 to 24 months prior to randomisation <u>Multiple fractures</u> BMD T-score ≤ -2.5, and ≥2 mild vertebral fractures OR BMD T-score ≤ -2.0, and ≥2 moderate or severe vertebral fractures	Based on ARCH trial ITT population with single/multiple fractures at varying BMD thresholds who were predominantly treatment naïve	Treated osteoporosis patients, AND Received <12 months continuous anti-resorptive therapy, AND With prevalent fracture, AND BMD T-score ≤ -2.5, AND Multiple clinical fractures or single hip/vertebral fracture
Multiple clinical fractures including 1 in the previous 24 months, AND BMD T-score ≤ -2.5, AND Received <12 months anti-resorptive therapy			
Second line setting (additional requested subpopulations, excluding patients eligible under existing PBS listing)			
Multiple minimal trauma fractures including ≥1 symptomatic new fracture after 12 months of anti-resorptive therapy, AND BMD T-score ≤ -2.5 and > -3.0	No data	Not modelled	Treated osteoporosis patients, AND Received ≥12 months continuous anti-resorptive therapy, AND With prevalent fracture, AND BMD T-score ≤ -2.5 and > -3.0, AND Fracture while on treatment
Single symptomatic new fracture after 12 months of anti-resorptive therapy, AND BMD T-score ≤ -2.5	No data	Not modelled	Treated osteoporosis patients, AND Received ≥12 months continuous anti-resorptive therapy, AND No prevalent fracture, AND BMD T-score ≤ -2.5, AND Fracture while on treatment

Source: constructed during the evaluation

4.3 There were inconsistencies in the subpopulation definitions of very high risk between the restriction, clinical evidence, economic model and financial estimates. No clinical data or economic model were presented for the requested second line population in addition to those currently eligible under the existing PBS listing.

4.4 The resubmission did not consider emerging discussions surrounding optimal treatment sequencing of osteoporosis treatments. Some international guidelines recommend that in patients at very high fracture risk, initial treatment with an anabolic agent is optimal (International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) 2020 update). Given that treatments with anabolic agents are limited to 12-24 months, there is potential for earlier use to achieve greater effects on BMD and fracture risk if followed by persistent use of anti-resorptives. The IOF/ESCEO guidelines contrasted this scenario with potentially lower gains should anabolic agents be used following anti-resorptive therapy. This thesis regarding greater benefit with earlier use of anabolic agents appears to be supported by post-hoc analyses of BMD outcomes in trials of romosozumab (see para 6.23 below). The pre-PBAC response noted that NICE recently recommended a wider role for anabolic therapy than is currently available on the PBS. NICE guidance stated that romosozumab is recommended as an option for treating severe osteoporosis in people after menopause who are at high risk of fracture, only if they have had a major osteoporotic fracture (spine, hip, forearm or humerus fracture) within 24 months (so are at imminent risk of another fracture).[1]

4.5 Overall, the ESC agreed with the evaluation that the appropriateness of the proposed place in therapy in first- and second-line settings was uncertain given the lack of clarity surrounding the definition of very high/imminent risk and optimal treatment sequence (i.e. earlier versus later-line use).

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

5 Comparator

5.1 The resubmission nominated alendronate as the main comparator. The PBAC previously considered alendronate was the appropriate comparator in the first line setting and that teriparatide was the appropriate comparator for the restricted second line setting. However, the PBAC had also previously noted that comparative evidence against denosumab would have been informative as it is the therapy most likely to be replaced in the first line and broader second line setting (para 7.9, romosozumab PSD, November 2018 PBAC meeting and para 7.4, romosozumab PSD, March 2020 PBAC meeting).

[1] National Institute for Health and Care Excellence, (2022) Romosozumab for treating severe osteoporosis. Technology appraisal guidance. www.nice.org.uk/guidance/ta791

5.2 The resubmission acknowledged that denosumab is the therapy most likely to be replaced in practice. However, the resubmission claimed that a robust comparison with romosozumab was not feasible due to a lack of direct comparative trial data. The resubmission claimed that alendronate was a reasonable proxy for anti-resorptive therapies as most treatments were listed on the PBS based on therapeutic equivalence to alendronate. Denosumab was listed on a cost-minimisation basis compared to zoledronic acid which in turn was listed on a cost-minimisation basis compared to alendronate (PBS therapeutic relativity sheets, effective date: April 2014). Under these circumstances, it was argued that alendronate may also be an appropriate comparator in the additional second line population requested in the resubmission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed how the drug was currently used in clinical practice and indicated the expanded second line listing may address concerns regarding inequity in access for patients aged 70 years and who may have started anti-resorptive therapy before having a fracture depending on their BMD. The clinician also considered that the use of anabolic agents in the first-line setting was appropriate in those at highest risk of fracture recurrence. The PBAC considered that the hearing was informative as it provided a clinical perspective on access concerns.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (8) and organisations (7) via the Consumer Comments facility on the PBS website.

6.3 The comments from individuals who would like access to the drug to treat their own health condition or other interested individuals described the impact of osteoporosis on the people who have the condition and who have experienced fractures. The comments also describe the benefits of romosozumab in terms of helping to prevent fractures and the associated pain and disability they can cause.

6.4 The comments from health care professionals emphasised the points raised by consumers in terms of the impact of fractures and the benefits of romosozumab in prevention of these events. The comments also raised concern regarding inequity in access as a result of the current PBS criteria.

6.5 The comments from Australian Menopause Society, Australian & New Zealand Bone & Mineral Society (ANZBMS), Australian Rheumatology Association and Austin Health/University of Melbourne describe the benefits of romosozumab in terms of bone formation and the importance of not delaying effective treatment until after a

second fracture. The ANZBMS proposed a clinical management algorithm for individuals at high risk of future fractures. Although the algorithm clinical criteria were different to the first line restriction criterion the ANZBMS suggested that there was enough clinical information to support the definition of high-risk patients as individuals who had evidence a recent (i.e. last 24 months) hip or clinical vertebral fracture or at least 2 clinical fractures (including 1 in the last 24 months) and a recent BMD T score of ≤ -2.5.

6.6 The comments from Healthy Bones Australia, Musculoskeletal Australia and the Australian Women's Coalition Inc outlined the costs associated with treating osteoporosis related fractures and the fracture benefits potentially arising from broader access to romosozumab.

Clinical trials

6.7 The following comparisons were previously considered by the PBAC at the November 2018, July 2019 and March 2020 PBAC meetings:

- Direct comparison of BMD and fracture outcomes with romosozumab versus alendronate in postmenopausal women with osteoporosis who were predominantly naïve to anti-resorptive therapy (ARCH).
- Direct comparison of BMD outcomes with romosozumab versus teriparatide in postmenopausal women with osteoporosis who were previously treated with anti-resorptive therapy (STRUCTURE).
- 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.
- Supportive direct comparison of BMD outcomes with romosozumab versus placebo in men with osteoporosis (BRIDGE).
- Supportive non-inferiority analysis of BMD outcomes with the marketed formulation of romosozumab compared to the romosozumab formulation used in the key trials (Study 156).
- Supportive direct comparison of BMD outcomes from a Phase 2 dose ranging study (Study 326) comparing romosozumab, alendronate, teriparatide and placebo.

6.8 The resubmission was based on a direct comparison of romosozumab versus alendronate in the ARCH trial only. The resubmission excluded all other identified trials as ARCH was the only trial comparing romosozumab with an anti-resorptive agent and included fracture outcomes. The exclusion of the STRUCTURE trial (BMD outcomes only) was inadequately justified given PBAC's previous concerns surrounding the applicability of the ARCH trial to patients previously treated with anti-resorptives. Likewise, the exclusion of the FRAME placebo-controlled trial was inadequately justified as it provided evidence of residual efficacy associated with the follow-up use of denosumab after 12 months of romosozumab. These trials were included during the evaluation.

6.9 The following post-hoc subgroup analyses were provided with the resubmission and used to estimate the size of the eligible population in the financial estimates. These data had not previously been considered by the PBAC:

- Post-hoc analysis of baseline fracture history in the ARCH trial to determine the proportion of patients with BMD T-score ≤ -2.5 who have a history of multiple clinical fractures (any site) OR at least one hip or clinical vertebral fracture.
- Post-hoc analysis of fracture outcomes in subgroups stratified by baseline lumbar spine BMD T-scores and number of prior fractures (vertebral or non-vertebral reported in patient history) in the alendronate arm of the ARCH trial.

6.10 During the evaluation, other post-hoc analyses of BMD outcomes in romosozumab trials (ARCH, FRAME, STRUCTURE and Study 326) were identified and included as supportive evidence.

6.11 The resubmission used results from an indirect comparison of fracture outcomes between denosumab (FREEDOM trial) and alendronate (FIT-VFA, FIT-CFA trials) using placebo as a common reference, to inform a sensitivity analysis with denosumab as an alternative comparator in the economic model. These results were previously considered by the PBAC which considered that denosumab appears similar to alendronate with respect to comparative efficacy (Section 8, denosumab PSD, March 2012 PBAC meeting). There are no available data directly comparing romosozumab and denosumab.

6.12 Details of the trials included in the resubmission and during the evaluation are presented in the table below.

Table 4: Included trials and associated reports

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
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

Source: Table 2.2.1, p 31 and Appendix 3 of the resubmission

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

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
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	Postmenopausal women with osteoporosis and prior fracture	Fractures	Patient characteristics, fracture risk, treatment efficacy, incidence of cardiovascular events
Romosozumab followed by denosumab vs placebo followed by denosumab						
FRAME	7,180	MC, R, PC First year: DB Later years: OL 3 years	Low	Postmenopausal women with osteoporosis	Fractures	Not used
Romosozumab vs teriparatide						
STRUCTURE	436	MC, R, OL, AC 12 months	Unclear	Postmenopausal women with osteoporosis who had received prior anti-resorptive therapy	BMD	Not used

Source: Section 2.4, pp32-38 of the resubmission; FRAME trial report; STRUCTURE trial report
Abbreviations; AC, active-controlled; DB, double blind; MC, multi-centre; OL, open label; R, randomised

Comparative effectiveness

6.14 Key fracture outcomes reported with romosozumab versus alendronate (both followed by alendronate treatment) in the ARCH trial (secondary prevention population; predominantly naïve to anti-resorptive therapy) are summarised in the table below.

Table 6: Key fracture outcomes reported in the ARCH trial

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

Source: Section 2.5.1, pp39-40 of the resubmission
Abbreviations: HR, hazard ratio; NR, not reported; RR, risk ratio
Bolding indicates results that remained statistically significant after adjustments for multiplicity testing. Exploratory outcomes (e.g. clinical vertebral fractures and hip fractures) were not adjusted for multiplicity. Short term (12 month) fracture outcomes were not adjusted for multiplicity.
Results highlighted in orange were used in the economic analysis

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

6.16 The resubmission presented a post-hoc analysis of the ARCH trial to determine the proportion of patients with a BMD T-score of ≤ -2.5 and a history of multiple clinical

fractures or at least one hip/clinical vertebral fracture (see table below). These data have not previously been considered by the PBAC.

Table 7: Post-hoc analysis of baseline fracture history in patients with BMD T-score ≤-2.5 in the ARCH trial

Subgroup definition	Romosozumab/alendronate (N = 2,046)	Alendronate/alendronate (N = 2,047)
Patients with baseline BMD T-score ≤-2.5 at lumbar spine, total hip or femoral neck	1,951	1,946
Patients with baseline BMD T-score ≤-2.5 at lumbar spine, total hip or femoral neck, AND History of multiple clinical fractures (any) OR at least one hip fracture OR at least one clinical vertebral fracture [a]	1,127	1,139

Source: Table 4.2-3, p114 of the resubmission

[a] As reported in subject medical history

6.17 Based on this analysis, 95% the trial population had a baseline BMD T-score ≤ -2.5. The subgroup meeting both BMD threshold and fracture criteria represented 55% of the trial population. It was unclear what proportion would meet the proposed eligibility criteria for first line romosozumab treatment as baseline fracture history in this subgroup was not specific in terms of timing. No patient characteristics or fracture outcomes for these subgroups were presented in the resubmission. The ESC considered that underlying fracture risk in the ARCH trial may not be representative of the proposed PBS first line population given trial enrolment was not specific to patients with recent fractures only, with only a little over half of the trial population meeting the proposed PBS criteria for fracture without consideration of the timing of fractures.

6.18 The resubmission also provided a post-hoc analysis of selected fracture outcomes in subgroups stratified by baseline lumbar spine BMD T-scores and number of prior fractures (vertebral or non-vertebral reported in patient history) in the alendronate arm of the ARCH trial. These data have not previously been considered by the PBAC. Results indicate that patients with multiple fractures (vertebral or non-vertebral regardless of symptoms or recency) are at higher risk of subsequent fracture compared to treated patients with a single fracture. This pattern was observed for new vertebral and non-vertebral fractures. There was no clear pattern in terms of differences in fracture risk between subgroups based on BMD T-score thresholds. Results were limited by relatively smaller sample sizes in patients with BMD T-scores of ≤ -2.5 to > -3. The interpretation of these results was limited by the lack of patient characteristics and lack of outcomes for the romosozumab/alendronate arm.

6.19 In the FRAME placebo-controlled trial (mixed primary and secondary prevention population; predominantly treatment-naive), treatment with romosozumab followed by denosumab was associated with statistically significant decreases in vertebral (includes clinical vertebral) fractures over three years compared to placebo followed by denosumab. Romosozumab was also associated with a reduction in clinical fractures compared to placebo in the first year of treatment but the residual effect while using denosumab in later years was uncertain. There were no statistically significant differences in non-vertebral fractures between treatment arms.

6.20 Fracture outcomes and quality of life measures were not assessed in the STRUCTURE trial (secondary prevention in patients previously treated with anti-resorptive therapy). 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.

6.21 There are no data on fracture outcomes with romosozumab compared to alendronate in patients previously treated with anti-resorptives.

6.22 The changes to BMD observed with both romosozumab and teriparatide in patients previously treated with bisphosphonate therapy (STRUCTURE) were smaller than those reported in patients who were predominantly naïve to bisphosphonate treatment (FRAME and ARCH).

6.23 Multiple post-hoc analyses of BMD outcomes in trials of romosozumab (ARCH, FRAME, STRUCTURE and Study 326) were identified during the evaluation. These data have not previously been considered by the PBAC. The results suggest that the use of romosozumab after anti-resorptive therapy provides smaller BMD gains (measured as relative effects) compared to the use of romosozumab before anti-resorptive therapy.

6.24 An overview of the FRAME (romosozumab/denosumab versus placebo/denosumab) and FREEDOM (denosumab versus placebo) trials suggest that both romosozumab/denosumab and denosumab are associated with reductions in the incidence of fracture compared to placebo/denosumab and placebo, respectively. Relative treatment benefits for comparable fracture outcomes appeared similar, however, comparisons between trials were limited by differences in underlying fracture risk and treatments received in the comparator arm (patients in the placebo arm of the FRAME trial received denosumab after 12 months of placebo). Overall, the comparative efficacy of romosozumab versus denosumab remains uncertain.

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

6.26 The PBAC previously considered the long-term comparative efficacy of romosozumab versus alendronate was uncertain and that maintenance of treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy (para 7.10, romosozumab PSD, November 2018 PBAC meeting). In July 2019, the PBAC considered that the limited available data from Study 326 suggest that treatment effects associated with romosozumab are rapidly lost after discontinuation of subsequent anti-resorptive therapy (paragraph 7.5, romosozumab, PSD, July 2019 PBAC meeting). The PBAC reiterated these concerns at the March 2020 PBAC meeting and recommended that the utilisation of anti-resorptive therapy following cessation of romosozumab should be reviewed after an appropriate period post listing (para 7.14, romosozumab PSD, March 2020 PBAC meeting). No data were presented in the resubmission to address these concerns. The length of time post listing was inadequate at the time of evaluation for this review given romosozumab has a recommended 12-month treatment course and it was only listed on 1 April 2021.

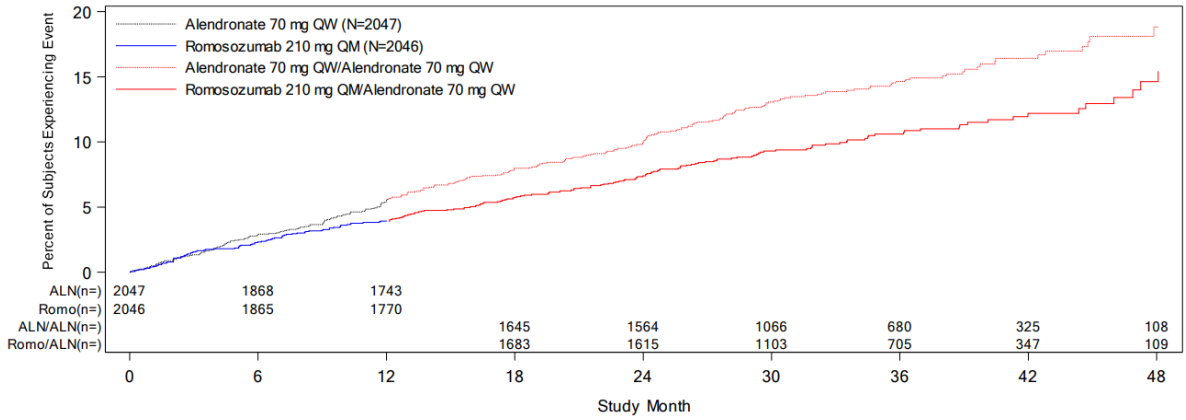
6.27 At the October 2020 meeting, the DUSC reviewed the utilisation of denosumab based on a 10% PBS sample analysis of prescriptions supplied from January 2014 to June 2019. The report indicated approximately 50% of patients remain on denosumab at 4 years after treatment initiation (including treatment breaks; longer follow-up sensitivity analysis). This estimate was lower than assumed at Year 4 in the economic model of the resubmission (81.5% without mortality and 75.8% with assumed mortality) based on 95% annual persistence.

6.28 In May 2022, the DUSC Secretariat conducted an analysis of the utilisation of anti-resorptive therapy after stopping teriparatide. The analysis captured patients who filled a teriparatide script between 1 April 2017 and 31 March 2018 (N = 1,454). The results indicated that 46% (664/1,454) of patients successfully transitioned to anti-resorptive therapy, defined as having at least 2 anti-resorptive scripts, the first of which was supplied within 2 months after stopping teriparatide. The ESC noted that this was lower than estimated in the analysis presented in the July 2019 romosozumab submission that suggested approximately 70% of patients continued with anti-resorptive therapy based on patients having at least one anti-resorptive script within 6 months after stopping teriparatide. The ESC noted the results also indicated relatively poor long-term persistence to anti-resorptive therapy, with 49% (716/1,454) of patients remaining persistent at 1 year, declining to 25% (361/1,454) at 3 years after cessation of teriparatide.[2]

6.29 The PSCR argued that the ARCH trial data shows maintenance of treatment effect for at least 2 years following discontinuation of romosozumab with the continued separation of the Kaplan-Meier curves (see Figure 1) and stated that this 'residual' treatment effect does not appear to be declining. As utilisation data indicate persistence with anti-resorptive therapy is lower than observed in clinical trials (see paragraphs 6.27 and 6.28), the ESC considered that convergence by 4 years would be more likely in clinical practice.

[2] Persistence estimates were based on patients having at least 1 anti-resorptive script after stopping teriparatide, and subsequent anti-resorptive scripts within allowed treatment gaps.

Figure 1 Time to first clinical fracture – ARCH full analysis set



Source: Figure 1, p1, PSCR

Comparative harms

6.30 Adverse event data from the included romosozumab trials have previously been considered by the PBAC.

6.31 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.

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

6.33 In regard 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 8 shows a summary of serious cardiovascular events reported in the ARCH trial.

Table 8: 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 12-12, p193 of the ARCH trial report

6.34 The resubmission also provided an overall summary from a sponsor-conducted report on the cardiovascular safety of romosozumab. The report aimed to further investigate the imbalance in serious cardiovascular events observed in the ARCH and BRIDGE clinical trials but not in the FRAME trial. This report had been considered by the PBAC in previous submissions.

6.35 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 did note that the incidence of cardiovascular events in the alendronate arm of the ARCH trial was unexpectedly low in the first year and that the relative difference between treatments reduced over time. The report also explored plausible biological mechanisms for the increase in cardiovascular events but stated that no specific mechanism could be identified based on genetic studies, pre-clinical models or epidemiological data. The report concluded that a causal relationship between romosozumab and serious cardiovascular events could not be confirmed or refuted based on the available data.

6.36 The resubmission also provided five Periodic Safety Update Reports (PSURs) published from 2019 with the most recent report capturing the 8 January 2021 to 7 July 2021 period. These data had not previously been considered by the PBAC.

6.37 Important identified risks were hypersensitivity, hypocalcaemia and immunogenicity (i.e. development of antibodies to romosozumab). Important potential risks were

osteonecrosis of the jaw, atypical femoral fracture, serious cardiovascular events of myocardial infarction and stroke, hyperostosis, foetal risk and serious infections. Missing information included osteoporosis rebound effects and safety in patients with renal impairment. No new safety signals were identified during the most recent reporting interval.

6.38 For each PSUR, the sponsor conducts a review of published literature for cardiovascular safety information pertaining to romosozumab. Overall, the resubmission claimed the cardiovascular safety review did not provide any new safety information. The resubmission stated that the risk-benefit profile of romosozumab remains positive and the current label language adequately informs both patients and physicians of the potential risks associated with romosozumab use and provides risk minimisation measures for patient management.

Benefits/harms

6.39 On the basis of direct evidence presented in the resubmission (ARCH trial), for every 1000 patients treated with romosozumab in comparison to alendronate over one year (primary treatment):

- Approximately 15 fewer patients would have a clinical fracture;
- Approximately 6 additional patients would have a serious cardiovascular event.

6.40 On the basis of direct evidence presented in the resubmission (ARCH trial), for every 1000 patients treated with romosozumab followed by alendronate in comparison to alendronate alone over a median of 33 months (primary and subsequent treatment):

- Approximately 33 fewer patients would have a clinical fracture;
- Approximately 4 additional patients would have a serious cardiovascular event.

Clinical claim

6.41 There were no major changes to the clinical evidence provided in the resubmission compared to previous submissions (November 2018, July 2019 and March 2020).

6.42 The resubmission described romosozumab as superior in terms of efficacy and inferior in terms of safety compared to alendronate due to the potential for increased risk of cardiovascular events with romosozumab.

6.43 The PBAC previously considered that fracture outcomes data from the ARCH trial supported a claim of superior efficacy of romosozumab followed by alendronate compared to alendronate alone. However, in contrast to the proposed population (restricted second line setting), the ARCH trial only provided evidence for romosozumab use in patients who were predominantly naïve to anti-resorptive therapy (para 7.8, romosozumab PSD, March 2020 PBAC meeting).

6.44 The PBAC previously considered that serious events of myocardial infarction and stroke remained an important potential risk with romosozumab and considered the claim of inferior comparative safety was reasonable (para 7.9, romosozumab PSD, March 2020 PBAC meeting).

6.45 The following evidence gaps were previously noted by the PBAC and were not addressed in the resubmission:

- The lack of comparative evidence against denosumab as the therapy most likely to be replaced (para 7.9, romosozumab PSD, November 2018 PBAC meeting; para 7.4, romosozumab PSD, March 2020 PBAC meeting). The PSCR noted that a comparison with denosumab was included in the resubmission as a sensitivity analysis in the economic evaluation.
- The lack of long-term comparative efficacy data for romosozumab and that maintenance of treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy. The PBAC considered that the utilisation of anti-resorptive therapy following cessation of romosozumab should be reviewed after an appropriate period post listing to investigate the success of transitioning patients to anti-resorptives (para 7.6, romosozumab PSD, March 2020 PBAC meeting). The ESC noted that in the May 2022 DUSC Secretariat analysis only 46% (664/1,454) of patients successfully transitioned to anti-resorptive therapy after stopping teriparatide (see paragraph 6.28).

6.46 The magnitude of benefit associated with romosozumab versus alendronate in the proposed first line setting was uncertain. There were concerns with the applicability of risk profiles of patients in the ARCH trial to the PBS population due to potential differences in disease severity characterised by number of fractures, BMD T-scores, fracture location, fracture severity and fracture timing. There are likely to be differences in the magnitude of benefit associated with romosozumab between patients with single versus multiple prior fractures. The PSCR acknowledged that differences in fracture risk across patient groups would lead to differences in the absolute magnitude of benefit associated with romosozumab versus alendronate. However, the PSCR claimed that the proposed PBS population is likely to be at higher risk than the ARCH trial population which it argued will translate to greater absolute benefit with romosozumab. The ESC considered there may be a role for romosozumab in the first line setting. However, as it was difficult to reconcile the proposed clinical criteria for first line therapy with the inclusion criteria of the ARCH trial the ESC considered this may not be for the PBS population nominated in the resubmission (see paragraph 6.17).

6.47 It was unclear whether the clinical evidence adequately supports the clinical claim of superior efficacy in the additional second line subpopulations. There are no fracture outcomes data in this population and limited BMD outcomes data based on post-hoc analyses of romosozumab trials. The results suggest that the use of romosozumab after anti-resorptive therapy provides smaller BMD gains (measured as relative effects) compared to the use of romosozumab before anti-resorptive therapy. The ESC considered that there were no robust data presented in the resubmission to support expansion of the second line listing.

6.48 The PBAC considered the claim of superior comparative effectiveness was reasonable for the first line setting in treatment naïve patients, however the magnitude of the

effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab. The PBAC considered the claim of superior comparative effectiveness for the additional second line subpopulations was uncertain due to data limitations.

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

Economic analysis

6.50 The original submission for romosozumab (first- and second-line settings), considered at the November 2018 PBAC meeting, included a cost-effectiveness analysis of romosozumab versus alendronate. The PBAC considered that the analysis did not form a reliable basis for decision-making due to the overestimation of fracture risk and treatment effect, the assumption of continuing treatment effect (which relied on adherence and persistence rates unlikely to be achieved in the PBS population), and potentially unreliable fracture disutilities (para 7.13, romosozumab PSD, November 2018 PBAC meeting).

6.51 A cost-effectiveness analysis was not presented in the July 2019 resubmission, which focused on romosozumab for the second line setting only. The PBAC considered that it was unclear whether romosozumab would be cost-effective if used in a broader population than patients who currently use teriparatide (para 7.1, romosozumab PSD, July 2019 PBAC meeting).

6.52 The March 2020 resubmission of romosozumab for the second line setting included the economic model comparing romosozumab and alendronate from the November 2018 submission with key changes to selected cost inputs only. At that time, the PBAC noted that the economic model, which was fundamentally unchanged from the November 2018 submission, was unreliable for decision-making and hence could not be used to assess the cost-effectiveness of romosozumab in the broader second line population (para 7.12, romosozumab PSD, March 2020 PBAC meeting).

6.53 The current resubmission presented a cost-effectiveness analysis of romosozumab versus alendronate in patients with severe osteoporosis. The economic model was a cost-utility analysis based on data from the ARCH trial and other modelled variables.

6.54 The resubmission acknowledged that the economic evaluation was essentially representative of the cost-effectiveness of romosozumab versus alendronate in the first line setting given the ARCH trial population was predominantly treatment naive.

6.55 The resubmission acknowledged that the cost-effectiveness of romosozumab in the expanded second line setting was uncertain, however, the resubmission claimed that there was historical PBAC precedence of recommending second line use of osteoporosis medications based on evidence in the first line setting. The ESC noted that no documentation was provided in the resubmission and considered that this claim was poorly justified.

6.56 The resubmission assumed that relative treatment effects in the ARCH trial are generalisable to the second line setting. The ESC noted that no data were provided in the resubmission to support this assumption. Results from post-hoc analyses of romosozumab trials suggest potentially lower BMD gains should anabolic agents be used following anti-resorptive therapy (see paragraph 6.23). The impact of differences in the magnitude of BMD gains on fracture risk reduction was uncertain.

6.57 The resubmission claimed the expanded second line population is at higher fracture risk than the proposed first line population as it includes patients with the same BMD threshold requirement of ≤ -2.5 but they are older, have longer disease duration and higher fracture burden. Assuming constant relative treatment effects, higher underlying fracture risk would translate to a larger reduction in the incidence of fractures. The ESC considered that no data were provided in the resubmission to support this assumption. It was unclear whether the expanded second line population are at a higher fracture risk compared to the first line population given the removal of the multiple fracture requirement.

6.58 The table below presents the key components of the economic evaluation.

Table 9: Key components of the economic evaluation

Component	Summary
Treatments	Romosozumab/alendronate versus alendronate
Time horizon	20 years in the model base case (to age 94) versus 3 years in the ARCH trial
Outcomes	Life years and quality adjusted life years (QALYs)
Methods used to generate results	Markov cohort model with tunnel states (half-cycle corrected)
Health states	7 health states including 3 on-treatment health states (no fracture/other fracture, post- hip fracture, post-vertebral fracture), 3 off-treatment health states (no fracture/other fracture, post- hip fracture, post-vertebral fracture) and dead.
Cycle length	Annual
Transition probabilities	Transition probabilities for fracture in the on-treatment health states were derived from the alendronate arm of the ARCH trial. Treatment effect estimates for the romosozumab/alendronate arm were derived from the ARCH trial for the first 3 years then assumed to diminish in a linear fashion until convergence of fracture risks with the alendronate arm by Year 6. Treatment discontinuation was assumed to be 5% yearly. Transition probabilities for fracture in the off-treatment health states were derived from the alendronate arm of the ARCH trial and adjusted using fracture risk multipliers. The incidence of serious cardiovascular events was derived from the ARCH trial. Probability of death was based on Australian life tables adjusted using fracture-related mortality multipliers. 78% of QALYs occur in the extrapolated period. Incremental costs were accrued in the trial period and were offset over time primarily due to reduced fracture costs.
Costs	Drug acquisition costs were estimated using the proposed effective price for romosozumab and published DPMQ for alendronate and denosumab. Administration costs were based on MBS costs for GP and nurse administrations. Acute fracture costs were derived from the ICUROS study (Watts 2013), inflated from 2012 estimates to 2021 costs. Cardiovascular event management costs were based on acute hospitalisation and additional costs during the initial 12 months (readmissions and out of hospital costs) (Ioannides-Demos 2010). Cardiovascular monitoring costs were based on MBS costs for blood tests, electrocardiograms, and specialist visits.
Health related quality of life	Baseline utility, incident fracture QALY loss and ongoing fracture disutilities were derived from the Australian cohort of the ICUROS study (Abimanyi-Ochom 2015). The cardiovascular event disutility was based on a published disutility for an acute myocardial infarction (Sullivan 2011).
Discount rate	Revised base case in the evaluation used 5% per annum (1.5% used in the base case of the resubmission)
Software package	Excel

Source: Table 3.1-2, p61 of the resubmission

6.59 Multiple revisions were made to model inputs to address significant concerns raised by the ESC at the November 2018 meeting including the extrapolation of treatment effect, fracture risks, mortality, utility values and cardiovascular events. There were additional changes to the model structure with the inclusion of off-treatment health states, and all cost inputs have been revised. The economic analysis in the current resubmission was fundamentally different to the model previously considered by the PBAC.

6.60 There was an error in the vertebral and other fracture cost inputs in the economic model of the resubmission. The cost of a vertebral fracture was used as the cost of other fractures and vice versa. The PSCR acknowledged the evaluation correctly identified an error in the attribution of fracture costs in the economic model. The ESC noted this was corrected during the evaluation in the revised base case.

6.61 All patients start in the baseline health state of no incident fracture, with an elevated mortality risk due to prior prevalent fracture. In each annual cycle, patients can have no event or experience a hip fracture, vertebral fracture, other fracture, or death. Patients experiencing multiple fracture events accrue the costs and consequences of each event and have ongoing chronic costs and consequences based on the most severe event (hip fracture > vertebral fracture > severe osteoporosis with no fracture/other fracture). The model uses tunnel states to adjust mortality risk based on time since fracture.

6.62 Patients receive romosozumab for one year followed by alendronate or alendronate only throughout the course of the model. In each cycle, patients who are alive can discontinue treatment and enter corresponding off-treatment health states of no fracture/other fracture, hip fracture or vertebral fracture. In each cycle, patients in the off-treatment health states can also have no event or experience a hip fracture, vertebral fracture, other fracture, or death; however, these patients are at an elevated fracture risk compared to those remaining on treatment. Patients who are off treatment have no treatment costs and accrue the same fracture-related costs and consequences as on-treatment patients.

6.63 The resubmission acknowledged that the use of the cohort model structure limited the ability to track multiple fractures at the same site, which necessitated the use of incidence rather than event rates in the model and restricted the attribution of fracture-related costs and consequences. A microsimulation would have greater ability to track patients when many health states are of relevance as well as when patients are assumed to be at changing risk of incurring multiple events with long term consequences, as is the case with osteoporosis.

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

Table 10: Key drivers of the model

Description	Method/Value	Impact
Magnitude of treatment effect	Treatment effects modelled based on data from the ARCH trial. The estimated cost-effectiveness of romosozumab is sensitive to uncertainty around the point estimates used in the model.	High, favours romosozumab
Extrapolation of treatment effect	The resubmission claimed that 12-month, 24-month and primary analysis period (median 33 months) outcomes from the ARCH trial show sustained treatment benefit beyond discontinuation of romosozumab after 12 months. Therefore, the resubmission assumed that treatment efficacy associated with romosozumab would diminish in a linear fashion between Years 4-6, after which the romosozumab arm is attributed the same fracture risks as the alendronate arm.	High, favours romosozumab
Circumstances of use	The resubmission assumed treatment adherence of 90% based on drug exposure data from the ARCH trial, applied as an ongoing fixed reduction to drug costs only. The resubmission assumed annual treatment persistence of 95% for all modelled treatments. Modelled adherence and persistence are unlikely to reflect both trial-based and real-world circumstances of use. No long-term adherence and persistence data were provided in the resubmission.	High, favours romosozumab

Source: constructed during the evaluation

6.65 The resubmission claimed that 12-month, 24-month and primary analysis period (median 33 months) outcomes from the ARCH trial show sustained treatment benefit

beyond discontinuation of romosozumab after 12 months. Therefore, the resubmission assumed that treatment benefit would not immediately diminish to zero after the 3-year trial period. In the base case, the resubmission assumed that treatment efficacy associated with romosozumab would diminish in a linear fashion between Years 4-6, after which the romosozumab arm is attributed the same fracture risks as the alendronate arm. No long-term data are available in support of the comparative efficacy of romosozumab versus alendronate beyond the trial duration. The PSCR claimed the extrapolation of treatment effects over 6 years in the economic model is conservative given the ARCH trial data shows maintenance of treatment effect for at least 2 years following discontinuation of romosozumab (see Figure 1). The ESC noted that no new data were presented supporting longer term treatment benefit and considered convergence at 4 years would be more likely to reflect a real world setting (see paragraph 6.29). The pre-PBAC response noted the argument made by ESC that convergence by 4 years would be more likely as utilisation data indicate persistency with anti-resorptive therapy is lower than observed in clinical trials (see paragraph 6.29). The pre-PBAC response argued that the model separately accounted for this treatment discontinuation by assuming zero efficacy in patients who discontinue. The pre-PBAC response stated that the ESC suggestion of convergence by 4 years would have the effect of immediately removing all extrapolation of treatment benefits for the proportion of patients remaining on treatment.

6.66 The resubmission assumed treatment adherence of 90% based on drug exposure data from the ARCH trial, applied as an ongoing fixed reduction to drug costs only. The approach used to estimate imperfect adherence may not be appropriate as the trial-based drug exposure did not differentiate between treatment adherence (i.e. extent to which patients conformed to the timing, dosage and frequency of the drug) and persistence (i.e. duration of time from treatment initiation to discontinuation). The resubmission's approach is likely to overestimate trial-based non-adherence given 10% of patients discontinued in the first year of the trial. The resubmission did not adequately justify the assumption of equivalent treatment adherence between all modelled treatments. Overall, trial-based adherence estimates may not be representative of real-world adherence, particularly in terms of long-term use of alendronate and denosumab.

6.67 The resubmission assumed annual treatment persistence of 95% for all modelled treatments. Patients who discontinue treatment no longer accrued drug and administration costs and were attributed elevated fracture risk. No justification was provided for the assumed persistence estimate. The assumption of equivalent levels of persistence between all modelled therapies was inappropriate given differences in terms of mode of administration, dosing frequency and total treatment duration. The PSCR claimed the implementation of 95% yearly persistence estimates in the economic model was conservative, as fracture incidence based on the ITT population of the ARCH trial inherently accounts for treatment discontinuations. The ESC noted alternative persistence rates were tested in sensitivity analyses (see Table 13), and

considered it was unclear why these analyses would show such an increase in ICER if the effectiveness outcomes applied in the model inherently incorporate a degree of discontinuation and hence were conservative as proposed by the PSCR. In addition, the ESC considered the assumed persistence rates were inconsistent with clinical practice given the May 2022 DUSC Secretariat analysis indicated only 46% of patients successfully transitioned to anti-resorptive therapy after stopping teriparatide (see paragraph 6.28).

6.68 During the evaluation, a comparison of trial-based versus modelled fracture estimates was conducted to validate the model (see Table 11).

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

	Romosozumab/alendronate	Alendronate/alendronate	Incremental difference
Cumulative incidence of fractures in the ARCH trial (Years 1-3)			
Clinical fractures	10.62%	14.60%	-3.98%
- Hip fractures	2.22%	3.80%	-1.58%
- Vertebral fractures	1.69%	3.69%	-2.00%
- Other fractures [a]	6.71%	7.11%	-0.40%
Cumulative incidence of fractures in the model (Years 1-3)			
Clinical fractures	11.08%	14.69%	-3.62%
- Hip fractures	2.29%	3.55%	-1.25%
- Vertebral fractures	1.48%	3.23%	-1.75%
- Other fractures	7.30%	7.91%	-0.62%
Cumulative incidence of fractures in the model (Years 4-20)			
Clinical fractures	51.86%	52.66%	-0.80%
- Hip fractures	12.81%	13.11%	-0.30%
- Vertebral fractures	12.48%	12.92%	-0.43%
- Other fractures	26.56%	26.63%	-0.07%

Source: constructed during the evaluation using the 'Evenity_CEA_Mar22' Excel economic model of the resubmission and additional data from Figure 14-4.4, p901; Figure 14-4.7, p907; Figure 14-4.8, p909 of the ARCH trial report

[a] Estimates were calculated during the evaluation with the same approach used in the resubmission. The incidence of other fractures was calculated as total incident clinical fractures – incident hip fractures – incident clinical vertebral fractures.

6.69 The comparison indicated slightly higher fracture incidence in the modelled population compared to the trial population. The resubmission claimed that the application of imperfect treatment persistence resulted in an overestimation of the incidence of fractures and underestimation of relative treatment effects of romosozumab versus alendronate, over the first three years of the model compared to the trial. This claim was validated during the evaluation, however, numerical differences remained between trial- and model-based estimates. The reasons for the numerical differences were the inclusion of mortality multipliers and differences between data sources and approaches used to derive the trial- and model-based estimates. Trial-based estimates in the table above were extracted from Kaplan-Meier curves of time-to-first event analyses whereas modelled estimates were based on calculated annualised fracture incidence using primary/secondary endpoints in the trial (24 months or primary analysis period).

6.70 While the majority of fractures in the model occurred beyond the duration of the trial, the majority of the incremental difference between treatment arms occurred during the first three years. Removal of modelled treatment discontinuation (i.e. 100%

persistence) yielded a similar pattern in the extrapolated period, with a reduction in fracture incidence in both arms and marginal increase in the incremental difference in favour of romosozumab.

6.71 The resubmission assumed constant fracture risk over time. The ESC noted this was inconsistent with the resubmission's claim that patients with a recent fracture are at high imminent risk of a subsequent fracture, that formed part of the resubmissions justification of the targeted first line population. This approach was also inconsistent with published economic evaluations that calculated changing risk over time based on changing patient characteristics (e.g. age, fracture burden).

6.72 The resubmission did not adequately justify the use of inverted treatment effect estimates from the meta-analysis of the FIT trial cohorts (alendronate placebo-controlled trial) to quantify elevated fracture risk in patients who have stopped romosozumab and/or alendronate in the economic model. There are concerns with the robustness of the meta-analysis and applicability of these estimates to the PBS population given the data are relatively old (conducted in the mid-1990s) and the trial used lower than currently recommended doses of alendronate.

6.73 The resubmission estimated mortality multipliers based on the Dubbo Osteoporosis Epidemiology Study that recruited older Australians who sustained a fracture between 1989 and 2007. The results from the Dubbo Osteoporosis Epidemiology Study indicate an association between osteoporotic fracture and increased mortality but do not demonstrate causation. Additionally, the data are relatively old and may not be applicable to current practice.

6.74 The impact of cardiovascular events was implemented as a fixed incremental cost (first year only) and ongoing disutility in the romosozumab arm only based on the between arm difference in the incidence of serious cardiovascular events reported in the ARCH trial. The ESC noted the resubmission assumed no mortality impact associated with cardiovascular events. The ESC considered that this assumption was not appropriate as it was inconsistent with the trial. The pre-PBAC response noted that cardiovascular deaths were reported in a similar proportion of patients in both treatment arms: 58 (2.8%) subjects in the romosozumab/alendronate group and 55 (2.7%) subjects in the alendronate/alendronate group. The pre-PBAC response argued that, consistent with the evidence, the model did not apply a difference in mortality but did include a disutility and cost associated with a potential difference in the incidence of serious cardiovascular events.

6.75 During the evaluation, an expanded stepped economic evaluation was conducted to calculate a revised base case using corrected fracture costs and a 5% (rather than the 1.5% used in the resubmission) discount rate (see table below).

Table 12: Results of the stepped economic evaluation

Step and component	Romosozumab/alendronate	Alendronate/alendronate	Increment
Step 1: Trial-based efficacy and modelled annual fracture incidence based on the ARCH trial, 3 year horizon, drug and administration costs[a]			
Costs	$	$	$
Patients without fracture	0.8925	0.8540	0.0385
Incremental cost per additional patient free of any incident fracture			$[1]
Step 2: Include drug adherence and persistence[a]			
Costs	$	$	$
Patients without fracture	0.8877	0.8511	0.0366
Incremental cost per additional patient free of any incident fracture			$[1]
Step 3: Include cardiovascular monitoring and event costs[a]			
Costs	$	$	$
Patients without fracture	0.8877	0.8511	0.0366
Incremental cost per additional patient free of any incident fracture			$[1]
Step 4: Include acute fracture costs[a]			
Costs	$	$	$
Patients without fracture	0.8877	0.8511	0.0366
Incremental cost per additional patient free of any incident fracture			$[2]
Step 5: Include osteoporosis utility/disutility values and cardiovascular event disutility[a]			
Costs	$	$	$
QALYs	2.4952	2.4852	0.0099
Incremental cost per QALY gained			$[3]
Step 6: Modelled fracture risks (constant annualised fracture risks from the ARCH trial), modelled treatment efficacy (trial-based efficacy for 3 years then risk convergence by year 6), 20 year time horizon[a]			
Costs	$	$	$
QALYs	11.8691	11.8252	0.0439
Incremental cost per QALY gained			$[4]
Step 7: Include mortality multipliers[a]			
Costs	$	$	$
QALYs	10.4841	10.4235	0.0606
Incremental cost per QALY gained			$[4]
Step 8: Include 5% discount[a]			
Costs	$	$	$
QALYs	7.6781	7,6353	0.0428
Incremental cost per QALY gained (revised base case)			$[5]

Source: constructed during the evaluation using the 'Evenity_CEA_Mar22' Excel economic model of the resubmission
Abbreviation: QALY, quality adjusted life year
[a] Estimates were calculated during the evaluation
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$45,000 to < $55,000*
[3] *$155,000 to < $255,000*
[4] *$25,000 to < $35,000*
[5] *$35,000 to < $45,000*

6.76 In the revised base case, treatment with romosozumab followed by alendronate was associated with a cost per QALY gained of $35,000 to < $45,000 compared to alendronate alone for the treatment of severe osteoporosis in the first line setting.

6.77 The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation.

6.78 For every 1000 patients treated with romosozumab/alendronate versus alendronate and followed up for 20 years, the economic evaluation (using undiscounted costs) estimates that there would be:

- romosozumab drug and administration costs of $0 to < $10 million, and alendronate drug costs of $0 to < $10 million (including treatment adherence and persistence).
- increased cardiovascular event and monitoring costs of $305,000; with cardiovascular events associated with reduced quality of life.
- 44 new fractures avoided comprising 15 hip fractures, 22 vertebral fractures and 7 other fractures; which would be a net cost saving in acute and chronic costs, be associated with improved quality of life and result in an average of 27.5 life years gained.

6.79 Results of sensitivity analyses for the revised base case using a 5% discount rate and including corrected fracture costs are summarised in the table below.

Table 13: Results of sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Revised base case (5% discount rate, corrected fracture costs)[a]	$[redacted]	0.0428	$[redacted]1
Discount rate (base case 5% discount rate)[a]			
3.5%	$[redacted]	0.0472	$[redacted]2
1.5% (submission's base case with corrected fracture costs)	$[redacted]	0.0542	$[redacted]2
0%	$[redacted]	0.0606	$[redacted]2
Time horizon (base case 20 years)[a]			
3 years	$[redacted]	0.0095	$[redacted]3
5 years	$[redacted]	0.0168	$[redacted]4
10 years	$[redacted]	0.0317	$[redacted]5
Comparator (base case alendronate drug costs and fracture risks based on the ARCH trial)[a]			
Denosumab (denosumab drug and administration costs; treatment effect of HR 0.58 applied to vertebral fracture risk)	$[redacted]	0.0331	$[redacted]1
Denosumab (denosumab drug and administration costs; no adjustments to fracture risk)	$[redacted]	0.0428	$[redacted]2
Treatment discontinuation (base case 5% per year in both arms)[a]			
No discontinuation, both arms	$[redacted]	0.0468	$[redacted]2
10% per year, both arms	$[redacted]	0.0392	$[redacted]1
20% per year, both arms	$[redacted]	0.0331	$[redacted]5
Romosozumab/alendronate: 5% per year; alendronate/alendronate: 10% per year	$[redacted]	0.0659	$[redacted]6
Romosozumab/alendronate: 10% per year; alendronate/alendronate: 5% per year	$[redacted]	0.0162	$[redacted]7
100% discontinuation in year 1, both arms	$[redacted]	0.0102	$[redacted]7
No discontinuation in year 1 and 100% discontinuation in year 2, both arms	$[redacted]	0.0228	$[redacted]8
No discontinuation in the first 2 years and 100% discontinuation in year 3, both arms	$[redacted]	0.0343	$[redacted]5
No discontinuation in the first 3 years and 100% discontinuation in year 4, both arms	$[redacted]	0.0416	$[redacted]1
No discontinuation in the first 4 years and 100% discontinuation in year 5, both arms	$[redacted]	0.0451	$[redacted]1
Mortality multipliers (base case severe osteoporosis: 1.41; 0-5 years after a fracture: 2.21)[a]			
No multipliers (i.e. no survival benefit with romosozumab)	$[redacted]	0.0321	$[redacted]5

Analyses	Incremental cost	Incremental QALY	ICER
Lower multiplier for 0-5 years after a fracture: 1.81	$[redacted]	0.0365	$[redacted][1]
Magnitude of treatment effect (base case hazard ratios for hip 0.62, vertebral 0.41 and other 0.92)[a]			
No impact on hip fracture (HR: 1.00)	$[redacted]	0.0224	$[redacted][4]
Smaller hip fracture risk reduction (HR: 0.92)	$[redacted]	0.0266	$[redacted][8]
Larger hip fracture risk reduction (HR: 0.42)	$[redacted]	0.0535	$[redacted][6]
Smaller vertebral fracture risk reduction (HR: 0.71)	$[redacted]	0.0301	$[redacted][9]
Larger vertebral fracture risk reduction (HR: 0.24)	$[redacted]	0.0499	$[redacted][2]
No impact on other fracture (HR: 1.00)	$[redacted]	0.0418	$[redacted][1]
Treatment effect duration (base case fixed for 3 years then linear decrease until convergence by 6 years)[a]			
Fixed for 3 years, convergence by 4 years	$[redacted]	0.0340	$[redacted][5]
Fixed for 3 years, convergence by 5 years	$[redacted]	0.0386	$[redacted][1]
Fixed for 4 years, convergence by 5 years	$[redacted]	0.0433	$[redacted][1]
Fixed for 4 years, convergence by 6 years	$[redacted]	0.0473	$[redacted][2]
Fixed for 5 years, convergence by 6 years	$[redacted]	0.0513	$[redacted][2]
Multivariate analysis[b]			
Treatment discontinuation and treatment effect duration (base case 5% per year in both arms with treatment effect duration fixed for 3 years then linear decrease until convergence by 6 years)			
Treatment discontinuation 20% per year, both arms; treatment effect duration fixed for 3 years, convergence by 4 years.	$[redacted]	0.0282	$[redacted][9]

Source: constructed during the evaluation using the 'Evenity_CEA_Mar22' Excel economic model of the resubmission
Abbreviation: HR, hazard ratio; QALY, quality adjusted life year
[a] Estimates were calculated during the evaluation
[b] Estimates were calculated during the preparation of the ESC Advice
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$25,000 to < $35,000*
[3] *$155,000 to < $255,000*
[4] *$95,000 to < $115,000*
[5] *$45,000 to < $55,000*
[6] *$15,000 to < $25,000*
[7] *$115,000 to < $135,000*
[8] *$75,000 to < $95,000*
[9] *$55,000 to < $75,000*

6.80 Results of the sensitivity analyses indicated that the model was most sensitive to the magnitude of treatment benefit, the extrapolation of treatment benefits beyond the trial duration and treatment discontinuation assumptions.

6.81 The impact of treatment discontinuation using time-varying persistence estimates could not be adequately assessed due to model structure. Results of alternative scenarios (fixed persistence followed by 100% discontinuation) suggest that perfect persistence for 5 years is needed to achieve an incremental cost per QALY gained of less than $35,000 to < $45,000. The model was also sensitive to any differences in treatment persistence between arms. The ESC noted that a treatment discontinuation rate of 20% per year, in both arms, increased the ICER from $35,000 to < $45,000 per QALY gained in the base case to $45,000 to < $55,000 per QALY gained. The ESC considered that, given the poor persistence with anti-resorptive therapy evident in the March 2022 DUSC Secretariat analysis (see paragraph 6.28), a 20% treatment discontinuation rate would likely be the minimum discontinuation rate anticipated in clinical practice.

6.82 As outlined in paragraph 6.29, the ESC considered that convergence by 4 years would be more likely in clinical practice. The ESC noted that assuming the treatment effect was fixed for 3 years, with convergence by 4 years, increased the ICER to $45,000 to < $55,000 per QALY gained.

6.83 Adjustment of both discontinuation and convergence increased the ICER to $55,000 to < $75,000 per QALY gained.

6.84 The ESC noted the structure of the economic model did not allow sensitivity analyses to assess the impact of fatal cardiovascular events. The ESC considered a model that allowed a mortality impact associated with cardiovascular events would be more consistent with the clinical trial evidence. The pre-PBAC response argued that cardiovascular deaths were reported in a similar proportion of patients in both treatment arms in the ARCH trial (see paragraph 6.74).

6.85 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.

6.86 The resubmission presented a sensitivity analysis using denosumab as an alternative comparator. Annual fracture risks were based on the estimates derived for the alendronate arm in the base case, with an adjustment to vertebral fracture risk based on improved treatment efficacy associated with denosumab compared to alendronate. Hip and other fracture risks were unadjusted. The resubmission assumed the same relative treatment benefit of romosozumab versus alendronate would be applicable to the comparison between romosozumab and denosumab. No data were provided in support of this assumption.

Drug cost/patient/year

Table 14: Drug cost per patient for romosozumab/alendronate

	ARCH trial	Economic model	Financial estimates
Treatment adherence	Not reported [a]	90% [b]	90%
Treatment persistence	Not reported; approximately 90% of patients remained in the study at 1 year	95% [c]	Not included
Romosozumab doses/scripts	Mean 10.8 doses over 1 year	10.26 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	Not included
Romosozumab drug cost per patient	-	$ in Year 1 [f]	$ over a year [g]
Follow-up alendronate drug cost per patient	-	$189 [h] per year in patients remaining on treatment in subsequent years	Not included

Source: Section 3.6, pp94-97 of the resubmission; Financial analysis final Excel workbook of the resubmission

[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
[d] Assuming 90% adherence and 95% persistence, applied to 12 doses
[e] Assuming 90% adherence, applied to 12 doses
[f] $[redacted] (proposed effective DPMQ) x 10.26 scripts
[g] $[redacted] (proposed effective DPMQ) x 10.8 scripts/year
[h] $16.13 (March 2022 DPMQ, PBS Item 8511Y) x 11.7 scripts/year

Estimated PBS usage & financial implications

6.87 This resubmission was not considered by DUSC. The resubmission used a mixed epidemiological/market share approach to estimate the utilisation and financial impact of romosozumab, based on the following additional subpopulations excluding patients already eligible for romosozumab under the existing listing:

- First line population who have received less than 12 months anti-resorptive therapy with multiple clinical fractures or a single hip/clinical vertebral fracture, and BMD T-score ≤ -2.5
- Second line population with multiple fractures including at least one symptomatic fracture after 12 months anti-resorptive therapy, and BMD T-score ≤ -2.5 and > -3.0.
- Second line population with a single symptomatic fracture after 12 months anti-resorptive therapy, and BMD T-score ≤ -2.5.

6.88 The definition of the first line population was agnostic to fracture timing, which was inconsistent with the proposed restriction that required at least 1 fracture to be recent (within previous 24 months).

6.89 The resubmission used similar data sources and assumptions to those used in the March 2020 submission to derive the size of the eligible populations in the following order: treated osteoporosis patients; patients treated for less than 12 months and at least 12 months; patients with or without a prior fracture.

6.90 All eligible population estimates including the population eligible for first line therapy were based on treated osteoporosis patients only. The requirement that patients should receive prior anti-resorptive therapy (for less than 12 months) in order to be eligible for romosozumab treatment was inconsistent with the proposed place in therapy of romosozumab as initial treatment in treatment-naïve patients. This criterion is also part of the proposed PBS restriction; however, the intent of this criterion was uncertain with no justification provided in the resubmission. The PSCR stated the proposed 'first-line' listing was intentionally worded to allow access to romosozumab in the complementary population of patients who have either not yet started osteoporosis therapy or have received an anti-resorptive agent for a very short time (< 12 months) and have the necessary fracture and BMD profile that would indicate treatment with romosozumab would be the better clinical approach to address imminent fracture risk. The ESC agreed with the evaluation that as the estimates were based on treated osteoporosis patients only they were inconsistent

with the intent outlined in the PSCR to allow use of romosozumab in treatment-naïve patients.

6.91 The resubmission used a 10% PBS sample analysis to estimate the number of patients receiving osteoporosis treatments in November 2021, extrapolated to 2022-2027 assuming 3.4% annual growth. The treated population estimates could not be validated due to poor documentation in the resubmission. The applied growth rate was based on relatively old data (2014-2015 PBS utilisation data from the DUSC 2016 osteoporosis report) and was lower than growth rates of 5.6-5.8% per year from 2019-2021 reported in the 10% PBS sample analysis of the resubmission.

6.92 The proportions of patients meeting PBS eligibility criteria were estimated from fracture history and BMD T-scores of female patients in the Geelong Osteoporosis Study and assumptions. The Geelong Osteoporosis Study is a longitudinal population-based cohort study to investigate the epidemiology of osteoporosis in Australia. The study enrolled an age-stratified sample of adult women (recruited in 1993-1997) and men (recruited between 2001-2006) from the regional city of Geelong, Australia.

6.93 The applicability of the Geelong Osteoporosis Study to the PBS population may be limited for the following reasons:

- Patient characteristics (e.g. BMD T-scores) and fracture histories were derived from estimates that are nearly 30 years old and may not be representative of current clinical practice (with widespread use of newer osteoporosis treatments).
- Data used to derive key inputs for financial estimates were based on a sample of the general population that may not be representative of patients seeking care for osteoporosis
- It was unclear whether estimates from the female cohort of the Geelong Osteoporosis Study are representative of males with osteoporosis.

6.94 The derivation of the proportion of patients meeting the fracture criteria in each subpopulation was complex, based on multiple sources and assumptions (summarised in the table below).

Table 15: Proportions of patients meeting the fracture criteria in each subpopulation

Parameter	Value applied and source	Comment
First line population		
Patients with a prior fracture and BMD less than -2.5	32.5%. Analysis of a sample from the Geelong Osteoporosis Study. In the subgroup with fracture, 5.3% of those age ≤ 69 years and 41.5% of those age ≥70 years had BMD ≤-2.5. A weighted proportion was calculated assuming 25% were age ≤ 69 years and 75% were age ≥70 years.	Estimates from the Geelong Osteoporosis Study (GOS) are nearly 30 years old and may not be applicable to current practice. The resubmission did not justify the application of data that included untreated patients from the GOS to treated population estimates.
Patients with multiple fractures or a single hip/clinical vertebral fracture	57%. Midpoint based on estimates from the ARCH trial (58%) and analysis using data from the Geelong Osteoporosis Study and AusICUROS study (56%).	Neither analysis considered recency of fracture, which was inconsistent with the proposed PBS restriction.

Parameter	Value applied and source	Comment
	A post-hoc analysis of the ARCH trial was conducted, stratifying patients by baseline BMD and fracture history. Of the subgroup with BMD ≤-2.5, 58% of patients had a history of either multiple clinical fractures or a single hip/clinical vertebral fracture. Based on a subgroup analysis of patients with a prior fracture in the Geelong Osteoporosis Study (stratified by age groups with age distribution assumption), the resubmission estimated 27.9% of patients had multiple fractures. The resubmission estimated 28.6% of patients had a single hip/vertebral fracture by applying the incidence of hip/vertebral fractures from the AusICUROS study (39.6%) to the proportion of patients without multiple fractures (calculated as 100%-27.9% = 72.1%). The final estimate was calculated as the sum of the proportion with multiple fractures and the proportion with a single hip/vertebral fracture (27.9% + 28.6% = 56.5%).	Estimates based on the Geelong Osteoporosis Study are relatively old and may not be applicable to current practice.
Second line population with multiple fractures, BMD ≤-2.5 and >3.0		
Patients with a prior fracture and BMD ≤-2.5 and >-3.0	12.9%. Based on data from the Geelong Osteoporosis Study (GOS) and denosumab FREEDOM extension study. The resubmission estimated the proportion of patients with a prior fracture and BMD ≤-3 as 17.2% and the corresponding proportion with BMD ≤-2.5 and >-3 as 15.3%, based on a subgroup analysis of patients with fracture from the GOS. The resubmission claimed adjustments to these estimates were necessary to account for BMD treatment effects, estimated from on an ad-hoc analysis of lumbar spine BMD T-scores in the cross-over arm (placebo to denosumab) from an open-label extension study of denosumab (extension of FREEDOM trial). The analysis indicated that 57% of placebo patients with BMD ≤-3 achieved a BMD >-3 after 24 months of treatment with denosumab. Of the 17.2% of patients with a prior fracture and BMD ≤-3, the resubmission estimated that 9.7% would have a BMD ≤-3 despite treatment (57% x 17.2%) and the remaining 7.5% would achieve a BMD >-3. The resubmission assumed that 57% of these patients would have a BMD of ≤-2.5 and >-3 and the remainder would have a BMD >-2.5, yielding 4.2% of treated patients with BMD of ≤-2.5 and >-3 (calculated as 57% x 7.5%). Of the 15.3% of patients with a prior fracture and BMD ≤-2.5 and >-3, the resubmission estimated that 57% of patients would remain with BMD ≤-2.5 and >-3 despite treatment, yielding 8.7% of treated patients with BMD of ≤-2.5 and >-3 (calculated as 57% x 15.3%). The total proportion of treated patients with a prior fracture and BMD ≤-2.5 and >-3.0 was calculated as 4.2% + 8.7% = 12.9%.	This estimate was synthesised using sources of data that were not exchangeable (Geelong Osteoporosis Study of the general population and FREEDOM trial population) and may not be applicable to the PBS population. The resubmission appears to have misinterpreted the results of the ad-hoc analysis of the FREEDOM extension study that reported a 57% relative reduction in the proportion of patients with BMD ≤-3 (i.e. those who achieved a BMD >-3). Based on these results, 43% of patients have BMD ≤-3 despite treatment, not 57% of patients. The calculations were complex and difficult to follow, with multiple adjustments to account for BMD treatment effects based on assumptions that were inadequately justified.
Patients with an on-treatment fracture	20.94%. Calculated using an estimated risk of fracture of 29.3% presented in the March 2020 submission, adjusted using a relative risk ratio of 0.715 derived from ARCH trial data. This 29.3% fracture risk estimate was derived using 4 individual 5-year fracture risk estimates (42%, 55%, 61%, 84%) using the	The ESC previously raised concerns with the incident fracture rate that was inappropriately derived from an individual risk calculator and assumed patient characteristics (para 6.81, romosozumab PSD,

Parameter	Value applied and source	Comment
	Garvan Fracture risk calculator. A flat annual fracture rate of 7.7% was calculated using the midpoint of this range, weighted by gender distribution (80% women). A 30% downward adjustment was applied to the estimate to account for osteoporosis treatment effects. An average duration of therapy for patients on at least 12 months continuous therapy was estimated as 4.8 years based on a 10% PBS sample analysis. Excluding the first year of therapy, the calculated duration of therapy was 3.8 years. The annual fracture rate of 7.7% was multiplied by 3.8 years to yield a proportion of patients with fracture of 29.3%. The resubmission conducted a post-hoc analysis of clinical fracture in the alendronate arm of the ARCH trial, with subgroups stratified by baseline lumbar spine BMD T-scores and number of any prior fracture. The risk ratio was calculated using the cumulative incidence of clinical fracture (over median follow-up of 2.75 years) in patients with multiple fractures and a BMD T-score of ≤-2.5 to >-3 and those with a BMD T-score of ≤-3 in the ARCH trial (calculated as 0.111/0.155 = 0.715).	March 2020 PBAC meeting). This was not addressed in the resubmission. The estimated incident fracture risk should not be considered reliable as it was based on the same approach with further adjustments using an additional data source and assumptions to derive the fracture risk in the target population.
Second line population with a single fracture and BMD ≤-2.5		
Patients without a prior fracture and BMD ≤-2.5	22.6%. In treated patients with a prior fracture, the resubmission estimated 9.7% have BMD ≤-3.0, and 12.9% have BMD ≤-2.5 and >-3.0 (source and derivation described above for patients with a prior fracture and BMD ≤-2.5 and >-3.0).	The resubmission inappropriately assumed that BMD T-scores based on patients with a prior fracture would be generalisable to patients without a prior fracture.
Patients with an on-treatment fracture	15.59%. Calculated using an estimated risk of fracture of 29.3% presented in the March 2020 submission (described above), adjusted using a relative risk ratio of 0.5328 derived from ARCH trial data. The resubmission estimated the cumulative incidence of clinical fracture (over median follow-up of 33 months) in patients with a single fracture and BMD score of ≤-2.5 to >-3.0 and ≤-3.0 (combined) as 8.28% (27/326) based on a post-hoc subgroup analysis of ARCH trial data. A risk ratio was calculated using the cumulative incidence of clinical fracture in this subgroup versus patients with multiple fractures and BMD T-score of ≤-3 (calculated as 0.0828/0.155 = 0.5328).	The estimated incident fracture rate should not be considered reliable as it was based on an inappropriately derived risk estimate (see above).

Source: Section 4, pp110-118 of the resubmission; Financial analysis final Excel workbook of the resubmission

6.95 The incident fracture rate applied to the restricted second line population requested in the March 2020 submission was used as the basis of on-treatment fracture risks estimated in the expanded second line populations. The ESC previously considered the following as issues of concern (para 6.81, romosozumab PSD, March 2020 PBAC meeting):

- 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 individual patient characteristics to estimate population-level risk; and

- the adjustment used to approximate a prevalent fracture rate from the incident fracture rate (based on average duration of therapy) could not be validated due to inadequate documentation and appeared to have anomalous results.

6.96 The concerns previously raised in March 2020 were not addressed in the resubmission. The resubmission used the same estimate with further adjustments using ARCH trial data and additional assumptions to derive the fracture risk in the target populations.

6.97 The table below presents the estimated use and financial impact of romosozumab to the PBS/RPBS.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Treated osteoporosis patients	[redacted][1]	[redacted][16]	[redacted][16]	[redacted][16]	[redacted][16]	[redacted][24]
First line population						
Received <12M treatment (32.79%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Patients with prior fracture (75%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][2]
BMD ≤-2.5 (32.5%)	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][21]	[redacted][21]	[redacted][21]
Multiple clinical fractures or single hip/clinical vertebral fracture (57%)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients initiating romosozumab	[redacted][6]	[redacted][6]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][11]
Second line population with multiple fractures, BMD ≤-2.5 and >-3.0						
Received ≥12M treatment (67.21%)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][22]	[redacted][22]	[redacted][22]
Patients with prior fracture (75%)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][7]	[redacted][7]
Patients receiving 1L romosozumab [a]	-	[redacted][6]	[redacted][6]	[redacted][11]	[redacted][11]	[redacted][11]
Patients without 1L romosozumab	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
BMD ≤-2.5 and >-3.0 (12.9%)	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][4]
On-treatment fracture (20.94%)	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][11]	[redacted][11]	[redacted][11]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients initiating romosozumab	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Second line population with a single fracture and BMD ≤-2.5						
Received ≥12M treatment (67.21%)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][22]	[redacted][22]	[redacted][22]
Without prior fracture (25%)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
BMD ≤-2.5 (22.6%)	[redacted][17]	[redacted][17]	[redacted][17]	[redacted][17]	[redacted][5]	[redacted][5]
On-treatment fracture (15.59%)	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Uptake	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients initiating romosozumab	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Total estimated utilisation of romosozumab						
First line scripts	[redacted][4]	[redacted][18]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Second line scripts (multiple fractures, BMD ≤-2.5 and >3.0)	[redacted][11]	[redacted][17]	[redacted][5]	[redacted][9]	[redacted][9]	[redacted][9]
Second line scripts (single fracture, BMD ≤-2.5)	[redacted][6]	[redacted][11]	[redacted][11]	[redacted][11]	[redacted][17]	[redacted][17]
Total scripts	[redacted][12]	[redacted][3]	[redacted][3]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of romosozumab						
PBS/RPBS cost of romosozumab less copay	$[redacted][13]	$[redacted][19]	$[redacted][20]	$[redacted][23]	$[redacted][23]	$[redacted][23]
PBS/RPBS cost offset from displaced anti-resorptives	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]	-$[redacted][14]
Net financial implications						
Net PBS/RPBS cost	$[redacted][13]	$[redacted][19]	$[redacted][19]	$[redacted][20]	$[redacted][20]	$[redacted][20]
MBS costs due to increased cardiovascular monitoring [b]	$[redacted][15]	$[redacted][15]	$[redacted][15]	$[redacted][15]	$[redacted][15]	$[redacted][15]
Net cost to Government	$[redacted][13]	$[redacted][19]	$[redacted][20]	$[redacted][20]	$[redacted][20]	$[redacted][23]

Source: Table 4.2-4, p114; Table 4.2-5, p115; Table 4.2-6, p115 of the resubmission

Abbreviation: M, months

[a] Based on patients receiving 1st line romosozumab in the preceding year

[b] Includes additional costs due to increased specialist visits, electrocardiography and blood tests over 1 year of romosozumab treatment

The redacted values correspond to the following ranges:

[1] 600,000 to < 700,000
[2] 200,000 to < 300,000
[3] 100,000 to < 200,000
[4] 50,000 to < 60,000
[5] 30,000 to < 40,000
[6] 5,000 to < 10,000
[7] 400,000 to < 500,000
[8] 300,000 to < 400,000
[9] 40,000 to < 50,000
[10] 500 to < 5,000
[11] 10,000 to < 20,000
[12] 80,000 to < 90,000

[13] *$10 million to < $20 million*
[14] *net cost saving*
[15] *$0 to < $10 million*
[16] *700,000 to < 800,000*
[17] *20,000 to < 30,000*
[18] *90,000 to < 100,000*
[19] *$20 million to < $30 million*
[20] *$30 million to < $40 million*
[21] *60,000 to < 70,000*
[22] *500,000 to < 600,000*
[23] *$40 million to < $50 million*
[24] *800,000 to < 900,000*

6.98 The estimated net cost to Government including PBS/RPBS cost offsets and additional MBS costs was $10 million to < $20 million in Year 1, increasing to $40 million to < $50 million in Year 6, a total of $100 million to < $200 million over 6 years.

6.99 Overall, the ESC considered the approach used in the resubmission failed to adequately identify the pool of patients who would be eligible for treatment with romosozumab, particularly those eligible for first line therapy. Many of the estimates used to define the population eligible for first line treatment (e.g. prior fracture, BMD ≤ -2.5, risk of multiple fractures or single hip/vertebral fracture) were based on sources that included untreated patients but were applied to treated patient estimates. It may be more appropriate to use an epidemiological approach using an incident osteoporosis population rather than the prevalent population treated for less than 12 months.

6.100 Estimates of the first line population do not account for recency of fracture, which was inconsistent with the proposed PBS restriction.

6.101 The derivation of the eligible populations was also dependent on similar data sources and approaches used in the March 2020 submission that were considered issues of concern by the ESC. During the evaluation, a comparison of predicted versus actual utilisation of romosozumab on the PBS was conducted. There were 2,852 romosozumab scripts dispensed after 11 months of listing (April 2021 to February 2022) compared to 10,000 to < 20,000 scripts predicted in the first year in the March 2020 submission, with teriparatide maintaining the majority market share in 2021 (more than 9,000 scripts). The reasons for the large difference were uncertain, however, the utilisation data for romosozumab on the PBS was immature and increasing on a month-to-month basis.

6.102 Uptake rates were assumed based on previously used uptake rates in the March 2020 submission, adjusted to account for 100% anabolic agent market share in the expanded listings. Uptake rates assumed for the restricted second line setting may not be applicable to the requested first line and expanded second line settings.

6.103 Based on the resubmission's estimates the additional severe osteoporosis population treated with romosozumab represents approximately % of all patients treated for osteoporosis, with the majority of patients receiving romosozumab as first line treatment %) followed by second line in those with multiple fractures and BMD ≤ -2.5 and > -3.0 (%), and second line in those with a single hip/vertebral fracture and BMD ≤ -2.5 (%). The ESC considered these estimates should not be considered reliable given the eligible second line population should be based on a larger patient population ever treated with osteoporosis medications (for at least 12 months),

whereas the eligible first line population would be based on a substantially smaller incident severe osteoporosis population who are treatment-naïve and experienced at least one recent clinical fracture.

6.104 Cost offsets due to displacement of anti-resorptives may be overestimated as the number of scripts were only adjusted using a 90% adherence rate based on the administration of romosozumab in the ARCH trial. This is particularly relevant when considering the displacement of therapies in the second line setting, as the resubmission did not account for less than ideal persistence to anti-resorptives, as reported in the DUSC 2020 review of denosumab and the May 2022 analyses of anti-resorptive use after teriparatide.

Quality Use of Medicines

6.105 The resubmission stated that the sponsor has a significant presence and reach in the osteoporosis setting, providing an extensive education program that covers specialists, GPs and patients. The resubmission claimed that this presence will be leveraged to provide initiatives to support the quality use of romosozumab, including successful transition to anti-resorptive therapy upon completion of romosozumab treatment.

6.106 There are multiple ongoing post-marketing surveillance studies and published reviews assessing the risk of serious cardiovascular events associated with romosozumab. To date, the available evidence has been unable to rule in or rule out a causal relationship between romosozumab and serious cardiovascular adverse events.

Financial Management – Risk Sharing Arrangements

6.107 The resubmission claimed the sponsor is willing to agree to a revised deed for romosozumab, extending the current risk-sharing arrangement for a further 5 years. The resubmission proposed that the new financial caps be the sum of the existing caps with the addition of financial estimates presented for the additional first- and second-line populations. The sponsor proposed a % rebate on any expenditure above the caps in place of the current hard caps. The PBAC agreed with the ESC that the nominated caps were highly uncertain as they were associated with significant uncertainties regarding the size of the eligible and treated populations.

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

7 PBAC Outcome

7.1 The PBAC did not recommend romosozumab for the treatment of severe osteoporosis in the first line setting, nor the expanded listing in the second line setting. The PBAC considered the ARCH trial supported a claim of superior efficacy of romosozumab followed by alendronate compared to alendronate alone in treatment naïve patients; however, the magnitude of benefit was likely overestimated compared to the clinical effectiveness in the Australian treatment setting due to prior use of, poor transition

to and lower persistence with anti-resorptive therapy post romosozumab. The PBAC considered the comparative effectiveness for the additional second line subpopulations was uncertain due to data limitations. The PBAC noted an economic analysis was presented for romosozumab in the first line setting and considered that revised inputs and assumptions were required, along with a price reduction, to achieve acceptable cost-effectiveness. The PBAC considered the cost-effectiveness of romosozumab in the expanded second line setting was unable to be adequately assessed using the data presented. The PBAC considered that the size of expanded population was poorly defined and the financial estimates were highly uncertain.

7.2 The PBAC noted the input from individuals, health care professionals and organisations highlighting the potential role of romosozumab in the first line setting in those at highest risk of fracture recurrence. In addition, the comments described concerns regarding inequity in access associated with the current romosozumab PBS listing. The PBAC considered there is likely a clinical need for earlier use of romosozumab in patients at very high risk of fracture, noting that a number of international guidelines support the earlier use of anabolic agents in such patients (see paragraph 4.4).

7.3 The clinical criteria in the requested first line restriction was based on a synthesis of fracture location, number of fractures, clinical symptoms, recency of fracture and BMD T-score. The PBAC considered the clinical criteria as presented in the submission did not appear consistent with the range of very high risk groups identified in published guidelines or the ARCH trial eligibility criteria. The PBAC agreed with the ESC that there were inconsistencies in the subpopulation definitions of very high risk between the restriction, clinical evidence, economic model and financial estimates. The pre-PBAC response provided a combined single restriction for romosozumab which encompassed both first- and second-line use and included reference to minimal trauma fracture history. The PBAC considered a combined single restriction that included reference to minimal trauma fractures as part of identification of very high risk patients was consistent with existing osteoporosis listings and would likely be appropriate.

7.4 The PBAC considered that alendronate, as a proxy for anti-resorptive therapy, was appropriate as the nominated comparator. However, the PBAC reiterated its previous advice that denosumab would be the therapy most likely to be replaced in practice (see Table 2).

7.5 The resubmission was based on a direct comparison of romosozumab versus alendronate in the ARCH trial, conducted in patients predominantly naïve to anti-resorptive therapy. The PBAC noted that treatment with romosozumab followed by 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 (see paragraph 6.15).

7.6 The PBAC noted that no new data were presented in the resubmission to support an expanded second line listing. The resubmission assumed that relative treatment effects in the ARCH trial are generalisable to the second line setting. In addition, the PBAC noted the results from post-hoc analyses of romosozumab trials suggest potentially lower BMD gains should anabolic agents be used following anti-resorptive therapy (see paragraph 6.23), although the Committee considered the impact of lower BMD gains on fracture risk was uncertain.

7.7 The PBAC recalled previous concerns that the long-term comparative efficacy of romosozumab was uncertain and that maintenance of the treatment effect after discontinuation of romosozumab would likely depend on persistence with anti-resorptive therapy (see paragraph 6.26). The PBAC noted the May 2022 DUSC Secretariat analysis reported only 46% (664/1,454) of patients successfully transitioned to anti-resorptive therapy after stopping teriparatide (see paragraph 6.28). The PBAC considered concerns regarding maintenance of treatment effect after discontinuation of romosozumab were relevant to both the first- and second-line settings.

7.8 Overall, the PBAC reiterated its previous consideration that fracture outcomes data from the ARCH trial supported a claim of superior efficacy of romosozumab followed by alendronate compared to alendronate alone. The claim of superior comparative effectiveness was reasonable for the first line setting in treatment naïve patients, but was uncertain in the second line setting due to data limitations. Overall, the PBAC considered the magnitude of benefit in the Australian population was uncertain due to known poor long-term persistence on anti-resorptive therapy.

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

7.10 The PBAC recalled that in November 2018 and March 2020 the Committee considered the cost-effectiveness analysis of romosozumab versus alendronate presented was unreliable for decision-making (see paragraphs 6.50 and 6.52). The PBAC noted that in this resubmission multiple revisions were made to the model inputs to address previous concerns (see paragraph 6.59). The PBAC agreed with the ESC that key issues for the revised model included the extrapolation of treatment benefits beyond the trial duration, treatment discontinuation assumptions and applicability to the second line setting. The PBAC considered there was high uncertainty in the extrapolation of treatment effects over 6 years given the lack of long-term efficacy data beyond the 3-year trial duration. Although the modelled treatment effect declines to zero incremental difference by year 6, the PBAC considered that the magnitude of treatment effects is uncertain and dependent on persistence to anti-resorptive therapy. The PBAC agreed with the ESC that convergence at 4 years would be more likely to reflect a real world setting, and noted this increased the ICER from a base case of $35,000 to < $45,000 per QALY to $45,000 to < $55,000 per QALY gained. The PBAC considered the 95% yearly persistence to anti-resorptive therapy appeared inconsistent with clinical practice (see paragraphs 6.27 and 6.28). The PBAC agreed with the ESC that a 20% discontinuation rate would likely be the minimum

discontinuation rate anticipated in clinical practice. The PBAC considered both the adjustment of discontinuation (treatment discontinuation 20% per year, both arms) and convergence by 4 years appropriate and noted this increased the ICER to $55,000 to < $75,000 per QALY gained. The PBAC considered the resulting ICER unacceptably high and considered a price reduction would likely be required to achieve cost-effectiveness under this revised scenario.

7.11 The PBAC noted an economic analysis was not presented for romosozumab in the expanded second line setting. The PBAC considered the cost-effectiveness of romosozumab in this expanded setting was unable to be adequately assessed using the data presented. The PBAC considered that due to the uncertainty of the clinical benefit compared to alendronate in treatment experienced patients, a cost-minimisation approach was more appropriate in the expanded second-line setting.

7.12 The PBAC considered the approach used to estimate the eligible population failed to identify the pool of patients who would be eligible for treatment with romosozumab. In addition, the PBAC considered the treated population estimates were highly uncertain, based on previously assumed uptake rates for the restricted second line setting that may not be applicable to the requested first line and expanded second line settings. As such, the PBAC advised the estimates could not be considered reliable and would need to be revised in any future resubmission.

7.13 The PBAC considered a resubmission for romosozumab should address the following issues:

- Revise the economic model to include a treatment discontinuation of 20% per year and convergence by 4 years as outlined in paragraph 7.10.
- A price reduction to achieve an ICER no higher than the revised base case ICER in this submission, using the revised economic model.
- Explore a weighted average price between first and second-line settings using cost-minimisation to anti-resorptive therapy to determine a price for the expanded second line setting.
- Revise the financial estimates to address concerns regarding the approach taken to determining the eligible and treated patient population.
- Propose an appropriate risk sharing arrangement to address any residual uncertainty regarding the population size, that takes into account that the current romosozumab listing is subject to a [redacted]% rebate for expenditure above the subsidisation caps, and Commonwealth expenditure in the current population has been significantly lower than estimated at time of listing.

7.14 The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.15 The PBAC considered that it would be appropriate to allow general practitioners to continue treatment with romosozumab once it had been commenced by a Specialist/Consultant Physician and advised that this change could be made to the current listing as outlined in paragraph 8.1. The PBAC considered that for clarity the

Treatment Criteria should remove 'Must be treated by a Specialist'. The PBAC did not consider a Streamlined Authority was appropriate for continuing treatment, given the requirement for a lifetime maximum of 12 months therapy should be checked by Services Australia.

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

Outcome:
Not recommended

8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
ROMOSOZUMAB					
romosozumab 105 mg/1.17 mL injection, 2 x 1.17 mL syringes	12301K	1	2	5	evenity

Restriction Summary / Treatment of Concept:		
		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:** 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 1800 888 333.
Prescribing rule level		**Administrative advice:** No increase in the maximum quantity or number of units may be authorised.
Prescribing rule level		**Administrative advice:** No increase in the maximum number of repeats may be authorised.
Prescribing rule level		**Administrative advice**: Special Pricing Arrangements apply.
		Indication: Severe established osteoporosis
		Treatment Phase: Initial treatment
		Clinical criteria:
		Patient must be at very high risk of fracture.
		AND
		Clinical criteria:
		Patient must have a bone mineral density (BMD) T-score of -3.0 or less.
		AND
		Clinical criteria:
		Patient must have had 2 or more fractures due to minimal trauma
		AND
		Clinical criteria:
		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
		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 therapy
	AND
	Clinical criteria:
	Patient must not have received treatment with PBS-subsidised teriparatide; or
	Patient must have developed intolerance to teriparatide of a severity necessitating permanent treatment withdrawal within the first 6 months of therapy.
	Treatment criteria:
	Must be treated by a ~~Specialist; OR Must be treated by a~~ Consultant Physician.
	Prescribing Instructions: A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
	Prescribing Instructions: If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with this drug is initiated.
	Prescribing Instructions: If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with this drug is initiated.
	Prescribing Instructions: Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or 70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.
	Prescribing Instructions: Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.
Restriction Summary / Treatment of Concept:	
Concept ID (for internal Dept. use)	**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 not exceed a lifetime maximum of 12 months therapy
	Treatment criteria:
	Must be treated by a *medical practitioner identifying as either:* ~~Specialist, OR Must be treated by~~ *(i)* a Consultant Physician, *(ii) a General Practitioner*

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

9 Context for Decision

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

10 Sponsor's Comment

Amgen is disappointed with this outcome and will continue to work with the PBAC to provide improved access to romosozumab. Amgen would like to thank all of the healthcare professionals, professional societies, patient organisations and consumers for their support of the romosozumab submission.