# 7.05 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 resubmission requested a General Schedule Authority Required (Telephone/electronic) listing for the treatment of severe established osteoporosis. The PBAC previously considered romosozumab for severe osteoporosis in November 2018 (first- and second-line settings), July 2019 (second-line setting), March 2020 (second-line setting), and July 2022 (first- and expanded second-line settings). 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 | Patients with severe osteoporosis who are at very high risk of fracture defined as those with a BMD T-score of ≤-2.5 and have either: a recent hip or symptomatic vertebral fracture, or multiple fractures (including 1 recent symptomatic fracture) ~~AND received less than 12 months treatment with anti-resorptive therapy~~; ~~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 | In terms of fracture risk reduction, the efficacy achieved with romosozumab (12-month treatment course) followed by alendronate is superior to that achieved with alendronate alone.<br>Romosozumab could have an inferior safety profile compared with alendronate due to the potential identified risk of CV events with romosozumab. |

Source: Table 1.1-2, p14 of the resubmission.
~~Strikethrough~~ text indicates changes to the requested population from the July 2022 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 Table 2 summarises key matters of concern from the July 2022 romosozumab submission that are relevant to the current resubmission for a line-agnostic listing.

**Table 2: Summary of key matters of concern**

| Matter of concern | How the resubmission addresses it |
|---|---|
| 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 (para 3.5, romosozumab Public Summary Document (PSD), July 2022 PBAC meeting) | A revised line-agnostic listing was proposed. |
| The PBAC previously noted numerous issues with the data presented to support the restricted second-line listing of romosozumab including 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 July 2022 resubmission to address these concerns or support the expanded use of romosozumab in the second-line setting (para 3.15, romosozumab PSD, July 2022 PBAC meeting). | No new data were presented in the current resubmission to support the expanded use of romosozumab in the second-line setting. |
| PBAC considered there was high uncertainty in the economic model's extrapolation of treatment effects over 6 years given the lack of long-term efficacy data beyond the 3-year trial duration, uncertain magnitude of treatment effects, and dependence 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. PBAC considered the 95% yearly persistence to anti-resorptive therapy appeared inconsistent with clinical practice, and agreed with the ESC that a 20% discontinuation rate would likely be the minimum discontinuation rate anticipated in clinical practice (para 7.10, romosozumab PSD, July 2022 PBAC meeting). | Treatment discontinuation rates have been increased from 5% to 20% for both romosozumab and alendronate. The resubmission maintained that convergence over 6 years is reasonable based on ARCH trial data that shows sustained treatment benefit beyond discontinuation of romosozumab after 12 months, and implementation of the higher discontinuation rate.<br><br>The effective ex-manufacturer price has been reduced from $[redacted] to $[redacted]. The revised incremental cost per QALY gained is $45,000 to < $55,000. |
| The PBAC noted that an economic analysis was not presented for romosozumab in the expanded second-line setting and the cost-effectiveness of romosozumab in this population was unable to be adequately assessed using the data presented. (para 7.11, romosozumab PSD, July 2022 PBAC meeting).<br>The PBAC considered that 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 should be explored (para 7.13, romosozumab PSD, July 2022 PBAC meeting). | The resubmission maintained that the cost-effectiveness of romosozumab in the first-line setting is applicable to the expanded second-line population.<br><br>An effective DPMQ of $[redacted] was proposed for romosozumab across all lines of therapy, which represents a reduction versus the current second-line price (effective DPMQ $[redacted]). |
| The PBAC considered the approach used to estimate the eligible population in the financial estimates 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 (para 7.12, romosozumab PSD, July 2022 PBAC meeting). | The resubmission updated utilisation and financial estimates although used similar subpopulations, steps and data sources to the July 2022 resubmission. Uptake rates were unchanged from the July 2022 resubmission. |

| Matter of concern | How the resubmission addresses it |
|---|---|
| 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 % rebate for expenditure above the subsidisation caps, and Commonwealth expenditure in the current population has been significantly lower than estimated at time of listing (para 7.13, romosozumab PSD, July 2022 PBAC meeting). | An updated risk sharing arrangement was proposed, incorporating a [redacted]% rebate for expenditure above the subsidisation caps. |

Source: Table 1.1-1, pp13-14 of the resubmission; Romosozumab Public Summary Document, July 2022 PBAC meeting.
Abbreviations: ICER, incremental cost-effectiveness ratio.

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

# 3 Requested listing

3.1 At the July 2022 PBAC meeting, 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 (para 3.5, romosozumab PSD, July 2022 PBAC meeting). 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 (para 7.3, romosozumab PSD, July 2022 PBAC meeting). The resubmission proposed a combined, line-agnostic restriction for patients with severe osteoporosis.

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| ROMOSOZUMAB | | | | | |
| Romosozumab, 105mg/1.17mL injection, 2 x 1.17mL pre-filled syringes | $404.81 published price<br>$[redacted] effective price | 1 | 2 | 5 | Evenity |
| **Category / Program:** General Schedule (Code GE) | | | | | |
| **Prescriber type:** ☒Medical Practitioners | | | | | |
| **Restriction type:** ☒ Authority Required – Telephone, Electronic | | | | | |
| **Condition:** Osteoporosis | | | | | |
| **Indication:** Severe established osteoporosis | | | | | |
| **INITIAL RESTRICTION** | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must be at a very high risk of fracture; | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must have a bone mineral density (BMD) T-score of -2.5 or less; | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must have had a fracture due to minimal trauma; | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |
| Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months, OR | | | | | |
| Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months, | | | | | |
| **AND** | | | | | |
| **Clinical criteria:** | | | | | |

| |
|---|
| The treatment must be the sole PBS-subsidised therapy for this condition; |
| **AND** |
| **Clinical criteria:** |
| The treatment must not exceed a lifetime maximum of 12 months of PBS-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 consultant physician |
| **CONTINUING TREATMENT RESTRICTION** |
| **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 therapy of PBS-subsidised therapy. |
| **Treatment criteria:** |
| Must be treated by a medical practitioner identifying as either: (i) a Consultant Physician, (ii) a General Practitioner. |
| **GRANDFATHERED TREATMENT RESTRICTION** |
| **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 a 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 had a fracture due to minimal trauma prior to starting non-PBS-subsidised treatment with this drug for this condition; |
| **AND** |
| **Clinical criteria:** |
| Patient must have had at least 1 hip or symptomatic vertebral fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition, OR |
| Patient must have had at least 2 fractures including 1 symptomatic new fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition; |
| **AND** |
| **Clinical criteria:** |
| The treatment must be the sole PBS-subsidised therapy for this condition; |
| **AND** |
| **Clinical criteria:** |
| The treatment must not exceed a lifetime maximum of 12 months of PBS-subsidised therapy; |
| **AND** |

| **Clinical criteria:** |
|---|
| Patients 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 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.<br><br>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. |

3.2 The proposed published price is the same as the current price of romosozumab on the PBS for the treatment of severe osteoporosis in the second-line setting. The resubmission stated that the proposed effective DPMQ of $[redacted] (lower than the existing effective price of $[redacted]) would apply to both current and proposed listings. The Pre-Sub-Committee Response (PSCR) and pre-PBAC response reiterated that the sponsor has reduced the price of romosozumab to the extent possible and is unable to accommodate any further price reduction.

3.3 The requested restrictions are narrower than the TGA indication (patients with osteoporosis at a 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) and BMD T-scores.

3.4 A comparison of the clinical criteria proposed in the July 2022 pre-PBAC response and in the current resubmission are presented in Table 3.

**Table 3: Comparison of fracture criteria for initial restriction proposed in the July 2022 pre-PBAC response and in current resubmission**

| Criteria proposed at July 2022 pre-PBAC meeting | Criteria proposed in current resubmission |
|---|---|
| First or second-line<br>• Patient must have had at least 1 symptomatic minimal trauma fracture<br>• Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months, OR<br>• Patient must have had multiple symptomatic fractures including 1 in the previous 24 months, OR<br><br>Second-line<br>• ~~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.~~ | First or second-line<br>• Patient must have had a fracture due to minimal trauma AND<br>• Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months, OR<br>• Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months |

Source: para 3.5, romosozumab PSD, July 2022 PBAC meeting; Section 1.4.1, pp21-22 of the resubmission
Underlined and strikethrough text highlights differences between the specified criteria.

3.5 The current proposed restriction removed the criterion allowing one symptomatic new fracture (at any fracture location) after at least 12 months continuous therapy with an anti-resorptive agent.

3.6 The wording of the current proposed restriction for first- or second-line patients with multiple fractures would allow patients with any type of prior fracture (whether symptomatic or not) to be eligible for treatment, as long as one fracture within the previous 24 months is symptomatic. The resubmission did not provide any explanation or justification for this change from the wording proposed in the July 2022 pre-PBAC response.

3.7 The PSCR noted the July 2022 pre-PBAC meeting restriction stipulated a 'symptomatic' minimal trauma fracture whereas in the resubmission it was simply stated that a patient must have had a fracture due to minimal trauma. The PSCR stated that the word 'symptomatic' was inadvertently omitted from this criterion in the March 2023 submission and requested it be reinstated.

3.8 The resubmission positioned romosozumab as an alternative to anti-resorptive therapy for treatment-naïve or experienced patients who are diagnosed with osteoporosis and are eligible for PBS-subsidised therapy and who meet the following criteria:

- A fracture due to minimal trauma; and
- BMD T-score ≤-2.5, with multiple total fractures including at least one recent symptomatic fracture (prior 24 months); or
- BMD T-score ≤-2.5 and a single recent hip or symptomatic vertebral fracture.

3.9 The resubmission argued that beginning treatment with romosozumab followed by anti-resorptive therapy is a strategy that effectively reduces the risk of important fractures and produces faster and greater increases in BMD and bone strength than with any current osteoporosis treatment. The proposed place in therapy for first-line patients was essentially unchanged from the July 2022 resubmission and appeared to be based on a synthesis of factors incorporating fracture location, number of fractures, clinical symptoms, recency of fracture and BMD T-score.

3.10 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.

3.11 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 previously considered these claims were inadequately supported in the July 2022 resubmission, with no data presented supporting the treatment benefit of romosozumab in patients at imminent fracture risk (para 3.7, romosozumab, July 2022 PBAC meeting).

3.12 The proposed positioning of romosozumab in the second-line setting was based on consistency across lines of therapy in the proposed PBS restriction, resulting in a relaxation of clinical criteria in the current PBS listing for romosozumab that require patients to have multiple minimal trauma fractures and a BMD threshold of ≤-3.0 in addition to having an on-treatment symptomatic fracture. While the application of consistent eligibility criteria across both first- and second-line settings may reduce the complexities associated with overlapping populations, the resubmission provided no evidence or support from clinical guidelines to quantify the risk of fracture in the expanded second-line population. The pre-PBAC response acknowledged the lack of second-line fracture outcome data and stated that an alternative would be to revise the proposed listing such that second-line access be limited to the currently eligible population.

3.13 The resubmission requested grandfathering provisions for patients meeting the proposed clinical criteria. The sponsor estimated that approximately < 500 patients are currently privately funding romosozumab, but anticipated an increase in patient numbers with the introduction of a shared cost program, forecast to reach approximately 500 to < 5,000 patients in the next year. The resubmission stated that most of these patients are anticipated to be first-line patients who meet the proposed PBS eligibility criteria. The resubmission did not provide any further details to substantiate these estimates.

3.14 The resubmission requested an Authority Required (telephone/online PBS Authorities system) listing for all proposed restrictions. The ESC previously considered an Authority Required (telephone/online PBS Authorities system) listing may be more appropriate than a Streamlined Authority listing 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 (para 3.17, romosozumab PSD, July 2022 PBAC meeting).

3.15 It was difficult to reconcile the proposed BMD and fracture criteria with the key clinical evidence from the ARCH trial that recruited patients who met the following criteria:

- BMD T-score ≤-2.5 AND EITHER at least one moderate or severe vertebral fracture OR at least 2 mild vertebral fractures, OR

- BMD T-score ≤ -2.0 AND EITHER at least 2 moderate or severe vertebral fractures OR a fracture of the proximal femur that occurred within 3 to 24 months prior to randomisation.

*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 Romosozumab is a monoclonal antibody that binds and inhibits sclerostin, which has a dual effect on bone metabolism by both promoting bone formation and reducing bone resorption.

4.3 Four patient subgroups are being targeted in the resubmission in addition to the population eligible under the current PBS restriction. Patients would be eligible for treatment whether in a first- or second-line setting (i.e. regardless of prior anti-resorptive treatment history). All patients must have BMD T-scores ≤-2.5, and must have experienced a fracture due to minimal trauma: either a hip or symptomatic vertebral fracture in the previous 24 months, or multiple previous fractures including one symptomatic fracture in the previous 24 months.

4.4 There were inconsistencies in the subpopulation definitions between the requested restriction, clinical management algorithm, clinical evidence, economic model inputs, and the utilisation estimates. Throughout the resubmission, there were inconsistencies in the specification of clinical status of fractures for patients with multiple fractures (whether or not the previous or incident fracture/s were required to be 'symptomatic').

4.5 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. The resubmission noted that the applicability of the ARCH trial population to the target second-line population may be limited as the trial population was predominantly treatment naïve, and acknowledged that relative treatment efficacy associated with romosozumab in this population was uncertain. However, the resubmission and PSCR claimed there was historical PBAC precedence of recommending second-line use of osteoporosis medications based on evidence in the first-line setting. No new data were presented to support the assumption of constant treatment effects across lines of therapy. The resubmission did not consider emerging discussions surrounding optimal treatment sequencing of osteoporosis treatments, with some published international guidelines recommending earlier use of anabolic agents. These

discussions appear to be based on post hoc analyses of BMD outcomes in romosozumab trials suggesting the relative efficacy of romosozumab used after anti-resorptives is smaller than when romosozumab is used before anti-resorptives. The results of these analyses were limited by the lack of fracture outcomes.

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

# 5 Comparator

5.1 The resubmission's nomination of alendronate as the main comparator was unchanged from the July 2022 resubmission. The resubmission acknowledged that denosumab is the therapy most likely to be replaced in practice, but 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. The PBAC previously considered that alendronate, as a proxy for anti-resorptive therapy, was appropriate as the nominated comparator. At the July 2022 meeting, the PBAC reiterated its previous advice that denosumab would be the therapy most likely to be replaced in practice (para 7.4, romosozumab PSD, July 2022 PBAC meeting). A sensitivity analysis with denosumab as an alternative comparator, unchanged from the July 2022 resubmission, was included in the economic evaluation.

*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. In addition to reiterating points made in the pre-PBAC response the sponsor highlighted the advantage of the once monthly administration schedule of romosozumab and highlighted that osteoporosis was a national health priority area.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (3) and organisations (5) via the Consumer Comments facility on the PBS website. The comment from an interested individual stated that all measures need to be taken to prevent patients with osteoporosis suffering fractures. The comments from health care professionals along with Healthy Bones Australia, Healthy Bones Australia & Monash University, Australian Women's Coalition, Musculoskeletal Australia and CreakyJoints Australia described a range of benefits of treatment with romosozumab including high bone density gain and the potential to prevent fracture risk and described the drug as having a positive safety profile. The comments also noted the low quality of life experienced by sufferers of osteoporotic fractures, including pain, disability, anxiety, decreased independence as well as the burdens

associated with hospital admissions and rehabilitation post-fractures. Comments from health care professionals and Healthy Bones Australia & Monash University highlighted the anticipated benefits of first-line use of romosozumab, rather than use post anti-resorptive therapy.

## *Clinical trials*

6.3 The ESC noted that the clinical evidence presented in the resubmission was unchanged from the July 2022 resubmission, with the exception of additional safety data from recent Periodic Safety Update Reports.

6.4 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 PBAC previously considered that the exclusion of the STRUCTURE trial (BMD outcomes only) was inadequately justified given PBAC's 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 (para 6.8, romosozumab PSD, July 2022 PBAC meeting). These trials were included during the evaluation. A summary of post hoc analyses of BMD outcomes in trials of romosozumab (ARCH, FRAME, STRUCTURE and Study 326), which were identified during evaluation of the July 2022 romosozumab resubmission, are presented again for completeness.

6.5 Details of the trials included in the resubmission and during the evaluation are presented in Table 4.

**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, p26 and Appendix 3 of the resubmission

6.6 The key features of the included trials are summarised in Table 5.

**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<br>First year: DB<br>Later years: OL<br>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<br>First year: DB<br>Later years: OL<br>3 years | Low | Postmenopausal women with osteoporosis | Fractures | Not used |
| **Romosozumab vs teriparatide** | | | | | | |
| STRUCTURE | 436 | MC, R, OL, AC<br>12 months | Unclear | Postmenopausal women with osteoporosis who had received prior anti-resorptive therapy | BMD | Not used |

Source: Section 2.4, pp27-33 of the resubmission; Table 2.3-1, p27 of the resubmission; FRAME trial report; STRUCTURE trial report
Abbreviations; AC, active-controlled; DB, double blind; MC, multi-centre; OL, open label; PC, placebo controlled; R, randomised

## *Comparative effectiveness*

6.7 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 Table 6.

**Table 6: Key fracture outcomes reported in the ARCH trial**

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

Source: Section 2.5.1, pp34-36 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

6.8 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.

6.9 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.

6.10 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.

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

6.12 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).

6.13 Multiple post hoc analyses of BMD outcomes in trials of romosozumab (ARCH, FRAME, STRUCTURE and Study 326) 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.

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

6.15 No new data were presented in the resubmission to address the applicability of the ARCH trial data to the new proposed PBS population. The PBAC has previously raised 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, with likely differences in magnitude of benefit associated with romosozumab between patients with single versus multiple prior fractures. The sponsor has acknowledged that differences in fracture risk across patient groups would lead to differences in the absolute magnitude of benefit associated with romosozumab versus alendronate, but claimed that the proposed PBS population is likely to be at higher risk than the ARCH trial population, which would translate to greater absolute benefit with romosozumab (para 6.46, romosozumab PSD, July 2022 PBAC meeting). The PSCR restated this claim.

6.16 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 July 2022 resubmission to address these concerns, with the length of time post-listing inadequate (at the time of evaluating the July 2022 submission) for this review given romosozumab has a recommended 12-month treatment course and it was listed on 1 April 2021.

6.17 In May 2022, the DUSC Secretariat conducted an analysis of the utilisation of anti-resorptive therapy after stopping teriparatide. The analysis captured data from 1,454 patients who filled a teriparatide script between 1 April 2017 and 31 March 2018. 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 (para 6.28, romosozumab PSD, July 2022 PBAC meeting).

6.18 The current resubmission stated that early PBS data indicate that 70% of current initiations to anabolic therapy are to romosozumab, persistence to romosozumab is higher than to any other osteoporosis therapy and approximately 95% of romosozumab patients successfully make the transition back to anti-resorptive therapy (ART). The ESC noted that the resubmission did not provide any evidence to support this statement.

## *Comparative harms*

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

6.20 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.

6.21 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.

6.22 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 7 shows a summary of serious cardiovascular events reported in the ARCH trial.

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

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

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

6.23 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.

6.24 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.

6.25 The resubmission also provided five Periodic Safety Update Reports (PSURs) published from 2019 with the most recent report capturing the 8 January 2022 to 7 July 2022 period. The two most recent PSURs have not previously been considered by the PBAC.

6.26 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. The ESC noted that no new safety signals were identified during the most recent reporting interval.

6.27 The resubmission noted that there has been a decrease in the rate of reporting of post-marketing cases of serious cardiovascular events since PSUR 5. A decrease in the rate of reporting of events does not indicate a reduction in potential risk, and may reflect increased awareness of potential risks and more selective prescribing to patients with cardiovascular risk factors.

6.28 For each PSUR, the sponsor conducts a review of published literature for cardiovascular safety information pertaining to romosozumab. Since the July 2022 resubmission, there has been one additional publication included in the review (De Mare et al 2022, on the role of sclerostin in vascular calcification based on mouse models) but it had no impact on the risk-benefit profile of 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. The new data presented in the resubmission does not refute the potential risk of cardiovascular events.

## *Benefits/harms*

6.29 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.

6.30 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*

6.31 There were no major changes to the clinical evidence provided in the resubmission compared to previous submissions (November 2018, July 2019, March 2020, and July 2022).

6.32 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.

6.33 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 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 previously considered the comparative effectiveness for the additional second-line subpopulations was uncertain due to data limitations (para 7.1, romosozumab PSD, July 2022 PBAC meeting). The ESC advised that with no new clinical effectiveness data the above issues raised by the PBAC in July 2022 remained unchanged.

6.34 The PBAC previously considered the claim of inferior comparative safety was reasonable (para 6.49, romosozumab PSD, July 2022 PBAC meeting). The ESC noted the two most recent PSURs and considered the claim of inferior comparative safety remained reasonable.

6.35 The following evidence gaps were previously noted by the PBAC when considering previous romosozumab submissions (November 2018, March 2020, July 2022) and were not addressed in the resubmission:

- Lack of comparative evidence against denosumab as the therapy most likely to be replaced.
- No fracture outcomes data to support the efficacy of romosozumab in the expanded second-line population.
- Lack of long-term comparative efficacy data for romosozumab.
- Uncertain magnitude of benefit associated with romosozumab versus alendronate in the proposed first-line setting, and 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, and fracture location, severity and timing.

6.36 The PBAC reaffirmed its July 2022 advice that the claim of superior comparative effectiveness was reasonable for the first-line setting in treatment naïve patients, however the magnitude of effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab. In addition, the PBAC reaffirmed its July 2022 advice that the claim of superior comparative effectiveness

for the additional second-line subpopulations was uncertain due to data limitations (para 6.48, romosozumab PSD, July 2022 PBAC meeting).

6.37 The PBAC reaffirmed its July 2022 advice that the claim of inferior comparative safety was reasonable (para 6.49, romosozumab PSD, July 2022 PBAC meeting).

## *Economic analysis*

6.38 The resubmission presented a modelled economic evaluation of romosozumab versus alendronate in patients with severe osteoporosis. The economic model was a cost-utility analysis based on data from the ARCH trial (a predominantly treatment-naïve population) and other modelled variables.

6.39 The PBAC previously recommended that a cost-minimisation approach versus alendronate in treatment-experienced patients be conducted (given the uncertainty of the clinical benefit of romosozumab compared to alendronate in treatment experienced patients), with a price for the expanded listing determined using a weighted average price between first- and second-line settings (para 7.13, Romosozumab PSD, July 2022 PBAC meeting). The proposed price of romosozumab is based on the cost-effectiveness analysis only. The resubmission maintained the argument that the cost-effectiveness of romosozumab in the first-line setting is applicable to its use in the expanded second-line population. The PSCR and pre-PBAC response argued that the sponsor has reduced the price of romosozumab to the extent possible and is unable to accommodate consideration of a cost-minimisation with alendronate or any further reduction in price for this component of the listing expansion. The pre-PBAC response acknowledged the lack of an economic analysis for this component of the expansion and indicated if this was an issue for the PBAC then an alternative would be to revise the proposed listing such that second-line access be limited to the currently eligible population.

6.40 Table 8 below presents the key components of the economic evaluation.

**Table 8: 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 20% 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.<br><br>75% of incremental QALYs were accrued in the extrapolated period beyond 3 years. Incremental costs were accrued in the trial period and were partly 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 | 5% for costs and benefits. |
| Software package | Excel |

Source: Table 3.1-1, p54 of the resubmission
Abbreviations: QALY, quality adjusted life year

6.41 Key changes to the model compared to the July 2022 submission include:

- Acute fracture costs were revised to correct for an error identified in the July 2022 commentary (para 6.60, Romosozumab PSD, July 2022 PBAC meeting).
- Discount rates were increased from 1.5% to 5% in line with ESC's advice (para 6.52, Romosozumab ESC Advice, July 2022 PBAC meeting).
- Discontinuation rates were increased from 5% to 20% for both romosozumab and alendronate, as recommended by the PBAC (para 7.10, romosozumab PSD, July 2022 PBAC meeting).
- The price of romosozumab was reduced from a DPMQ of $ to $.
- Several inputs were updated to reflect the most recently published data sources (PBS pricing, MBS fees, ABS lifetables).

6.42 The resubmission maintained that applying romosozumab treatment effect convergence over 6 years was appropriate, based on ARCH trial data and implementation of a higher discontinuation rate, and considered that convergence at

4 years, considered by PBAC to more likely reflect a real-world setting (para 7.10, Romosozumab PSD, July 2022 PBAC meeting), was unrealistically conservative. The PSCR restated that applying convergence of treatment effects by 4 years in patients persistent to treatment implies the elimination of treatment effects beyond 3 years. The PSCR argued that in the ARCH trial, treatment effects observed at 12 months were either sustained or improved out to the primary analysis, approximately two years after the completion of romosozumab. The PSCR stated that based on sustained treatment effects post completion of romosozumab in ARCH, it was considered clinically implausible and overly conservative to apply zero extrapolation of treatment effects beyond three years in the model. Therefore, the PSCR maintained that application of convergence of treatment effects for persistent patients by year 6 (i.e., diminishing treatment effects in years 4 and 5) was reasonable. The ESC noted the annual cycle length of the economic model and that the modelled estimates were adjusted with a half-cycle correction. The pre-PBAC response argued that maintaining a modest amount of extrapolation of effect for romosozumab vs alendronate over years 4 and 5 was appropriate. In addition, the pre-PBAC response argued that applying both the treatment discontinuation of 20% per year and convergence by 4 years would be overly conservative.

6.43 The model structure was unchanged from the July 2022 submission. 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.

6.44 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.

6.45 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.

6.46 Key drivers of the economic model are summarised in Table 9 below.

**Table 9: 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 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 PBAC considered that convergence at 4 years would be more likely to reflect a real world setting (para 7.10, Romosozumab PSD, July 2022 PBAC meeting). | 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 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.<br><br>The resubmission assumed annual treatment persistence of 80% for all modelled treatments. Patients who discontinue treatment no longer accrued drug and administration costs and were attributed elevated fracture risk. The assumption of equivalent levels of persistence between all modelled therapies was inadequately justified given differences in terms of mode of administration, dosing frequency and total treatment duration.<br><br>Overall, 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

6.47 The resubmission presented a comparison of fracture incidence in the current model versus the July 2022 model. The comparison indicated a higher incidence of fractures and lower incremental differences between romosozumab/alendronate and alendronate in the current submission versus the July 2022 submission, consistent with the higher annual discontinuation rate used in the current submission (20% versus 5% in the July 2022 submission).

6.48 The resubmission assumed constant fracture risk over time, which was inconsistent with the resubmission's claim that patients with a recent fracture are at high imminent

risk of a subsequent fracture. 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).

6.49 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.

6.50 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 ESC noted the data are relatively old and may not be applicable to current practice. Overall, the ESC considered there is limited evidence to support the inclusion of mortality multipliers in the model.

6.51 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 resubmission assumed no mortality impact associated with cardiovascular events, which was inconsistent with the trial.

6.52 Table 10 presents a stepped economic evaluation from the July 2022 base case to the base case in the current resubmission.

**Table 10: Results of the stepped economic evaluation from July 2022 base case to current base case**

| Step and component | Romosozumab/alendronate | Alendronate/alendronate | Increment |
|---|---|---|---|
| **July 2022 submission base case** | | | |
| Costs | $ | $ | $ |
| QALYs | 9.4755 | 9,4213 | 0.0542 |
| Incremental cost/QALY gained | | | $ [1] |
| **5% discount rate (updated from 1.5% in submission base case)** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.6781 | 7.6353 | 0.0428 |
| Incremental cost/QALY gained | | | $ [2] |
| **Acute fracture costs corrected for error (July 2022 evaluation base case)** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.6781 | 7.6353 | 0.0428 |
| Incremental cost/QALY gained | | | $ [2] |
| **Discontinuation rate 20% (increased from 5%)** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.6163 | 7.5832 | 0.0331 |
| Incremental cost/QALY gained | | | $ [3] |
| **PBS/MBS cost inputs updated to October 2022 unit costs** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.6163 | 7.5832 | 0.0331 |
| **Incremental cost/QALY gained** | | | $ [3] |
| **ABS lifetables updated to 2018-2022 (from 2017-2019)** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.7083 | 7.6752 | 0.0331 |
| **Incremental cost/QALY gained** | | | $ [3] |
| **Romosozumab DPMQ $ (reduced from $ )** | | | |
| Costs | $ | $ | $ |
| QALYs | 7.7083 | 7.6752 | 0.0331 |
| **Incremental cost/QALY gained (resubmission base case)** | | | **$** [3] |

Source: Table 3.8-4, p102 of the resubmission.

Abbreviations: ABS, Australian Bureau of Statistics; DPMQ, dispensed price for maximum quantity; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; QALY, quality adjusted life year

*The redacted values correspond to the following ranges*

[1] *$25,000 to < $35,000*

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

[3] *$45,000 to < $55,000*

6.53 Treatment with romosozumab followed by alendronate was associated with a cost per QALY gained of $45,000 to < $55,000 compared to alendronate alone for the treatment of severe osteoporosis in the first-line setting. The PBAC previously considered that a revised economic model should achieve an ICER no higher than the revised base case in the July 2022 submission $35,000 to < $45,000 per QALY gained; para 7.13, Romosozumab PSD, July 2022 PBAC meeting). The ESC noted that this would require a reduction in the requested DPMQ from $ to $.

6.54 Compared with the July 2022 evaluation base case (which corrected errors in acute fracture costs and used a 5% discount rate) increasing the discontinuation rate from 5% to 20% had the largest impact on the resubmission's economic evaluation.

6.55 The resubmission also presented a stepped economic evaluation from trial-based modelled costs and outcomes to the resubmission's base case. The extrapolation of

treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation.

- For every 0 to < 5,000 patients treated with romosozumab/alendronate versus alendronate and followed up for 20 years, the economic evaluation (using undiscounted costs and outcomes) estimated that there would be:
  - Additional drug and administration costs of $0 to < $10 million for romosozumab followed by alendronate, compared with alendronate treatment alone.
  - Increased cardiovascular event and monitoring costs of $0 to < $10 million; associated with cardiovascular events and reduced quality of life.
  - 35 new fractures avoided, composed of 12 hip fractures, 17 vertebral fractures and 5 other fractures; which would save $0 to < $10 million in acute and chronic fracture costs, be associated with improved quality of life, and result in an average of 20.7 life years gained.

6.56 The results of key sensitivity analyses are summarised in Table 11.

**Table 11: Results of sensitivity analyses**

| Analysis | Incremental cost($) | Incremental QALYs | ICER($) | % change from base case |
|---|---|---|---|---|
| **Base case** | [redacted] | **0.0331** | [redacted] 1 | **-** |
| **Discount rate (base case 5%)** | | | | |
| 3.5% | [redacted] | 0.0363 | [redacted] 2 | -9% |
| 0% | [redacted] | 0.0462 | [redacted] 2 | -30% |
| **Time horizon (base case 20 years)** | | | | |
| 3 years [a] | [redacted] | 0.0083 | [redacted] 5 | +323% |
| 5 years [a] | [redacted] | 0.0138 | [redacted] 6 | +136% |
| 10 years | [redacted] | 0.0251 | [redacted] 4 | +31% |
| **Comparator (base case alendronate drug costs and fracture risks based on the ARCH trial)** | | | | |
| Denosumab (denosumab drug and administration costs; treatment effect of HR 0.58 applied to vertebral fracture risk) | [redacted] | 0.0252 | [redacted] 1 | +14% |
| Denosumab (denosumab drug and administration costs; no adjustments to fracture risk) [a] | [redacted] | 0.0331 | [redacted] 3 | -19% |
| **Treatment adherence (base case 90%, applied to drug costs only)** | | | | |
| Full adherence (100%) [a] | [redacted] | 0.0331 | [redacted] 1 | +15% |
| Reduced adherence (80%) [a] | [redacted] | 0.0331 | [redacted] 3 | -15% |
| **Treatment discontinuation (base case 20% per year in both arms)** | | | | |
| No discontinuation, both arms | [redacted] | 0.0469 | [redacted] 2 | -32% |
| 5% per year, both arms | [redacted] | 0.0428 | [redacted] 2 | -24% |
| Romosozumab/alendronate: 15% per year; alendronate/alendronate: 20% per year [a] | [redacted] | 0.0485 | [redacted] 2 | -40% |
| Romosozumab/alendronate: 20% per year; alendronate/alendronate: 15% per year [a] | [redacted] | 0.0206 | [redacted] 7 | +79% |
| **Background fracture risk (base case derived from alendronate arm of ARCH trial)** | | | | |
| Increased by 10% | [redacted] | 0.0362 | [redacted] 3 | -13% |
| Increased by 20% | [redacted] | 0.0392 | [redacted] 2 | -24% |
| Increased by 30% | [redacted] | 0.0422 | [redacted] 2 | -34% |
| **Mortality multipliers (base case severe osteoporosis: 1.41; 0-5 years after a fracture: 2.21)** | | | | |
| No multipliers (i.e. no survival benefit with romosozumab) | [redacted] | 0.0249 | [redacted] 4 | +31% |
| Lower multiplier for 0-5 years after a fracture: 1.81 | [redacted] | 0.0283 | [redacted] 4 | +16% |
| **Magnitude of treatment effect (base case hazard ratios for hip 0.62, vertebral 0.41 and other 0.92)** | | | | |
| No impact on hip fracture (HR: 1.00) [a] | [redacted] | 0.0170 | [redacted] 8 | +166% |
| Smaller hip fracture risk reduction (HR: 0.92) | [redacted] | 0.0204 | [redacted] 6 | +110% |
| Larger hip fracture risk reduction (HR: 0.42) | [redacted] | 0.0415 | [redacted] 2 | -35% |
| Smaller vertebral fracture risk reduction (HR: 0.71) | [redacted] | 0.0230 | [redacted] 4 | +53% |
| Larger vertebral fracture risk reduction (HR: 0.24) | [redacted] | 0.0387 | [redacted] 3 | -18% |
| No impact on other fracture (HR: 1.00) | [redacted] | 0.0323 | [redacted] 1 | +6% |
| **Treatment effect duration (base case fixed for 3 years then linear decrease until convergence by 6 years)** | | | | |
| Fixed for 3 years, convergence by 4 years | [redacted] | 0.0282 | [redacted] 4 | +26% |
| Fixed for 3 years, convergence by 5 years | [redacted] | 0.0309 | [redacted] 1 | +11% |
| Fixed for 4 years, convergence by 5 years | [redacted] | 0.0336 | [redacted] 3 | -2% |
| Fixed for 4 years, convergence by 6 years | [redacted] | 0.0356 | [redacted] 3 | -10% |
| Fixed for 5 years, convergence by 6 years | [redacted] | 0.0376 | [redacted] 3 | -18% |
| **Multivariate analysis** | | | | |
| No mortality multipliers; treatment effect fixed for 3 years, convergence by 4 years [b] | [redacted] | 0.0211 | [redacted] 7 | +66% |

Source: constructed during the evaluation using the 'Evenity_CEA_Mar23' spreadsheet provided with the resubmission
Abbreviation: HR, hazard ratio; QALY, quality adjusted life year
[a] Calculated during the evaluation

[b] Calculated during the preparation of the ESC Advice. The DPMQ would need to reduce from $[redacted] to $[redacted] to achieve an ICER of $35,000 to < $45,000per QALY gained.
*The redacted values correspond to the following ranges*
[1] *$45,000 to < $55,000*
[2] *$25,000 to < $35,000*
[3] *$35,000 to < $45,000*
[4] *$55,000 to < $75,000*
[5] *$155,000 to < $255,000*
[6] *$95,000 to < $115,000*
[7] *$75,000 to < $95,000*
[8] *$115,000 to < $135,000*

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

6.58 The ESC noted a multivariate analysis which removed mortality multipliers (see paragraph 6.46) and included convergence by 4 years increased the base case ICER from $45,000 to < $55,000 per QALY gained to $75,000 to < $95,000 per QALY gained.

6.59 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.

6.60 The structure of the economic model did not allow sensitivity analyses to assess the impact of fatal cardiovascular events.

6.61 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 12: Drug cost per patient for romosozumab/alendronate**

| | ARCH trial | Economic model | Financial estimates |
|---|---|---|---|
| Treatment adherence | Not reported [a] | 90%[b] | 90% [b] |
| Treatment persistence | Not reported; approximately 90% of patients remained in the study at 1 year | 80%[c] | Not included |
| Romosozumab doses/scripts | Mean 10.8 doses over 1 year | 8.64 doses in Year 1[d] | 10.8 scripts over a year [e] |
| Follow-up alendronate | Not reported | 11.7 scripts per year in patients remaining on treatment in subsequent years[f] | Not included |
| Romosozumab drug cost per patient | - | $[redacted] in Year 1[g] | $[redacted] over a year [h] |
| Follow-up alendronate drug cost per patient | - | $189[i] per year in patients remaining on treatment in subsequent years | Not included |

Source: Sections 3 and 4 of the resubmission, ARCH clinical study report.

[a] Drug exposure data (i.e. reported as mean doses administered) did not differentiate between adherence and persistence

[b] Calculated using drug exposure data from the ARCH trial, mean 10.8 doses divided by expected number of doses at full adherence and persistence (12 doses)

[c] Assumption based on PBAC advice

[d] Assuming 90% adherence and 80% persistence, applied to 12 doses

[e] Assuming 90% adherence, applied to 12 doses

[f] Assuming 90% adherence, applied to 13 doses

[g] $[redacted] (proposed effective DPMQ) x 8.64 scripts

[h] $[redacted] (proposed effective DPMQ) x 10.8 scripts/year

[i] $16.19 (October 2022 DPMQ, PBS Item 8511Y) x 11.7 scripts/year

## *Estimated PBS usage & financial implications*

6.62 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 are initiating osteoporosis treatment, with multiple symptomatic fractures or a single hip/symptomatic vertebral fracture, and BMD T-score ≤-2.5.
- Second-line population with multiple fractures including at least one symptomatic fracture whilst on osteoporosis treatment, and BMD T-score ≤-2.5 and >-3.0.
- Second-line population with a single hip/symptomatic vertebral fracture whilst on osteoporosis treatment, and BMD T-score ≤-2.5.

6.63 The resubmission stated that this section was heavily revised from the July 2022 resubmission. Some of the steps taken to estimate the eligible population in the current resubmission were changed to better match the new requested restriction. However, many of the data sources and steps were unchanged from the July 2022 resubmission. The PSCR noted the financial estimates continue to rely on the number of patients who receive PBS subsidised osteoporosis therapy as the source of the

starting population and indicates this was a conscious decision to minimise the number of assumptions in an already complex analysis.

6.64 A comparison of patient populations in the July 2022 resubmission, the current resubmission and the current requested PBS restriction are presented in Table 13.

**Table 13: Comparison of patient populations in July 2022 resubmission, current resubmission, and requested PBS restriction**

| Subpopulations | July 2022 resubmission | Current resubmission | Relevant sections of requested restriction (current resubmission) |
|---|---|---|---|
| First-line | - <12 months osteoporosis therapy<br>- BMD ≤-2.5<br>- with a prevalent fracture<br>- multiple symptomatic fractures, or<br>- single hip or symptomatic vertebral fracture | - initiating osteoporosis therapy<br>- BMD ≤-2.5<br>- with a prevalent fracture<br>- multiple symptomatic fractures, or<br>- single hip or symptomatic vertebral fracture<br>- (fracture assumed to be the reason for initiation of osteoporosis therapy and therefore recent) | - (no therapy specified)<br>- BMD ≤-2.5<br>- fracture due to minimal trauma<br>- ≥2 fractures, including one symptomatic new fracture in prior 24 months, or<br>- ≥1 hip or symptomatic vertebral fracture in last 24 months |
| Second-line population (expansion of existing PBS population) | - on osteoporosis therapy<br>- BMD ≤-2.5 and >-3.0<br>- multiple fractures, including at least one symptomatic fracture after 12 months anti-resorptive therapy | - on osteoporosis therapy<br>- BMD ≤-2.5 and >-3.0<br>- multiple fractures, including at least one symptomatic fracture whilst on therapy (in previous 24 months) | - (no therapy specified)<br>- BMD ≤-2.5 and >-3.0<br>- fracture due to minimal trauma<br>- ≥2 fractures, including one symptomatic new fracture in prior 24 months |
| Second-line population (single symptomatic fracture) | - on osteoporosis therapy<br>- BMD ≤-2.5<br>- single symptomatic fracture after 12 months anti-resorptive therapy. | - on osteoporosis therapy<br>- BMD ≤-2.5<br>- single hip or symptomatic vertebral fracture whilst on therapy, within prior 24 months. | - (no therapy specified)<br>- BMD ≤-2.5<br>- fracture due to minimal trauma<br>- ≥1 hip or symptomatic vertebral fracture in last 24 months |
| Grandfathered patients | Not estimated | Patients who are receiving privately-funded romosozumab in the year prior to listing | Prior to starting non-PBS-subsidised treatment:<br>- BMD ≤-2.5<br>- fracture due to minimal trauma<br>- ≥1 hip or symptomatic vertebral fracture in prior 24 months, or<br>- ≥2 fractures including one symptomatic new fracture in prior 24 months. |

Source: Section 4, pp106-114 of the resubmission; Evenity Financial analysis_Mar23 Excel workbook of the resubmission; Section 4, July 2022 romosozumab submission
Abbreviations: BMD, bone mineral density

6.65 The resubmission used a 10% PBS sample analysis to estimate the number of patients receiving osteoporosis treatments in 2021, extrapolated to 2023-2028 assuming 6.9% annual growth (based on growth rate of prevalent population between 2019-2021 from the 10% PBS sample). The treated population estimates could not be validated due to poor documentation in the resubmission. Eligible first-line patient numbers were based on the proportion of patients estimated to initiate treatment (or re-initiate treatment after a break of 2 or more years) in each year of listing.

6.66 Second-line patients were based on the total treated osteoporosis population, excluding patients utilising romosozumab in first-line treatment. Basing eligible

second-line patient estimates on treated osteoporosis patients who are persistent with therapy will exclude the larger pool of ever-treated osteoporosis patients.

6.67 The methods used to determine the proportion of patients with BMD ≤-2.5 (and <-3.0 for the expanded multiple fractures second-line population) were based on a subgroup analysis of patients with fracture from the Geelong Osteoporosis Study (unchanged from the July 2022 resubmission). Patient characteristics (eg 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 wider use of newer osteoporosis treatments), based on a sample of the general population that may not be representative of patients seeking care for osteoporosis, and of uncertain representativeness of males with osteoporosis.

6.68 In second-line patients, the resubmission then attempted to quantify the effects of anti-resorptive treatment on BMD, estimating the proportion of patients who would continue to meet the BMD criteria while on treatment. The resubmission acknowledged that these estimates may be conservative as patients who continue to fracture on treatment may have lower BMD than those who do not.

6.69 The derivation of the proportion of patients meeting the fracture criteria in each subpopulation was slightly simplified from the July 2022 resubmission, but continued to be based on multiple sources and assumptions (summarised in Table 14).

**Table 14: Inputs used to estimate fracture criteria in each subpopulation**

| Data | Value and source | Comment |
|---|---|---|
| **First-line population** | | |
| Patients with prior fracture | 75%. Analysis of a sample from the Geelong Osteoporosis Study. It was estimated that 66% of treated patients aged ≥70 years had a fracture. The resubmission assumed 100% of treated patients under 70 years had a prior fracture based on PBS eligibility criteria. Weighted based on age of 10% PBS sample. | Estimates from the Geelong Osteoporosis Study (GOS) are nearly 30 years old and may not be applicable to current practice. |
| Patients with multiple clinical 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%). The resubmission assumed that fracture is the precipitating event for initiation of osteoporosis treatment and hence will have occurred very recently (ie within the prior 24 months), as required by the proposed listing. | Estimates of multiple fractures in first-line patients were based on reports of multiple symptomatic (clinical) fractures (with one assumed to be recent), while the requested restriction specifies multiple fractures, with one recent symptomatic fracture. |
| **Second-line population (multiple fractures)** | | |
| Patients with prior fracture | 75%. Analysis of a sample from the Geelong Osteoporosis Study (same estimate used to estimate size of the first-line population, see above). | The magnitude of this proportion remains unclear as the data were based on a general population study (includes undiagnosed patients). |
| Patients with an on-treatment fracture | 10.04%. Annual clinical (symptomatic) fracture rate from the alendronate arm in ARCH (5.02%) multiplied by 2 (5.02 x 2 =10.04%). The resubmission assumed that the annual fracture rate, multiplied by 2, represented the proportion of patients with a recent fracture (in prior 24 months). | The use of a flat annual fracture rate assumes no changing risk of fractures over time (i.e. static population) and does not account for frequency and number of fractures in any given year. |
| **Second-line population (single hip or vertebral fracture)** | | |
| Patients without a prior fracture | 25%. Complement of estimated proportion of patients with a prior fracture (75%) based on the Geelong Osteoporosis Study and weighted by age from the 10% PBS sample analysis (see first-line listing above). | Using the complement of this weighted proportion was inappropriate as this second-line subpopulation were assumed to be all over 70 years of age (in order to qualify for PBS-subsidised osteoporosis treatment without a prevalent fracture). The complement of the proportion of patients aged ≥70 years with a prior fracture based on the GOS (100% - 66% = 34%) may have been more appropriate. |
| Patients with an on-treatment clinical vertebral or hip fracture | 2.29%. Annual clinical vertebral or hip fracture rate from the alendronate arm in ARCH (2.29%), first halved to reflect lower risk in population without a prior fracture, then multiplied by 2 to reflect the requirement for a fracture to be recent, ie within last 24 months. | While it was reasonable to assume that the population without a prevalent fracture would have a lower subsequent fracture risk than those in the ARCH trial (with prevalent fracture), there was no justification provided for the 50% reduction in the rate applied in the resubmission's estimates. [redacted]<br>The use of a flat annual fracture rate assumes no changing risk of fractures over time (i.e. static population) and does not account for frequency and number of fractures in any given year. |

Source: Section 4, pp106-114 of the resubmission; Evenity Financial analysis_Mar23 Excel workbook of the resubmission
Abbreviation: ECG, electrocardiography; DPMQ, dispensed price for maximum quantity.

6.70 Table 15 presents the estimated use and financial impact of romosozumab to the PBS/RPBS.

**Table 15: Estimated use and financial implications**

| | Year 1 (2023) | Year 2 (2024) | Year 3 (2025) | Year 4 (2026) | Year 5 (2027) | Year 6 (2028) |
|---|---|---|---|---|---|---|
| Treated osteoporosis patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **First-line population** | | | | | | |
| Initiate osteoporosis therapy (19.8%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients with prior fracture (75%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BMD ≤-2.5 (32.5%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Multiple clinical fractures or single hip/clinical vertebral fracture (57%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Uptake (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients initiating romosozumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous submission July 2022** | | | | | | |
| **Total first-line patients** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Second-line population (multiple fractures)** | | | | | | |
| On treatment, excluding 1L romosozumab uptake (n) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients with prior fracture (75%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| On-treatment fracture in past 24 months (10.04%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BMD ≤-2.5 and >-3.0 (7.5%) * | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Uptake (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients initiating romosozumab * | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Second-line population (single hip or symptomatic vertebral fracture)** | | | | | | |
| On treatment (100%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Without prior fracture (25%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| On-treatment hip/clinical vertebral fracture in past 24 mths (2.29%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BMD ≤-2.5 (49.0%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Uptake (%) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Patients initiating romosozumab | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous submission July 2022** | | | | | | |
| Total second-line patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Grandfathered patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total romosozumab patients *** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total scripts (10.8 scripts/year) [a] * | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated financial implications of romosozumab** | | | | | | |
| **PBS/RPBS cost of romosozumab less copay *** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous submission July 2022** | | | | | | |
| PBS/RPBS cost of romosozumab less copay | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| PBS/RPBS cost offsets from displaced anti-resorptives | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net financial implications** | | | | | | |
| **Net PBS/RPBS cost** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Previous submission July 2022** | | | | | | |
| Net PBS/RPBS cost | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Total MBS costs [b] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net cost to Government** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Table 4.4-2, p113; Table 4.2-3, p110; Table 4.2-4, p111; Table 4.2-5, p111; Table 4.3-1, p112; Table 4.5-2, p118 of the resubmission; Evenity financial analysis_Mar 23.xlsx excel workbook of the resubmission; Section 4, July 2022 romosozumab submission

Abbreviations: 1L, first-line; BMD, bone mineral density; DPMQ, dispensed price for maximum quantity.
[a] 12 scripts per year, with 90% adherence.
[b] Includes additional costs due to increased specialist visits, electrocardiography and blood tests over 1 year of romosozumab treatment
* Numbers corrected during the evaluation. The resubmission erroneously applied a flat 98.90% proportion across the "ever treated, no first-line romosozumab" step in calculating the number of patients eligible for second-line treatment with multiple fractures and BMD ≤-2.5 and >-3.0).
*The redacted values correspond to the following ranges:*

[1] *700,000 to < 800,000*
[2] *100,000 to < 200,000*
[3] *30,000 to < 40,000*
[4] *20,000 to < 30,000*
[5] *500 to < 5,000*
[6] *5,000 to < 10,000*
[7] *500,000 to < 600,000*
[8] *50,000 to < 60,000*
[9] *<500*
[10] *$0 to <$10 million*
[11] *$10 million to <$20 million*
[12] *net cost saving*
[13] *800,000 to < 900,000*
[14] *40,000 to < 50,000*
[15] *600,000 to < 700,000*
[16] *60,000 to < 70,000*
[17] *200,000 to < 300,000*
[18] *80,000 to < 90,000*
[19] *20 million to <$30 million*
[20] *10,000 to < $20,000*
[21] *$30 million to <$40 million*
[22] *900,000 to < 1,000,000*
[23] *70,000 to < 80,000*
[24] *40 million to <$50 million*
[25] *1,000,000 to < 2,000,000*

6.71 The estimated net cost to Government including PBS/RPBS cost offsets and additional MBS costs was $0 to < $10 million in Year 1, increasing to $20 million to < $30 million in Year 6, a total of $100 million to < $200 million over 6 years. These estimated costs were lower than in the July 2022 resubmission (total cost of $100 million to < $200 million over 6 years) due to a reduced effective DPMQ for romosozumab, and lower estimates of patient numbers in both first- and second-line populations.

6.72 The market share approach of determining eligible patients based on numbers of treated osteoporosis patients excludes the larger pool of ever-treated osteoporosis patients. An epidemiological approach considering the prevalent and incident osteoporosis population may give a more accurate starting point to estimate the overall eligible population.

6.73 The derivation of the proportion of patients meeting the fracture criteria in each subpopulation followed similar steps to the July 2022 resubmission, with some simplifications to the estimation of patients with an on-treatment fracture. However, the process remained complex, and was based on multiple sources and assumptions.

6.74 Estimates of multiple fractures in first-line patients were based on reports of multiple symptomatic (clinical) fractures (with one assumed to be recent), while the requested restriction specifies multiple fractures, with one recent symptomatic fracture. The population with a prevalent fracture (of any type, for example, a non-symptomatic vertebral fracture) and a recent symptomatic fracture will be larger than the population with multiple symptomatic fractures.

6.75 Uptake rates were the same as in the July 2022 resubmission, and 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.

6.76 The resubmission included an estimate of < 500 additional grandfathered patients who would receive romosozumab in the first year of listing. The sponsor estimated that around < 500 patients are currently privately funding romosozumab, but recent introduction of a shared cost program has increased forecast of patients to around 500 to < 5,000 patients in the next year. The submission assumed that 90% of these patients would meet the proposed PBS eligibility criteria as first-line patients, and of those, 50% would make the transition to PBS-subsidised therapy, giving a total of < 500 grandfathered patients. These estimates could not be verified.

6.77 Based on the resubmission's estimates the additional severe osteoporosis population treated with romosozumab represents approximately 0.6% to 1.4% of all patients treated for osteoporosis, with the majority of patients receiving romosozumab as first-line treatment (76.6%) followed by second-line in those with multiple fractures and BMD ≤-2.5 and >- 3.0 (15.6%), and second-line in those with a single hip/vertebral fracture and BMD ≤-2.5 (7.8%).

6.78 The ESC noted that many of the data sources and steps were unchanged from the July 2022 resubmission and considered significant uncertainties regarding the size of the eligible and treated populations remain.

## *Quality Use of Medicines*

6.79 The resubmission did not update the quality use of medicines information provided in the July 2022 resubmission. 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.

6.80 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*

6.81 The resubmission stated that the sponsor is willing to agree to a revised deed for romosozumab, proposing new financial caps using the sum of the existing caps (Table 16) and the financial estimates presented for the additional populations in the current submission (see Table 15). The sponsor proposed a [redacted]% rebate on any expenditure above the caps. This is an increase from the [redacted]% rebate offered in the July 2022 resubmission. The ESC considered the nominated caps were highly uncertain as they were associated with significant uncertainties regarding the size of the eligible and treated populations.

**Table 16 Current RSA for romosozumab in severe established osteoporosis (deed started 1st April 2021)**

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

Source: Compiled during the preparation of the ESC advice
*based on 11 months' data (1-Apr-2022 – 20-Feb-2023)

6.82 The pre-PBAC response provided the proposed overall financial caps which represent the sum of the commonwealth payment for the expanding listing calculated in this resubmission and the agreed caps for the current listing (Table 17). An adjustment to the contribution from the current caps was made in acknowledgement that initial romosozumab uptake under the current listing has been slower than anticipated (current year 1 caps for April 2021 – March 2022 have been shifted to 2023 for the proposed new overall caps). The pre-PBAC response stated the sponsor is willing to accept the [redacted]% rebate stipulated by the PBAC.

**Table 17 Proposed overall financial caps**

| | 2023 ($) | 2024 ($) | 2025 ($) | 2026 ($) | 2027 ($) | 2028 ($) |
|---|---|---|---|---|---|---|
| Current caps with time shift adjustment | [redacted] | | | | | |
| Commonwealth payment for expanded listing | | | | | | |
| Proposed new overall caps | | | | | | |

Source: Table 1 of pre-PBAC response
Note: Caps are based on calendar years and, if the submission is recommended, would require adjustment depending on the actual listing date.
* Additional year forecast based on immediately prior year-on-year growth.

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

# 7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (Telephone/electronic) listing of romosozumab for the treatment of severe osteoporosis in the first-line setting. The PBAC considered the clinical and cost-effectiveness evidence for romosozumab was adequate to support listing in the first-line setting but not an expansion to the current second-line listing. On this basis, the PBAC considered that romosozumab in the first-line setting provides, for some patients a significant improvement in efficacy over alendronate. The PBAC noted that the resubmission had addressed a number of its previous concerns with the economic model, but had not provided an economic

analysis for romosozumab in the expanded second-line setting (see paragraph 6.39). The PBAC's recommendation for listing was based on, among other matters, its assessment that romosozumab would be cost-effective in the first-line setting if its price was reduced such that the incremental cost-effectiveness ratio (ICER) was no higher than the revised base case in the July 2022 submission $35,000 to < $45,000 per QALY gained, see paragraph 6.53) and with a risk sharing arrangement (RSA) to address the uncertainty associated with the size of the eligible first-line population and also any residual concerns regarding the cost-effectiveness of romosozumab use in the first-line setting.

7.2 The PBAC noted the input from an individual, health care professionals and organisations highlighting the potential role of romosozumab in the first-line setting in those at highest risk of fracture recurrence. The PBAC reiterated its July 2022 advice that there is likely a clinical need for earlier use of romosozumab in patients at very high risk of fracture, noting that a number of international guidelines support the earlier use of anabolic agents in such patients (para 7.2, romosozumab Public Summary Document (PSD), July 2022 PBAC meeting).

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

7.4 The PBAC noted that the comparative effectiveness evidence presented was unchanged from the July 2022 resubmission. Hence, the resubmission was based on a direct comparison of romosozumab versus alendronate in the ARCH trial which was conducted in patients predominantly naïve to anti-resorptive therapy. The PBAC noted that treatment with romosozumab versus alendronate was associated with statistically significant decreases in vertebral fractures, clinical fractures and non-vertebral fractures over a median of 33 months compared to alendronate alone. The PBAC reiterated its July 2022 advice that the claim of superior comparative effectiveness was reasonable for the first-line setting in treatment naïve patients, however the magnitude of effect was uncertain due to poor transition to and persistence with anti-resorptive therapy post romosozumab (para 7.8, romosozumab PSD, July 2022 PBAC meeting).

7.5 The PBAC noted that no new data were presented in the resubmission to support an extended second-line listing. The resubmission assumed that relative treatment effects in the ARCH trial are generalisable to the second-line setting. The PBAC noted the pre-PBAC response acknowledgement of the lack of second-line fracture outcome data and proposed an alternative listing to limit second-line access to the currently eligible population (see paragraph 3.12). The PBAC reiterated its July 2022 advice that the claim of superior comparative effectiveness was uncertain in the second line setting due to data limitations (para 7.8, romosozumab PSD, July 2022 PBAC meeting).

7.6 The PBAC noted that the evidence presented for comparative harms was unchanged from the July 2022 resubmission, with the exception of additional safety data from

recent Periodic Safety Update Reports. The PBAC reiterated its July 2022 advice that the claim of inferior comparative safety was reasonable (para 7.9, romosozumab PSD, July 2022 PBAC meeting).

7.7 The PBAC noted that the economic model was a cost-utility analysis based on data from the ARCH trial (a predominantly treatment-naïve population) and other modelled variables. The PBAC recalled that in July 2022 it had recommended the economic model be revised to include a treatment discontinuation of 20% per year and convergence by 4 years. In July 2022, the Committee had also recommended a price reduction to achieve an ICER no higher than the revised base case in the July 2022 submission ($35,000 to < $45,000 per QALY gained). The PBAC noted that the resubmission model included a treatment discontinuation of 20% per year but did not include convergence by 4 years with the pre-PBAC response arguing that inclusion of both changes would be overly conservative. The PBAC accepted the scenario proposed in the resubmission (treatment discontinuation of 20% per year and convergence by 6 years) could be used to assess the cost-effectiveness of romosozumab in the first-line setting. However, the PBAC noted that while the resubmission included a price reduction (see paragraph 3.2), the resulting ICER was $45,000 to < $55,000 per QALY gained. The PBAC maintained that, as per the Committee's July 2022 recommendation, the ICER should be no higher than the revised base case ICER in the July 2022 submission. The PBAC advised that romosozumab would be considered cost-effective in the first-line setting if the price of romosozumab was reduced such that the ICER was no higher than $35,000 to < $45,000 per QALY gained. The PBAC considered it would be reasonable for this ICER to be achieved through a reduction in the price of romosozumab for the first-line setting and/or the existing second-line setting (as was proposed in the resubmission).

7.8 The PBAC noted that an economic analysis was not presented for romosozumab in the second-line setting. The PBAC noted that the sponsor was unable to accommodate the Committee's July 2022 request for a cost-minimisation with alendronate or any further reduction in price for this component of the listing expansion (see paragraph 6.39). The PBAC considered that the cost-effectiveness of romosozumab in the expanded second-line setting was unable to be adequately assessed using the data presented and hence an expansion to the current second-line listing could not be recommended.

7.9 The PBAC noted the ESC advice that many of the data sources and steps used to estimate the financial implications of listing romosozumab were unchanged from the July 2022 resubmission (see paragraph 6.78). However, the PBAC noted that for the current resubmission the eligible first-line patient numbers were based on the proportion of patients estimated to initiate an osteoporosis treatment in each year of listing rather than the July 2022 approach of using patients who had received prior anti-resorptive therapy for less than 12 months. The PBAC considered this revised approach reduced some of the uncertainty associated with the first-line estimates. The PBAC noted that grandfathered patients were assumed to meet the proposed PBS

eligibility criteria as first-line patients and considered their inclusion in the estimates as additional patients appropriate. As an expansion to the current second-line listing could not be recommended based on the data presented (see paragraph 7.8) the PBAC advised that the second-line population should be removed from the financial estimates. The PBAC considered that it was reasonable to accept the first-line population numbers presented as the maximum number of first-line patients to be treated per annum.

7.10 The PBAC considered that a RSA was appropriate to mitigate any residual uncertainties regarding the size of the eligible first-line population and any remaining concerns regarding the cost-effectiveness of romosozumab use in the first-line setting. The PBAC considered that the overall financial caps proposed in the pre-PBAC response (Table 17) would need to be adjusted for the removal of the second-line expanded listing population from the resubmission financial estimates and for the price reduction outlined in paragraph 7.7. The PBAC noted that the sponsor proposed a 100% rebate for any expenditure above the caps and considered this was appropriate.

7.11 With regard to the requested listing and restriction, the PBAC advised that:

- The listing should be restricted to the first-line setting with the following included in the clinical criteria for the initial and grandfathering restrictions 'Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab.'
- The clinical criteria should stipulate that the patient must have had a 'symptomatic' fracture due to minimal trauma.
- A time-limited grandfathering restriction is appropriate.

7.12 The PBAC advised that romosozumab is not suitable for prescribing by nurse practitioners.

7.13 The PBAC recommended that the Early Supply Rule should apply.

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

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

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

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

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

**Outcome:**
Recommended

# 8 Recommended listing

8.1 Add new item:

| **MEDICINAL PRODUCT medicinal product pack** | | **PBS Item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
|---|---|---|---|---|---|---|
| ROMOSOZUMAB | | | | | | |
| Romosozumab, 105mg/1.17mL injection, 2 x 1.17mL syringes | | NEW | 1 | 2 | 5 | Evenity |
| | | | | | | |
| **Restriction Summary edit [12486] / Treatment of concept edit [12475]** | | | | | | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** General Schedule (Code GE) | | | | | |
| | **Prescriber type:** ☒Medical Practitioners | | | | | |
| | **Restriction type:** ☒ Authority Required – Telephone, Electronic | | | | | |
| Prescribing rule level | **Administrative advice:** No increase in the maximum quantity or number of units may be authorised. | | | | | |
| | **Administrative advice:** No increase in the maximum number of repeats may be authorised. | | | | | |
| | **Administrative advice:** Special Pricing Arrangements apply. | | | | | |
| | **Administrative advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). | | | | | |
| | **Episodicity:** | | | | | |
| | **Severity:** ***Severe*** | | | | | |
| | **Condition:** ***Established*** **osteoporosis** | | | | | |
| | **Indication:** Severe established osteoporosis | | | | | |
| | **Treatment Phase:** Initial treatment | | | | | |
| | **Clinical criteria:** | | | | | |
| | Patient must not have received PBS-subsidised treatment with any of: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab; | | | | | |
| | **AND** | | | | | |
| | **Clinical criteria:** | | | | | |
| | Patient must be at a very high risk of fracture; | | | | | |
| | **AND** | | | | | |
| | **Clinical criteria:** | | | | | |
| | Patient must have a bone mineral density (BMD) T-score of -2.5 or less; | | | | | |
| | **AND** | | | | | |
| | **Clinical criteria:** | | | | | |
| | Patient must have had a symptomatic fracture due to minimal trauma; | | | | | |
| | **AND** | | | | | |
| | **Clinical criteria:** | | | | | |
| | Patient must have had at least 1 hip or symptomatic vertebral fracture in the previous 24 months, OR | | | | | |
| | Patient must have had at least 2 fractures including 1 symptomatic new fracture in the previous 24 months, | | | | | |

| | |
|---|---|
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be the sole PBS-subsidised therapy for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS subsidised therapy; |
| | **Treatment criteria:** |
| | Must be treated by a consultant physician |
| | **Prescribing Instructions:** Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application. |
| | **Prescribing Instructions:** A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. |
| | **Prescribing Instructions:** Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid. |
| | |
| | |
| **Restriction Summary edit [11475]/ Treatment of Concept: edit [11496]** | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE) |
| | **Prescriber type:** ☒ Medical Practitioners |
| | **Restriction type:** ☒ Authority Required – Telephone, Electronic |
| | **Treatment Phase:** Continuing treatment |
| | **Clinical criteria:** |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be the sole PBS-subsidised therapy for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy. |
| | **Treatment criteria:** |
| | Must be treated by a medical practitioner identifying as either: (i) a Consultant Physician, (ii) a General Practitioner. |
| | |
| **Restriction Summary [new] / Treatment of concept [new]** | |
| **Concept ID** (for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE) |
| | **Prescriber type:** ☒ Medical Practitioners |
| | **Restriction type:** ☒ Authority Required – Telephone, Electronic |
| | **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 not have received PBS-subsidised treatment with any of the following prior to initiating non-PBS-subsidised treatment with this drug for this condition: (i) anti-resorptive therapy, (ii) teriparatide, (iii) romosozumab; |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must be at a very high risk of fracture; |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a bone mineral density (BMD) T-score of -2.5 or less prior to starting non-PBS-subsidised treatment with this drug for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a symptomatic fracture due to minimal trauma prior to starting non-PBS-subsidised treatment with this drug for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had at least 1 hip or symptomatic vertebral fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition, OR |
| | Patient must have had at least 2 fractures including 1 symptomatic new fracture in the 24 months prior to starting non-PBS-subsidised treatment with this drug for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be the sole PBS-subsidised therapy for this condition; |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not exceed a lifetime maximum of 12 months of PBS and non-PBS-subsidised therapy; |
| | **Treatment criteria:** |
| | Must be treated by a consultant physician |
| | **Prescribing Instructions:** Details of fracture history including the date(s), site(s), the symptoms associated with the fracture(s) and the score of the qualifying BMD measurement must be provided at the time of application. |
| | **Prescribing Instructions:** A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body. |
| | **Prescribing Instructions:** Anti-resorptive therapies for osteoporosis include alendronate sodium, risedronate sodium, raloxifene hydrochloride, denosumab and zoledronic acid. |
| | **Administrative advice:** Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | **Administrative advice:** This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

***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 pleased that the PBAC recognises the clinical need for romosozumab and has recommended the first-line listing as proposed in the submission. However, the PBAC's condition on the ICER required for romosozumab results in a price that is below the cost Amgen can supply the medicine in Australia, which would make the listing commercially unviable. Now that the PBAC has recommended the listing, Amgen hopes that a path forward can be found to provide equitable 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.