Romosozumab for severe established osteoporosis: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

February 2024

Abstract

Purpose

To review the utilisation of romosozumab for severe established osteoporosis as well as medicines for the treatment of osteoporosis.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Romosozumab was first PBS-listed for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti-resorptive therapy on 1 April 2021.

Data Source / methodology

Data extracted from the PBS database maintained by Department of Health and Aged Care, processed by Services Australia were used for the analyses.

Key Findings

- In 2022, 725,017 patients were supplied 2,256,178 prescriptions for the treatment of osteoporosis.
- In 2021, 688,642 patients were supplied 2,215,894 prescriptions for the treatment of osteoporosis.
- Overall, patients were most commonly treated with denosumab.
- Utilisation of romosozumab was different from estimated. In its first year of listing, 705 patients were supplied 3,977 romosozumab prescriptions. In its second year of listing, 1,516 patients were supplied 8,739 prescriptions.
- Only 49% patients were identified to have successfully transitioned to an anti-resorptive after stopping treatment with romosozumab.

Purpose of analysis

To review the utilisation of romosozumab PBS listed for severe established osteoporosis (second-line setting) as well as other medicines for the treatment of osteoporosis, as requested by DUSC at its September 2023 meeting. In its consideration of romosozumab for severe established osteoporosis, the PBAC requested DUSC conduct a utilisation review of romosozumab including an investigation of the success of transitioning patients from romosozumab to anti-resorptive therapy.

Background

Clinical situation

Osteoporosis is a condition in which bones become weak and fragile increasing the risk of fractures. Osteoporosis is asymptomatic and often remains undiagnosed until a person presents with a fracture. Bone strength can be compromised to such an extent that a minor bump or a fall from standing height can cause a fracture (minimal trauma fracture). Some fractures, especially those in the vertebrae, never come to medical attention.[1,2,3]

Bone mineral density (BMD) describes the density and the mineral content of bones. It is measured via dual energy X-ray absorptiometry (DEXA) scanning, typically of the hip and spine. The result is reported as a T-score, which is the difference (in standard deviations) between the person's measurement and the reference standard of the mean BMD of young adults. People with a BMD of 2.5 or more standard deviations below normal peak bone mass (ie, a T-score of –2.5 or less) are considered to have osteoporosis.[5,6]

Estimates from the 2017–18 National Health Survey (NHS) suggest that approximately 924,000 Australians have osteoporosis, based on self-reported data. Osteoporosis is more common in older Australians and among women. More than a quarter of Australian women over the age of 75 years report having osteoporosis.[4]

The osteoporosis medicines included in this analysis were:

- anti-resorptive agents:
  - bisphosphonates alone and in combination with colecalciferol and/or calcium carbonate (alendronate, risedronate and zoledronic acid).
  - denosumab.
  - raloxifene.
- romosozumab.
- teriparatide.

[1] Australian Institute of Health and Welfare. Osteoporosis. Canberra: AIHW; 2019.
[2] The Royal Australian College of General Practitioners, Osteoporosis Australia. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age. East Melbourne: RACGP; 2017.
[3] Expert Group for Bone and Metabolism. Osteoporosis and minimal-trauma fracture [published June 2019]. Melbourne: Therapeutic Guidelines Limited; 2020.

- calcitriol.

Pharmacology

See Appendix A.

Therapeutic Goods Administration (TGA) approved indications

Table 1: TGA approved osteoporosis indications

Drug	TGA Indication
Alendronate and combinations	• Treatment of osteoporosis, including glucocorticoid-induced osteoporosis. • Treatment and prevention of glucocorticoid-induced osteoporosis in those patients on long term corticosteroid therapy.
Calcitriol	• Treatment of established osteoporosis diagnosed by objective measuring techniques, such as densitometry, or by radiographic evidence of atraumatic fracture. • Prevention of corticosteroid-induced osteoporosis in patients commencing oral steroid therapy in a dose and regimen expected to result in a significant bone loss.
Denosumab	• The treatment of osteoporosis in postmenopausal women. • Treatment to increase bone mass in men with osteopenia receiving androgen deprivation therapy for non-metastatic prostate cancer. • Treatment to increase bone mass in men with osteoporosis at increased risk of fracture. • Treatment to increase bone mass in women and men at increased risk of fracture due to long-term systemic glucocorticoid therapy.
Raloxifene	• Prevention and treatment of osteoporosis in post-menopausal women.
Risedronate and combinations	• Treatment of osteoporosis. • Treatment of glucocorticoid-induced osteoporosis. • Preservation of bone mineral density in patients on long term corticosteroid therapy.
Romosozumab	• 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.
Teriparatide	• Treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures. • Treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture.

Drug	TGA Indication
Zoledronic acid	• Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures. • Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures. • To increase bone mineral density in men with osteoporosis. • To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use. • To prevent glucocorticoid-induced bone mineral density loss.

Note: Some medicines have additional indications. See Product Information for details, available from the TGA (Product Information).

Dosage and administration

Table 2: Route and frequency of administration of osteoporosis medicines

Drug	Route and frequency of administration
Alendronate (incl. combination products)	Oral; weekly.
Calcitriol	Oral; twice daily.
Denosumab	Subcutaneous injection; once every six months.
Raloxifene	Oral; daily
Risedronate (incl. combination products)	Oral; daily, weekly or monthly
Romosozumab	Subcutaneous injection; monthly. Maximum of 12 months.
Teriparatide	Subcutaneous injection; daily. Maximum of 18 months.
Zoledronic acid	IV infusion; once per year

Source: TGA Product Information.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at October 2023)

Table 3: PBS listing of romosozumab

Item code	Name, form & strength, pack size	Max qty packs	Rpts	DPMQ	Brand name and manufacturer
12301K	romosozumab 105 mg/1.17 mL injection 2 × 1.17 mL syringes	1	5	$405.66	Evenity® Amgen Australia Pty Limited

Source: the PBS website.

Notes:

- No increase in the maximum quantity or number of units may be authorised.
- No increase in the maximum number of repeats may be authorised.
- Special Pricing Arrangements apply.

Restriction

Romosozumab is an Authority Required listing for severe established osteoporosis.

Treatment Phase: Initial treatment

Clinical criteria:

- Patient must be at very high risk of fracture, AND
- Patient must have a bone mineral density (BMD) T-score of -3.0 or less, AND
- Patient must have had 2 or more fractures due to minimal trauma, AND
- Patient must have experienced at least 1 symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses, AND
- The treatment must be the sole PBS-subsidised therapy for this condition, AND
- The treatment must not exceed a lifetime maximum of 12 months therapy, AND
- 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.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

If treatment with anti-resorptive therapy is contraindicated according to the relevant TGA-approved Product Information, details of the contraindication must be documented in the patient's medical record at the time treatment with this drug is initiated.

If an intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use of one anti-resorptive agent, alternate anti-resorptive agents must be trialled so that the patient achieves the minimum requirement of 12 months continuous therapy. Details must be documented in the patient's medical record at the time treatment with this drug is initiated.

Anti-resorptive therapies for osteoporosis and their adequate doses which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg per day or

70 mg once weekly, risedronate sodium 5 mg per day or 35 mg once weekly or 150 mg once monthly, raloxifene hydrochloride 60 mg per day (women only), denosumab 60 mg once every 6 months and zoledronic acid 5 mg per annum.

Details of prior anti-resorptive therapy, fracture history including the date(s), site(s), the symptoms associated with the fracture(s) which developed after at least 12 months continuous anti-resorptive therapy and the score of the qualifying BMD measurement must be provided at the time of application.

Treatment Phase: Continuing treatment

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition, **AND**
- The treatment must not exceed a lifetime maximum of 12 months therapy.

Treatment criteria: Must be treated by a medical practitioner identifying as either: (i) a consultant physician, (ii) a general practitioner.

An overview of the PBS restrictions for the other osteoporosis medicines considered in this review are shown below in Table 3. Like romosozumab, teriparatide is only listed for severe osteoporosis: two or more fractures due to minimal trauma, ≤ -3.0 BMD T-score and at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses.

Table 4: Summarised PBS restrictions as at October 2023

Drug	Minimal trauma	BMD -3.0 or less	BMD -2.5 or less	Corticosteroid -induced	Men
Alendronate and combinations	✓	✓	✓	✓	✓
Calcitriol	✓	×	×	×	✓
Denosumab	✓	✓	✓	×	✓
Raloxifene	✓	×	×	×	×
Risedronate and combinations	✓	✓	✓	✓	✓
Zoledronic acid	✓	✓	×	✓	✓

For details of the current PBS listing refer to the PBS website.

Date of listing on PBS

- Calcitriol: 1 December 1991
- Alendronate: 1 November 1996
- Raloxifene: 1 November 1999

- Risedronate: 1 February 2001
- Risedronate and calcium carbonate: 1 April 2006 (delisted 1 June 2023)
- Alendronate with colecalciferol: 1 August 2006
- Strontium: 1 April 2007 (delisted 1 August 2016)
- Risedronate and calcium carbonate with colecalciferol: 1 May 2008 (delisted 1 May 2018)
- Zoledronic acid: 1 December 2008
- Teriparatide: 1 May 2009
- Alendronate with colecalciferol and calcium carbonate: 1 June 2010 (delisted 1 October 2022)
- Denosumab: 1 December 2010
- Romosozumab: 1 April 2021

Details of osteoporosis medicines listing history can be found in Appendix B.

Changes to listing

1 January 2022

At its September 2021 intracycle meeting, the PBAC recommended the addition of the words "PBS-subsidised treatment" to "Patient must not have received treatment with romosozumab" for the teriparatide restriction and "Patient must not have received treatment with teriparatide" for the romosozumab restriction. This was to ensure that patients who previously self-funded their romosozumab or teriparatide treatment were not excluded from initiating treatment with teriparatide and romosozumab, respectively. The addition reflected the intent of the Committee's recommendation for romosozumab at the March 2020 PBAC meeting.

1 February 2023

At its July 2022 meeting, the PBAC considered that it would be appropriate to allow general practitioners to continue treatment with romosozumab once it had been commenced by a Specialist/Consultant Physician and advised that this change could be made to the current listing. The PBAC considered the treatment criterion "Must be treated by a Specialist" be removed from the continuing restriction for romosozumab.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC considered romosozumab for severe osteoporosis in November 2018 (first- and second-line settings), July 2019 (second-line setting), March 2020 (recommended second-line setting), July 2022 (first- and expanded second-line settings) and March 2023 (recommended first-line setting). At the time of this review, romosozumab is PBS listed for severe osteoporosis under a restricted second-line setting.

November 2018

The PBAC did not recommend the listing of romosozumab for the treatment of severe osteoporosis due to uncertainties in the clinical claims and the financial estimates and concerns regarding the safety profile.

For further details refer to the Public Summary Document from the November 2018 PBAC meeting.

July 2019

The PBAC did not recommend the listing of romosozumab for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti-resorptive therapy (later-line setting) due to concerns regarding the claim of comparative clinical effectiveness, the cardiovascular safety profile of the treatment and the uncertain size of the eligible patient population. The PBAC also considered the estimated financial implications were unacceptably high for a cost-minimisation analysis given it was not clear whether romosozumab would be cost-effective if it is used in a broader population than those patients who currently use teriparatide.

The submission presented a 10% PBS sample analysis to describe the use of anti-resorptives following teriparatide treatment cessation to address PBAC's concerns regarding successful transition and persistence to follow-up anti-resorptive therapy after stopping teriparatide. The analysis was based on patients who filled a teriparatide script between 1 April 2017 and 31 March 2018, with successful transition defined as having at least 1 anti-resorptive script within 6 months of stopping teriparatide. The Economic Sub-Committee (ESC) of the PBAC noted the definitions used appeared generous and may not adequately account for differences in duration of script coverage between treatments that can vary from 1 to 12 months and that the assumption of 1 script of any treatment following teriparatide would sufficiently define treatment switching, which is likely to overestimate the number of patients who are on continuous anti-resorptive therapy following teriparatide treatment. The PBAC was concerned that the analysis indicated approximately 30% of patients discontinue treatments for more than 6 months after stopping teriparatide.

For further details refer to the Public Summary Document from the July 2019 PBAC meeting.

March 2020

The PBAC recommended the listing of romosozumab for the treatment of severe osteoporosis in patients who have experienced a prior fracture while on anti- resorptive therapy. The PBAC considered there is a clinical need for additional treatment options for severe osteoporosis in the later-line setting. The PBAC considered that the concerns raised at the July 2019 meeting regarding the noninferiority claim were partially addressed by the more conservative cost-minimisation analysis presented in the resubmission. The PBAC considered that the remaining uncertainties could be managed by subsidisation caps through a risk sharing arrangement (RSA).

For further details refer to the Public Summary Document from the March 2020 PBAC meeting.

July 2022

The PBAC did not recommend romosozumab for the treatment of severe osteoporosis in the first line setting, nor the expanded listing in the second line setting (the BMD T-score ≤ -3 was increased to ≤ -2.5 and the removal of the requirement to have 2 or more fractures due to minimal trauma). The PBAC considered that the size of expanded population was poorly defined and the financial estimates were highly uncertain.

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

For further details refer to the Public Summary Document from the July 2022 PBAC meeting.

March 2023

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'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 and with a 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.

For further details refer to the Public Summary Document from the March 2023 PBAC meeting.

Previous reviews by the DUSC

September 2016

DUSC reviewed the utilisation of medicines for the treatment of osteoporosis including an assessment of the predicted and actual use of denosumab. Of note, it found:

- Rates of treatment with osteoporosis medicines declined by 15% between 2007 and 2014 despite reports of increasing prevalence of osteoporosis.
- Osteoporosis was more prevalent in women than men, with an estimated prevalence ratio in Australia of 3.8:1 for people over 50 years. The ratio of women to men aged 50 years or older treated with PBS osteoporosis medicines in 2015 was 3.9:1.
- Utilisation of denosumab had been much higher than expected. Approximately half of people starting osteoporosis therapy for the first time in 2015 were prescribed denosumab. A large number of people already on treatment with other medicines had switched to denosumab. In 2015, 57% of patients initiating denosumab had previously used at least one other osteoporosis drug.

For details of the DUSC consideration of osteoporosis medicines, including denosumab, refer to the Public Release Document from the September 2016 DUSC meeting.

October 2020

DUSC reviewed the use of denosumab for the treatment of osteoporosis. DUSC considered that there was a concerning proportion of patients who discontinued denosumab without subsequent osteoporosis therapy, placing them at greater risk of having bone fractures. DUSC advised there was a high need to educate prescribers and patients about the importance of continuing osteoporosis treatment, in particular to consider other treatment choices during breaks from current therapy.

For details of the DUSC consideration of denosumab refer to the Public Release Document from the October 2020 DUSC meeting.

Methods

Data extracted from the PBS claims database maintained by the Department of Health and Aged Care and processed by Services Australia were used for the analyses. Prescription data were extracted from 1 January 2015 up to and including 30 September 2023.

These data were used to determine the number of initiating and prevalent patients, number of prescriptions supplied, analyse patient demographics such as age and gender and to analyse prescriber type between 2018 and 2023. Initiating and prevalent patients were counted by calendar year. Prevalent patients were defined as the number of patients who received at least one supply of any osteoporosis medicine in the given calendar year. Initiating patients were defined as the number of patients who received their first supply of any osteoporosis medicine per calendar year since 2015.

An analysis of the transition to anti-resorptives following romosozumab treatment was conducted. A cohort of patients who initiated romosozumab treatment during its first year of listing (1 April 2021 to 31 March 2022) was selected. The expected end of the last romosozumab prescription was based on the expected coverage of the last script (30 days) with an allowed treatment gap of 60 days (i.e., 90 days from last dispense date). Anti-resorptive therapies of interest included alendronate, denosumab, raloxifene, risedronate and zoledronic acid with persistence estimates based on allowed treatment gaps of 60 days

from the expected end of the last prescription (variable between 28 days to 365 days). Successful treatment transition was defined as having at least 2 anti-resorptive prescriptions after stopping romosozumab.

A coadministration analysis between romosozumab and teriparatide was conducted. If teriparatide was supplied within 30 days of the first supply of romosozumab, and there was more than one occurrence of this supply, this was identified as a potential co-administration of romosozumab with teriparatide. To exclude possible switching between drugs, co-administration was only counted if there were at least two occurrences where a patient received romosozumab and teriparatide.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data.[4] The publicly available Services Australia Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

Overall utilisation

As shown in Table 5 and Figure 1 below, the number of patients treated with osteoporosis medicines has grown over time, with an average of approximately 98,000 patients initiating osteoporosis treatment annually from 2018 to 2022.

Table 5: Annual growth in the number patients initiating and treated with osteoporosis medicines

	2018 to 2019	2019 to 2020	2020 to 2021	2021 to 2022
Initiating patients	1%	-9%	8%	-1%
Prevalent patients	8%	5%	7%	5%

[4] PBS statistics. Australian Government Services Australia. Canberra. Available from http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp.

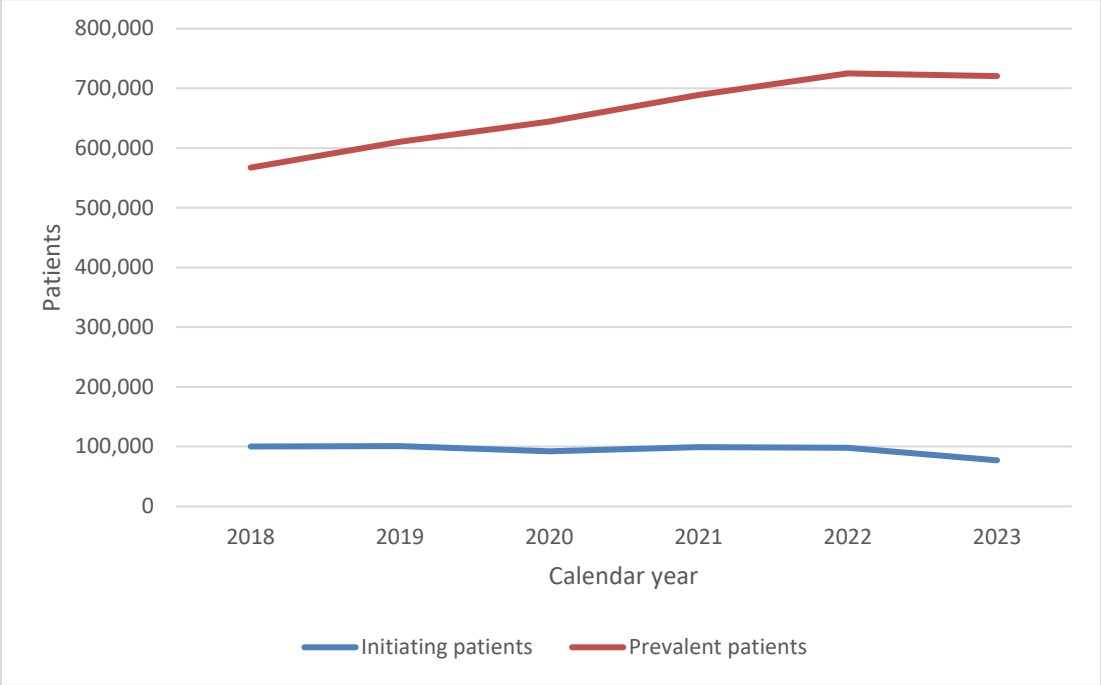

Figure 1: Initiating and prevalent patients treated with osteoporosis medicines by calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

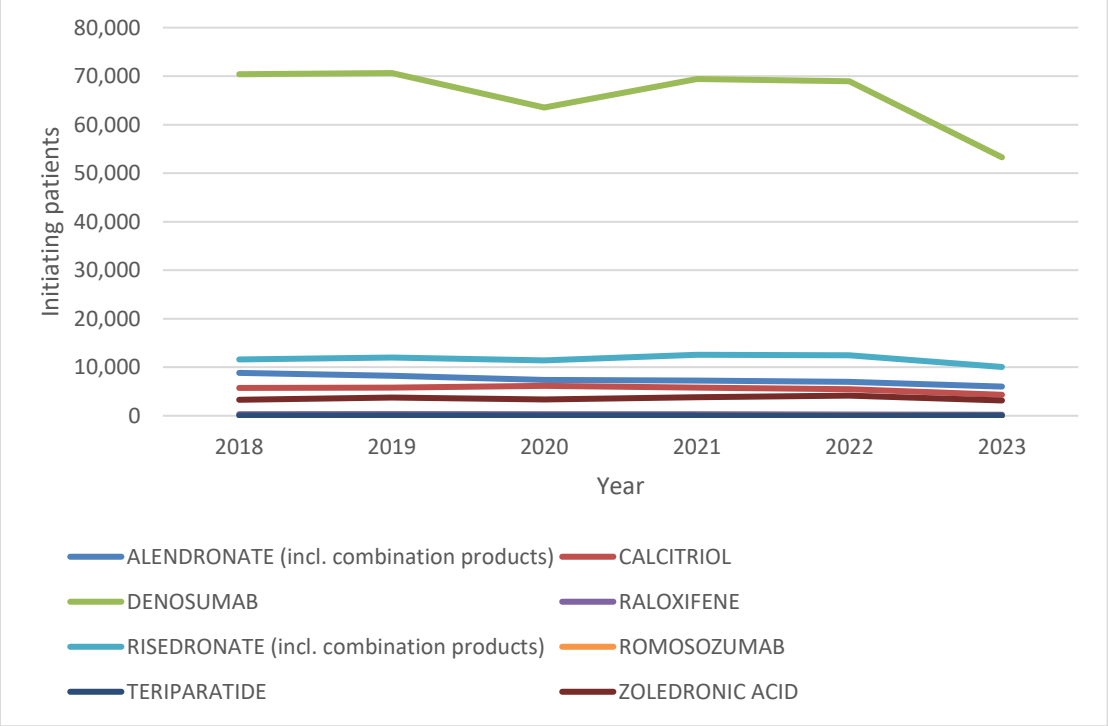

Figure 2: Initiating patients by drug and calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

In Figure 2, denosumab was the most common medicine patients initiated osteoporosis treatment with. The second and third most common medicine patients initiated with were bisphosphonates- alendronate and risedronate (including combination products).

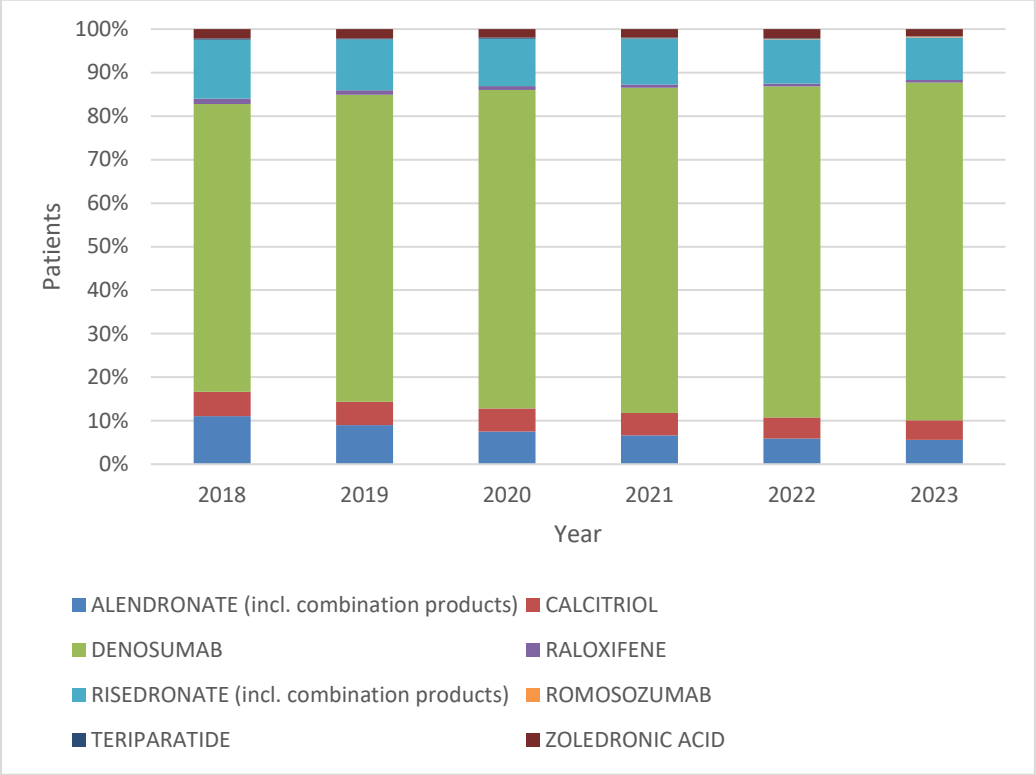

Figure 3: Patients treated with medicines for osteoporosis by drug and calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

In Figure 3, the proportion of patients treated with denosumab annually has been increased from 66% in 2018 to 76% in 2022. Of patients treated with osteoporosis medicines, less than one percent of patients were treated with romosozumab in 2022.

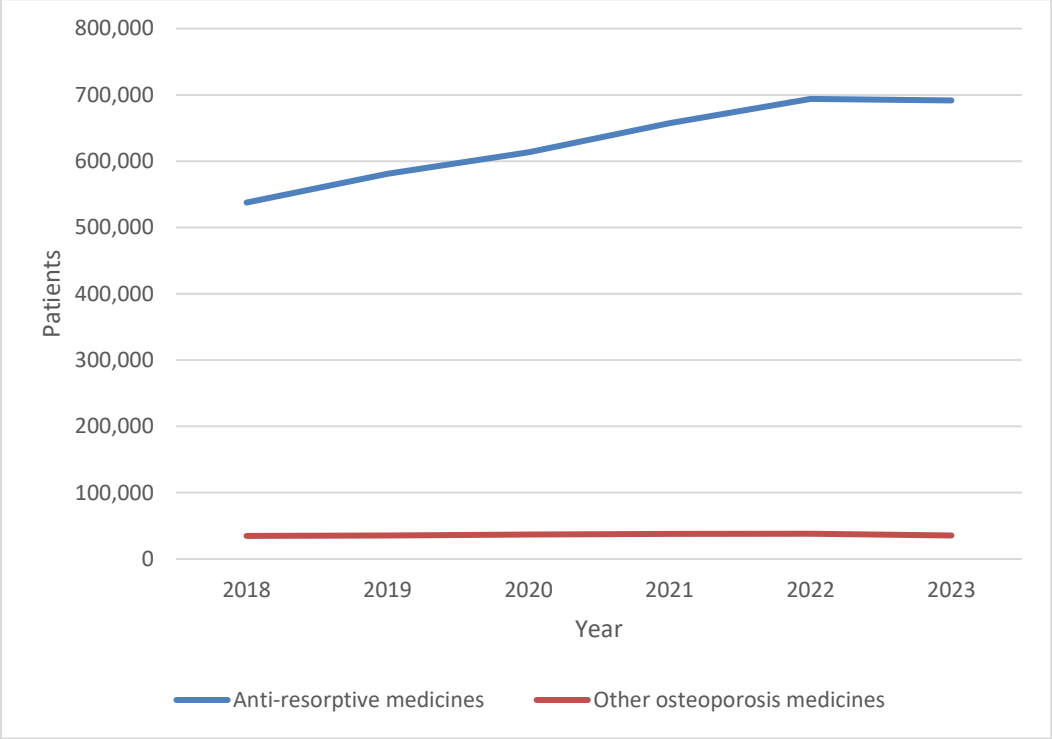

Figure 4: Patients treated with medicines for osteoporosis by calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

Figure 4 shows the majority of patients treated with osteoporosis medicines were with anti-resorptive medicines. Approximately 538,000 patients were treated with anti-resorptive medicines in 2018 and this increased to approximately 694,000 patients in 2022.

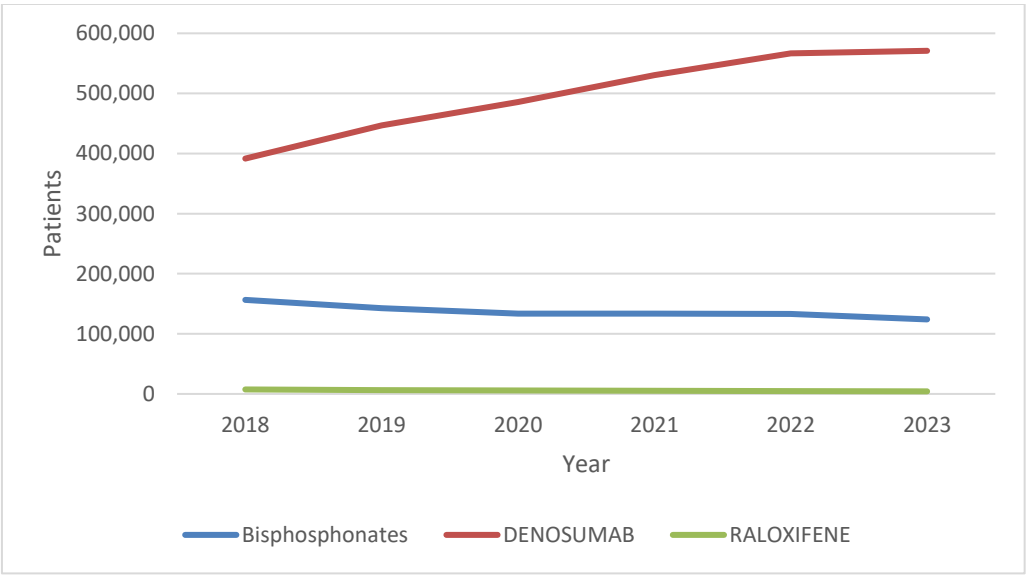

Figure 5: Patients treated with anti-resorptive medicines for osteoporosis by calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

In Figure 5, the anti-resorptive medicine patients were most treated with was denosumab. The number of patients treated with denosumab has increased over time, whereas the number of patients treated with bisphosphonates and raloxifene has been slightly decreasing over time.

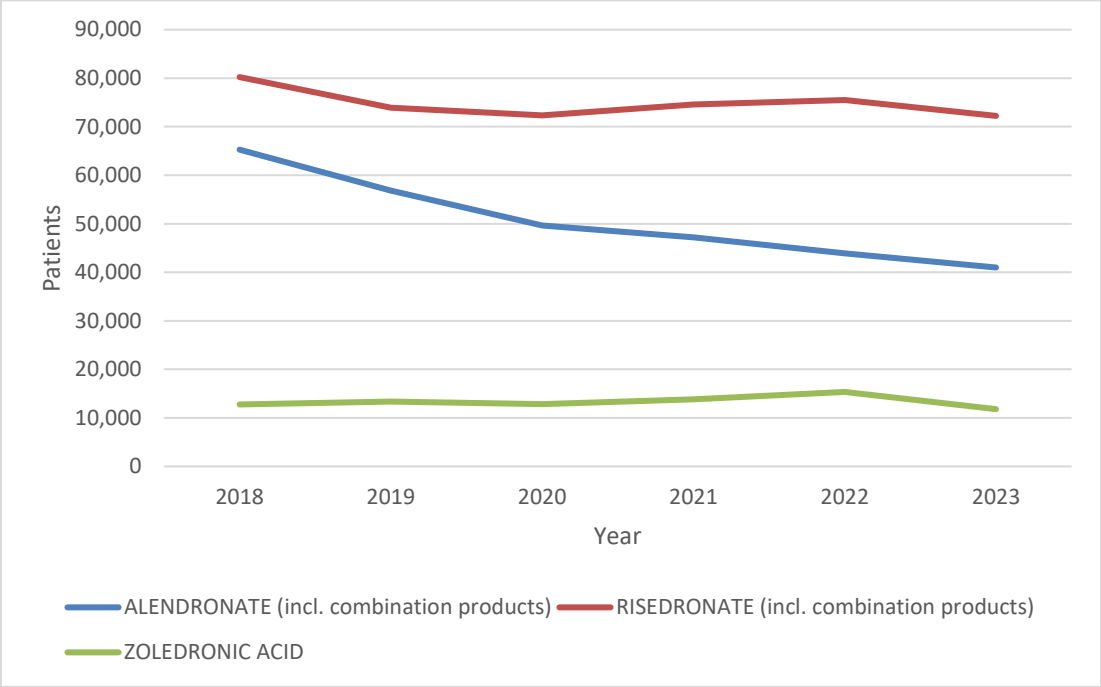

Figure 6: Patients treated with anti-resorptive bisphosphonate medicines for osteoporosis by calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

In Figure 6, the bisphosphonate medicine that most patients were treated with was risedronate (including its combination products).

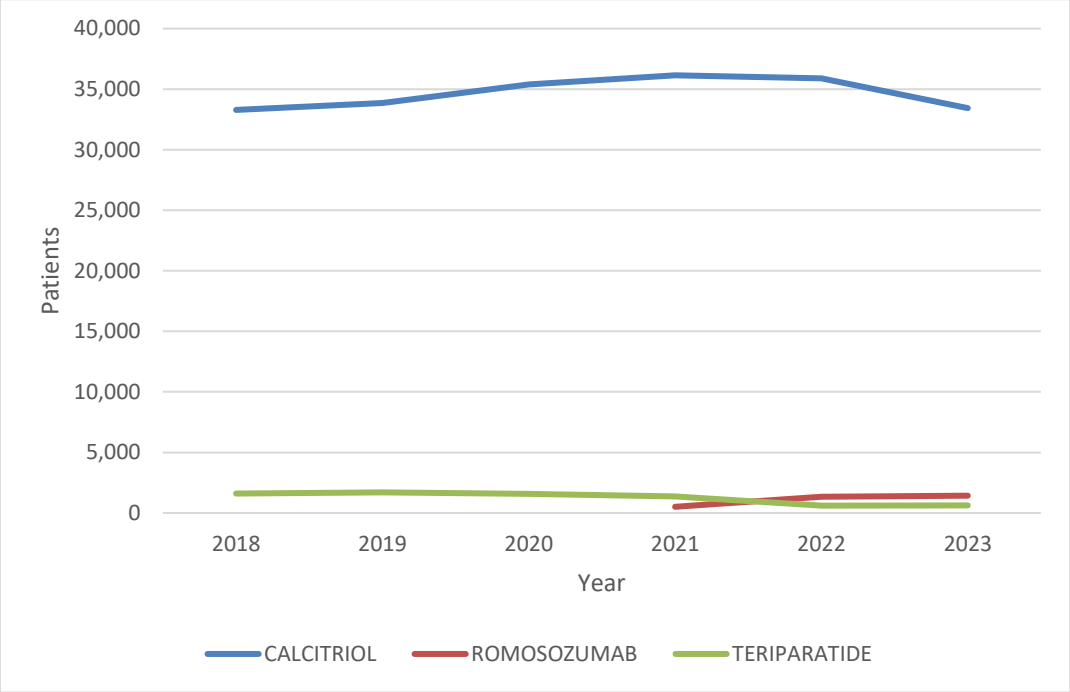

Figure 7: Patients treated other medicines for osteoporosis by calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

With regards to other medicines for the treatment of osteoporosis, most patients were treated with calcitriol. In 2021, more patients were treated with teriparatide compared to romosozumab, however from 2022 onwards, more patients were treated with romosozumab compared to teriparatide.

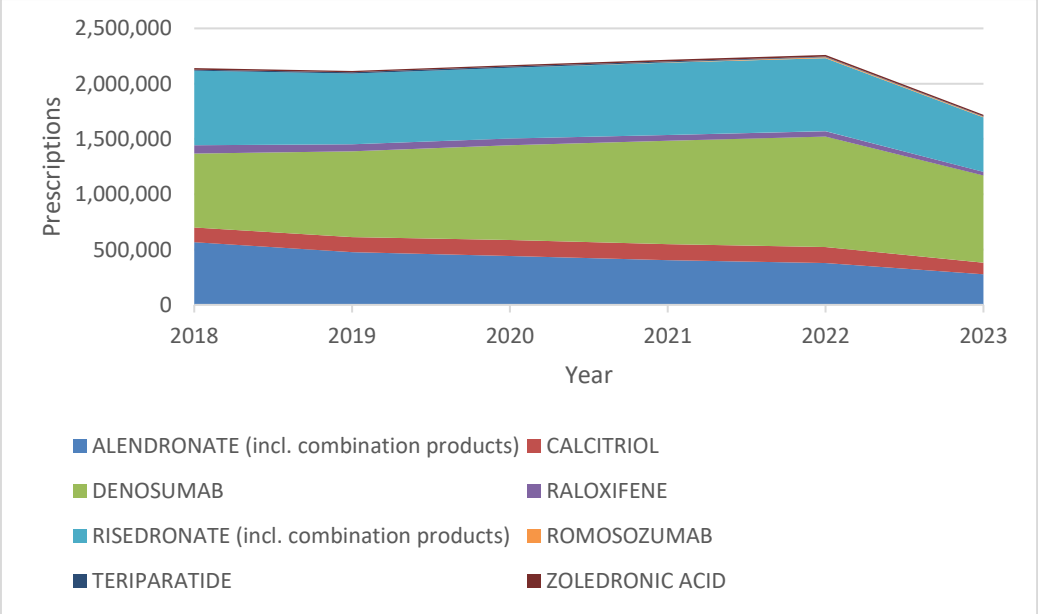

Figure 8: Osteoporosis medicine prescriptions supplied by drug and calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

Figure 8 shows the number of prescriptions supplied by calendar year. Similar to the trends observed in Figure 3, denosumab accounted for the majority of osteoporosis prescriptions supplied, followed by alendronate (incl. combination products) and risedronate (incl. combination products).

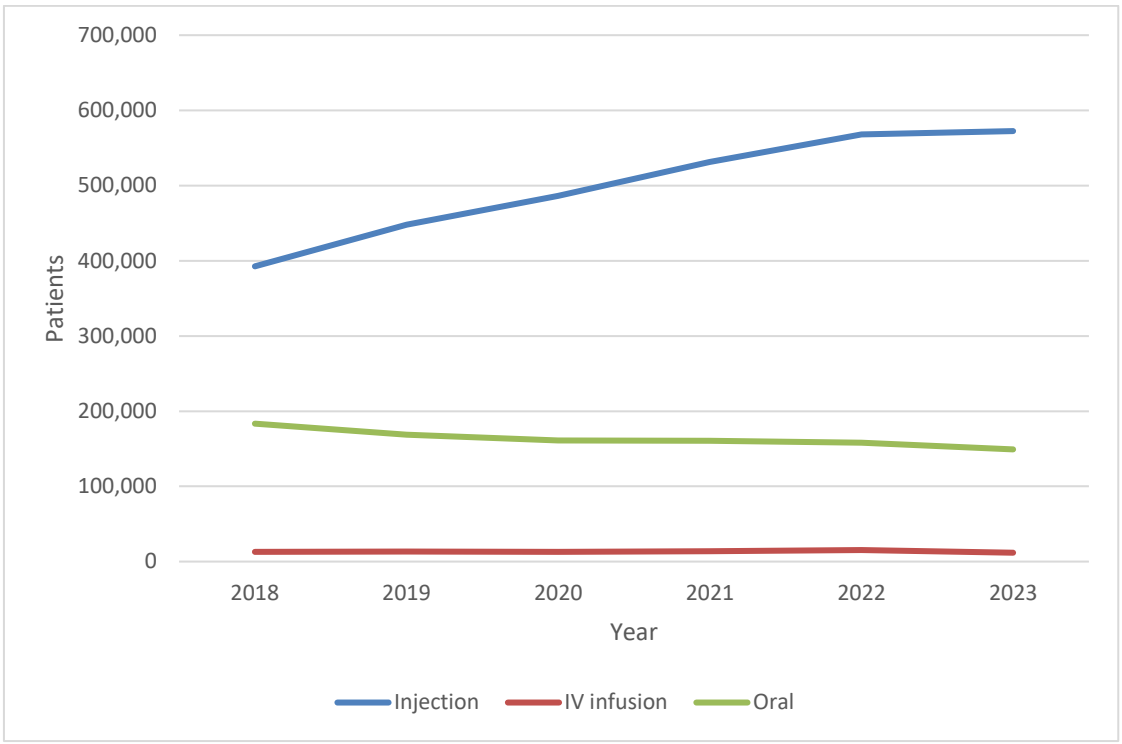

Figure 9: Number of patients treated by osteoporosis medicine form and calendar year.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive. Denosumab, romosozumab and teriparatide were classified as an injection; zoledronic acid was classified as an IV infusion; alendronate (incl. combination products), calcitriol and raloxifene, risedronate (incl. combination products) were classified as oral medicines.

With regards to medicinal form, most patients were treated with osteoporosis medicines in the form of injections across 2018 to 2023.

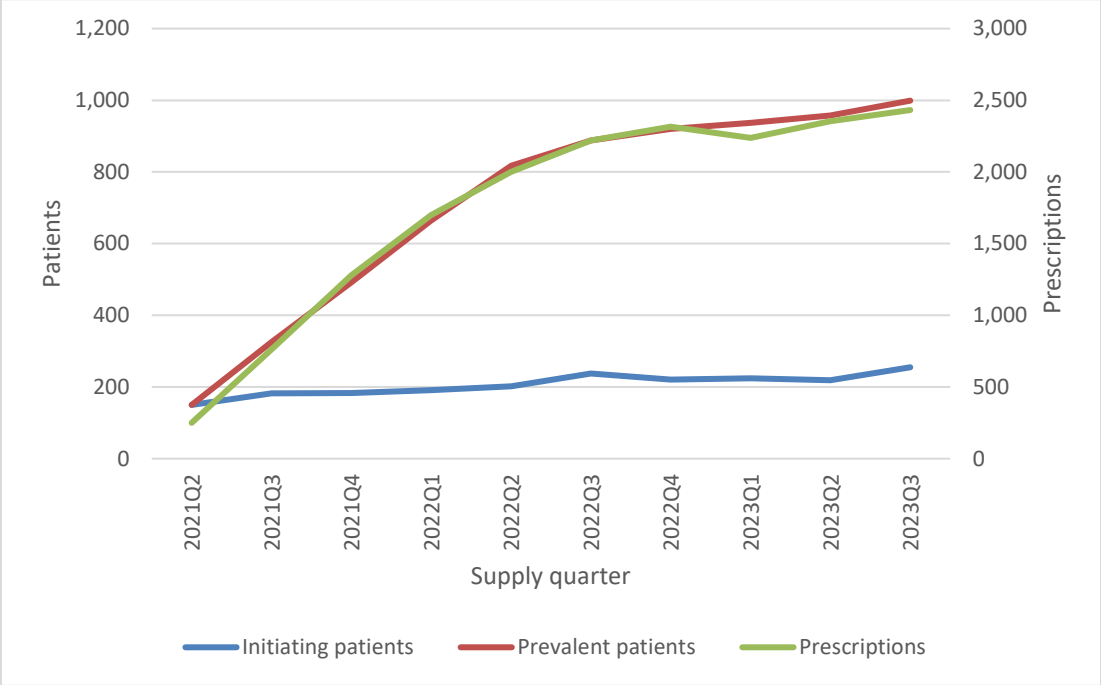

Figure 10: Initiating and prevalent romosozumab patients by supply quarter

In Figure 10, the number of patients treated with romosozumab has been increasing over time. There were 150 patients treated with romosozumab in 2021Q2, this has increased to 999 patients by 2023Q3. Approximately 200 patients initiate treatment with romosozumab per supply quarter.

Utilisation by relevant sub-populations/regions or patient level analysis

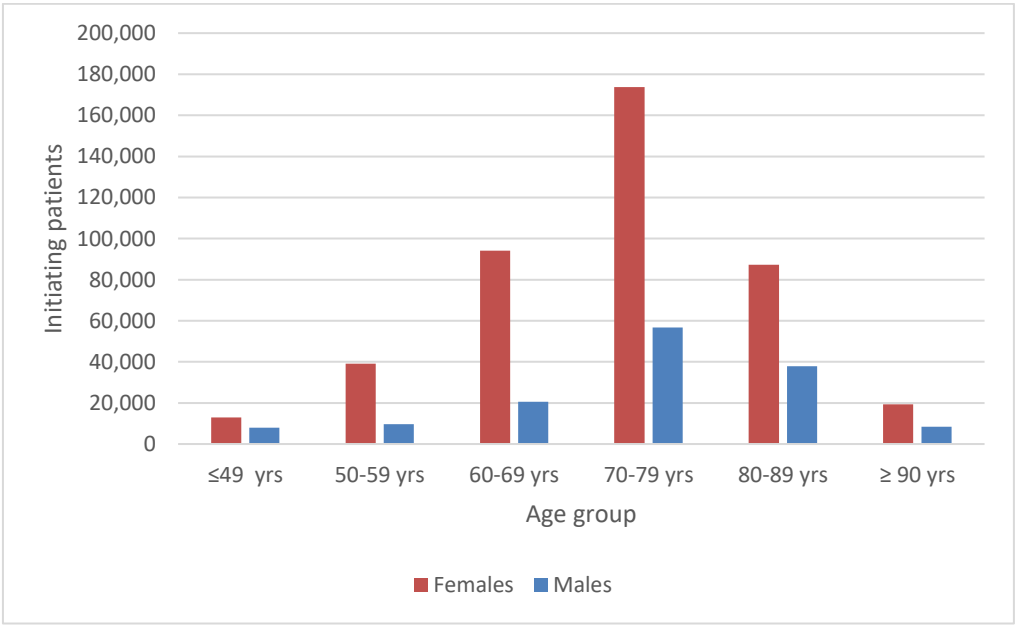

Figure 11: Age and gender distribution of initiating osteoporosis patients between 1 January to 30 September 2023

As shown in Figure 11, the most common age group of patients initiating treatments for osteoporosis were those aged between 70-79 years. The median age was 72 and 75 years for females and males, respectively.

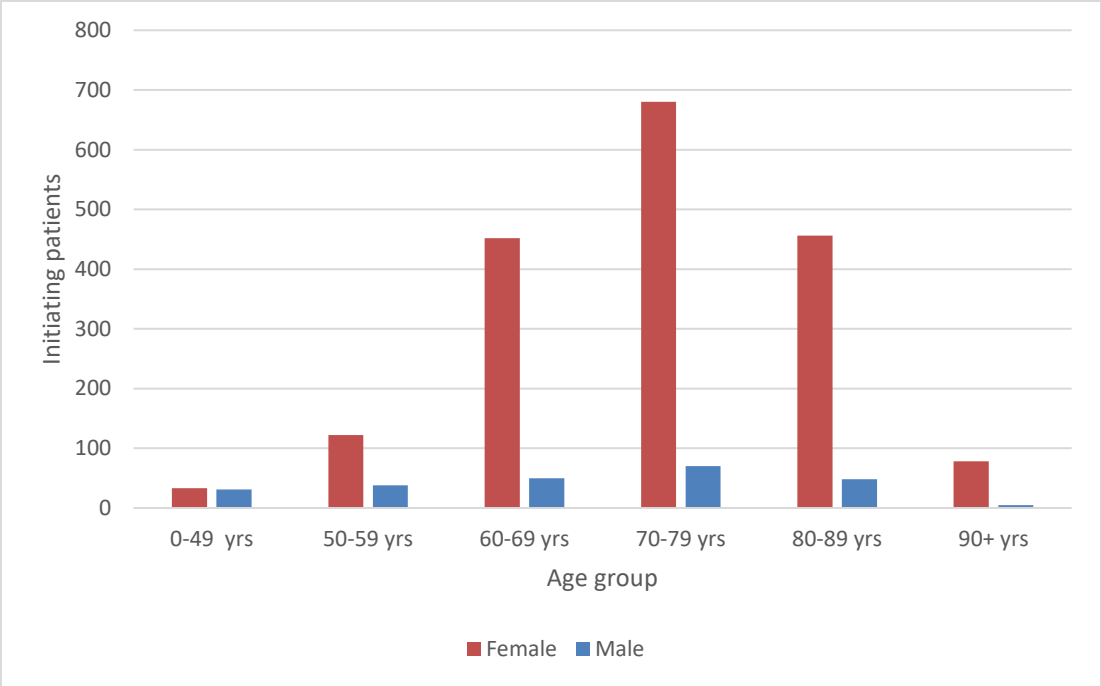

Figure 12: Age and gender distribution of initiating romosozumab patients

Similar to Figure 11 above, in Figure 12 the most common age group of patients initiating romosozumab treatment were those aged 70-79 years. Overall, the median age of initiating patients was 66 years. The median age for females and males initiating romosozumab treatment was 69 and 62 years, respectively.

Table 6: Utilisation of anti-resorptives after romosozumab (variable treatment gaps)

Defined treatment gap	Transitioned, n/N (%) [a]	Persistence ≥1 year, n/N (%) [b]
Within 2 months after romosozumab	343/705 (49%)	366/705 (52%)
Within 4 months after romosozumab	367/705 (52%)	402/705 (57%)
Within 6 months after romosozumab	381/705 (54%)	425/705 (60%)

Notes:

- Successful transition includes patients with ≥2 anti-resorptive scripts resulting in variable script coverage. For example, patients receiving oral anti-resorptives (alendronate, raloxifene and risedronate) would only have a 2-month expected coverage whereas patients on injectable anti-resorptives (denosumab, zoledronic acid) would have at least 1 year expected coverage.
- Persistence estimates were based on patients having at least 1 anti-resorptive script after stopping romosozumab, and subsequent anti-resorptive scripts within allowed treatment gaps.

As shown above, the results indicate that 49% of patients who initiated romosozumab during its first year of listing 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 romosozumab. The results also indicated relatively poor long term persistence to anti-resorptive therapy, with 51% of patients remaining persistent after 1 year after cessation of romosozumab.

Since PBS listing of romosozumab, less than 5 patients treated with romosozumab were identified to have potential coadministration with teriparatide.

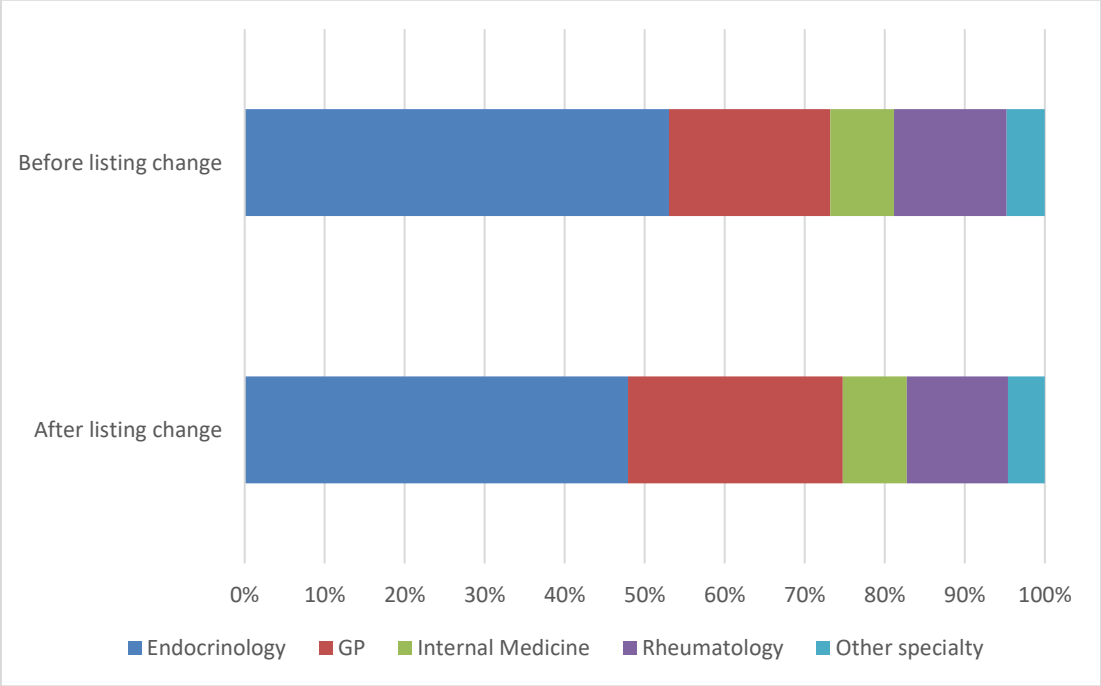

Figure 13: Proportion of continuing prescriptions by prescriber type, before and after GPs were allowed to continue romosozumab treatment.

As shown in Figure 13, prior to the listing change to allow GPs to continue romosozumab treatment, GPs accounted for 20.2% of continuing romosozumab prescriptions supplied. Following the listing change, this increased to 26.9% of continuing prescriptions.

Analysis of expenditure

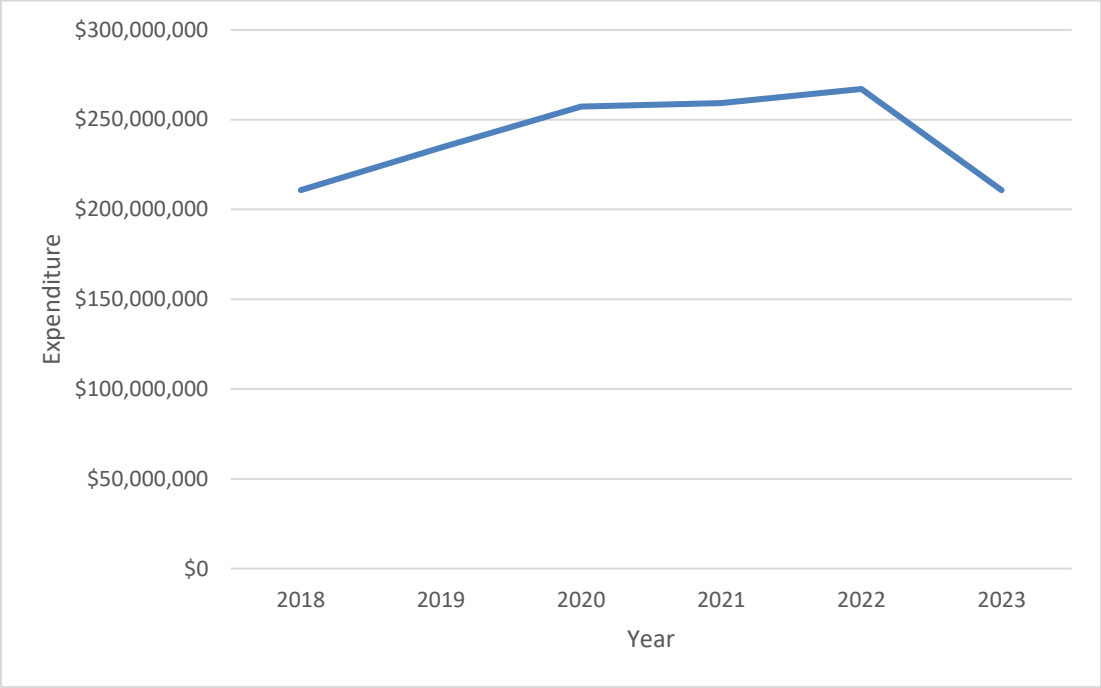

Figure 14: Annual expenditure of osteoporosis medicines, based on published prices.

Note: 2023 only includes nine months of data from January 2023 to September 2023, inclusive.

In Figure 14, annual expenditure based on published prices has been increasing over time. In 2018, annual expenditure was approximately $210 million, whereas in 2022, annual expenditure was approximately $260 million. The largest growth in expenditure was observed between 2018 to 2020, with an annual growth of between 10% to 14%, whereas between 2020 to 2022, expenditure growth was approximately 1% to 3% annually.

Approach taken to estimate utilisation

The March 2020 resubmission used an epidemiological/market share approach to estimate the utilisation and financial impact for romosozumab summarised in Table 7.

Table 7: Estimation of the number of treated romosozumab patients

	Value	Year 6[a]	Source and comment
Estimated eligible population			
Number of patients treated for osteoporosis	-	697,849	10% Medicare sample analysis of patients receiving osteoporosis treatments for the 12 months to June 2018 (552,227), extrapolated to 2020-2025 estimates based on growth rate of prevalent population (2014-2015) from the DUSC 2016 Osteoporosis report). May be underestimated as it only captures patients on active therapy. The DUSC 2016 report indicated there is an increasing number of patients who re-initiate therapy after a 2-year break.
Number of patients treated for ≥12 months	67.2%	469,057	10% Medicare sample analysis of patients who were on ≥12 months continuous therapy for 12 months to June 2018. It was difficult to interpret the analysis due to poor documentation. Estimates were lower than the November 2018 submission's estimates based on the DUSC 2016 Osteoporosis report (84.7%).
Patients with prior fracture	75%	351,793	Geelong Osteoporosis Study. The PBAC previously considered that the majority of treated osteoporosis patients have a prevalent fracture (November 2016 meeting, Consideration of the Report of DUSC). However, the magnitude of this proportion remains unclear as the data were based on a general population study (includes undiagnosed patients).
Treated patients with prior fracture and BMD ≤ -3	9.7%	34,089	Geelong Osteoporosis Study, 10% Medicare sample analysis, FREEDOM trial extension and multiple assumptions. Estimates from these sources may not be applicable to the treated population given the Geelong Osteoporosis Study population consists of diagnosed and undiagnosed participants. The applicability of the FREEDOM extension study population (primary osteoporosis) to the PBS population was unclear given limited detail provided in the resubmission. The resubmission appeared to misinterpret the data from the FREEDOM trial (use of relative reduction instead of proportion of patients below the BMD threshold).

	Value	Year 6[a]	Source and comment
Fracture while on anti-resorptive therapy	29.3%	9,974	Based on an assumed annual fracture rate derived from the Garvan Fracture risk calculator plus assumptions, multiplied by patient-years of exposure calculated from a 10% Medicare sample analysis. This estimate was uncertain due to concerns with the derived fracture rate (inappropriate application of risk synthesised from four individuals to estimate population risk, use of flat rate over time, unknown source for downward adjustment to treatment effects) and anomalous results from the 10% Medicare sample analysis.
Estimated use of romosozumab			
Romosozumab uptake calibration	[redacted][b]	[redacted]	Single uptake assumption derived through calibration to match previous utilisation estimates in the July 2019 submission. The uptake rates for romosozumab in the July 2019 submission were based on an assumed increasing capture of the existing anabolic agent market share and a larger addition of patients from market growth ([redacted]-fold expansion). The new uptake rates do not differentiate between these markets, as they are applied directly to the eligible patient population, but maintain the previous assumption of increasing uptake over time.

Source: Table 12 romosozumab Public Summary Document, March 2020 PBAC meeting.
[a] Number of treated patients estimated at each step in Year 6 of the financial estimates
[b] Uptake rates, Yr 1: [redacted]%, Yr 2: [redacted]%, Yr 3: [redacted]%, Yr 4-6: [redacted]%

Analysis of actual versus predicted utilisation

Table 8: Predicted versus actual utilisation of romosozumab

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

As shown above, utilisation of romosozumab was lower than estimated. In the first year of listing, the number of patients treated was [redacted]% lower than estimated and the number of prescriptions supplied was [redacted]% lower than estimated. In the second year of listing, the number of patients treated with romosozumab was [redacted]% lower than estimated and the number of prescriptions was [redacted]% lower than estimated.

There was a greater difference in the number of predicted and actual prescriptions supplied compared to the number of predicted and actual patients treated.

Discussion

As part of its recommendation at the March 2020 meeting, the PBAC requested DUSC conduct a utilisation review of romosozumab including an investigation of the success of transitioning patients from romosozumab to anti-resorptive therapy. As shown above, romosozumab utilisation was lower than estimated (Table 8) and only 49% patients who initiated romosozumab during its first year of listing transitioned to an anti-resorptive therapy (Table 6).

The Product Information for romosozumab states the requirement to transition to an anti-resorptive osteoporosis therapy to preserve bone mass. At its July 2022 meeting, the PBAC noted an analysis conducted by the DUSC Secretariat. Based on the same criteria in this report (at least two anti-resorptive prescriptions accounting for variable prescription coverage between drugs), only 49% of patients successfully transitioned to anti-resorptive therapy after stopping teriparatide. The PBAC considered concerns regarding the maintenance of treatment effect after discontinuation of romosozumab (paragraph 7.7, romosozumab Public Summary Document, July 2022 PBAC Meeting).

The PBAC's recommendation for romosozumab listing was based on, among other matters, its assessment that the cost-effectiveness of romosozumab would be acceptable if it were cost-minimised against teriparatide. It is noted although both romosozumab and teriparatide are both indicated for second-line therapy for osteoporosis, the coadministration analysis indicated the low potential for coadministration between them. From 2022 onwards, there was a greater number of patients treated with romosozumab compared to teriparatide (Figure 7). The greater utilisation of romosozumab compared to teriparatide may be due to the different dosing schedules between them (romosozumab administered monthly, whereas teriparatide is administered daily).

Several listing changes have occurred since the PBS listing of romosozumab. On 1 January 2021, the restrictions for romosozumab and teriparatide were amended to include the addition of 'PBS-subsidised treatment' to ensure patients who previously self-funded their romosozumab or teriparatide treatment were not excluded from PBS subsidised treatment. As shown above, the number of initiating romosozumab patients were relatively stable despite this listing change (Figure 10). On 1 February 2023, the treatment criterion "Must be treated by a Specialist" was removed from the continuing restriction for romosozumab as recommended by the PBAC at its July 2022 meeting. Prior to the listing change, GPs accounted for approximately 20% of continuing prescriptions. Following this listing change this has increased to approximately 27% of continuing prescriptions (Figure 13).

It is noted at the time of this analysis, romosozumab was listed for use in the second-line setting. At its March 2023 meeting, the PBAC recommended the listing be extended for use in the first-line setting, however the recommendation is yet to be implemented.

DUSC consideration

DUSC noted romosozumab utilisation was lower than estimated. The Pre-Sub-Committee Response (PSCR, p1) noted the lower than estimated utilisation was, "due to slower uptake than forecast as opposed to an overestimation of the size of the eligible patient population." DUSC considered the impact of the COVID-19 pandemic on treatment uptake. DUSC commented that during the pandemic, access to Bone Mineral Density testing was limited resulting in the underdiagnosis of osteoporosis.

DUSC noted on 7 December 2023, the TGA provided a safety update regarding romosozumab treatment.[5] The TGA noted its "investigation into the risk of myocardial infarction and stroke in patients taking romosozumab (Evenity) found that stronger warnings regarding these risks were needed in the Product Information (PI) and Consumer Medicine Information. Romosozumab use is now also contraindicated in patients with a history of myocardial infarction or stroke." DUSC noted the Sponsor provided information regarding the PI update in its PSCR. The PSCR noted the TGA was made aware of the discrepancy in published information relating to cardiovascular risk between Australia and that of Europe and the United States. Information related to cardiovascular risk has been noted since initial registration of romosozumab in Europe and the United States. The PSCR noted the recent TGA update was to align the Australian PI with the European Summary of Product Characteristics (SmPC). DUSC noted the PSCR (p2) stated, "there has not been a change in the CV benefit/risk profile of romosozumab nor upward trend on MI or stroke identified since the marketing approval of romosozumab globally." Although its post-marketing surveillance did not identify any new findings, DUSC considered the cardiovascular risks associated with romosozumab may have contributed to its lower than estimated utilisation.

DUSC noted only 49% patients were identified to have successfully transitioned to an antiresorptive after stopping treatment with romosozumab. The PSCR (p1), "acknowledges that transition to antiresorptive therapy is less than optimal and will make this a focus of future medical education and promotional efforts." DUSC considered possible reasons for the low transition to antiresorptive osteoporosis therapy. DUSC commented on the potential for mixed messaging regarding osteoporosis treatment pathways and noted the 'drug holidays' for patients treated with bisphosphonates. DUSC considered the low transition to antiresorptive to be a Quality Use of Medicines issue given the PI states the transition to antiresorptive osteoporosis therapy is required to preserve bone mass. DUSC commented on the importance of planning antiresorptive therapy continuation prior to initiating romosozumab treatment to ensure bone mass preservation, as the benefits associated with romosozumab treatment may not be realised unless patients continue onto antiresorptive therapy. DUSC considered the importance of educating prescribers and patients to ensure patients are transitioned to antiresorptive osteoporosis therapy.

[5] Therapeutic Goods Administration. New warnings of romosozumab (Evenity) cardiovascular risks. Available from: https://www.tga.gov.au/news/safety-updates/new-warnings-romosozumab-evenity-cardiovascular-risks

DUSC noted most patients were treated with denosumab. DUSC considered denosumab would be preferred in residential aged care facilities given its dosing schedule and ease of administration compared to other treatments for osteoporosis. DUSC considered the potential for the market share of denosumab to decrease. DUSC noted the adverse events associated with denosumab, where patients were at increased risk of fractures if they discontinued therapy. Additionally, DUSC noted the U.S Food and Drug Administration recently added a Boxed Warning for denosumab for increased risk of severe hypocalcaemia in patients with advanced chronic kidney disease.[6]

DUSC actions

DUSC requested the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

Amgen Australia Pty Limited: The sponsor has no comment.

[6] U.S. Food and Drug Administration. FDA adds Boxed Warning for increased risk of severe hypocalcemia in patients in advanced chronic kidney disease taking osteoporosis medicine Prolia (denosumab). Accessed from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-severe-hypocalcemia-patients-advanced-chronic-kidney-disease

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health and Aged Care has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, the Department of Health and Aged Care makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the Department of Health and Aged Care nor any Department of Health and Aged Care employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendices

Appendix A: Pharmacology as per Australian Product Information and the Australian Medicine Handbook

Bisphosphonates slow bone loss by reducing bone resorption. In addition, they bind strongly to bone mineral, thus forming a depot from which they are released as the bisphosphonate-containing bone is remodelled.

Denosumab is a fully human immunoglobulin G2 (IgG2) monoclonal antibody, which binds to the proteins responsible for bone resorption. This decreases bone resorption and increases bone mass and strength.

Raloxifene is a selective oestrogen receptor modulator that has been shown to prevent postmenopausal bone loss. It is an alternative drug for women with postmenopausal osteoporosis.

Romosozumab is a humanised monoclonal antibody that binds and inhibits sclerostin, a negative regulator of bone formation predominantly secreted by mature osteocytes. Romosozumab has a dual effect on bone, increasing bone formation and decreasing bone resorption.

Teriparatide is a synthetic form of human parathyroid hormone (PTH) and acts by increasing bone formation.

Calcium supplementation may reduce the rate of bone loss, particularly in late menopausal women with low dietary intake and without previous fragility fractures. The biologically active form of Vitamin D is responsible for endocrine functions for maintaining calcium homeostasis.

Appendix B: Osteoporosis drugs listing history

Date	Drug	Detail
1 December 1991	CALCITRIOL	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma.
1 August 1996	DISODIUM ETIDRONATE and CALCIUM CARBONATE	Listed on PBS on a cost-minimisation basis with calcitriol for established osteoporosis in patients with fracture due to minimal trauma.
1 November 1996	ALENDRONATE	Listed on PBS on a cost-effectiveness basis with calcitriol for established post-menopausal osteoporosis in patients with fracture due to minimal trauma.
1 November 1999	RALOXIFENE HYDROCHLORIDE	Listed on PBS on a cost-minimisation basis with alendronate for established post-menopausal osteoporosis in patients with fracture due to minimal trauma.
1 February 2001	RISEDRONATE	Listed on PBS on a cost-minimisation basis with alendronate for established post-menopausal osteoporosis in patients with fracture due to minimal trauma.
1 December 2005	CALCIUM	Delisting of calcium for patients other than those with chronic renal failure.
1 April 2006	ALENDRONATE (70 mg tabs), RISEDRONATE (5 mg and 35 mg tabs), RALOXIFENE HYDROCHLORIDE (60 mg), DISODIUM ETIDRONATE, CALCITRIOL	Restriction amended to sole therapy for established osteoporosis.
1 April 2006	RISEDRONATE and CALCIUM CARBONATE	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
1 August 2006	ALENDRONATE with COLECALCIFEROL	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
1 April 2007	STRONTIUM RANELATE	Listed on PBS on a cost-minimisation basis with alendronate for established post-menopausal osteoporosis in patients with fracture due to minimal trauma
1 April 2007	ALENDRONATE	Extension to patients 70 years or more at risk of fracture based on BMD test (-3.0 or less)

Date	Drug	Detail
1 July 2007	ALENDRONATE AND COMBINATIONS, RISEDRONATE AND COMBINATIONS, DISODIUM ETIDRONATE and CALCIUM CARBONATE, CALCITROL, RALOXIFENE HYDROCHLORIDE and STRONTIUM RANELATE	STREAMLINED process was introduced
1 August 2007	RISEDRONATE and COMBINATIONS	Extension to patients 70 years or more at risk of fracture based on BMD test (-3.0 or less)
1 November 2007	STRONTIUM RANELATE	Extension to patients 70 years or more at risk of fracture based on BMD test (-3.0 or less). Based on cost-minimisation with alendronate
1 December 2007	ALENDRONATE	Statutory price reduction.
1 December 2007	ALENDRONATE with COLECALCIFEROL	Partial 12.5% price reduction to alendronate component.
1 May 2008	RISEDRONATE and CALCIUM CARBONATE with COLECALCIFEROL	Listed on PBS for established osteoporosis in patients 70 years or older with a BMD T-score of -3.0 or less and for established osteoporosis in patients with fracture due to minimal trauma.
1 December 2008	ZOLEDRONIC ACID	Listed on PBS on a cost-minimisation basis with alendronate for established post-menopausal osteoporosis in women with fracture due to minimal trauma and for established osteoporosis in men with hip fracture due to minimal trauma.
1 February 2009	RISEDRONATE and COMBINATIONS	Extension to include treatment for corticoid-induced osteoporosis in a patient on at least three months high-dose corticosteroid therapy with a BMD (BMD) T-score of -1.5 or less.
1 April 2009	ZOLEDRONIC ACID	Extension to include treatment for osteoporosis in patients 70 years or older with a BMD T-score of -3.0 or less. Based on cost-minimisation with alendronate.
1 May 2009	TERIPARATIDE	Listed on PBS on a cost-effectiveness basis over alendronate for patients as the sole PBS subsidised treatment of severe

Date	Drug	Detail
		osteoporosis for patients with a very high risk of fracture who have: a BMD T-score of -3.0 or less; had two or more fractures due to minimal trauma; and experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at an adequate dose.
1 April 2010	ZOLEDRONIC ACID	Extension to include treatment for corticoid-induced osteoporosis in a patient on long-term, high-dose corticosteroid therapy with a BMD (BMD) T-score of -1.5 or less.
1 April 2010	ZOLEDRONIC ACID	Amending the listing to include men with established osteoporosis with fractures other than hip fracture due to minimal trauma, and men aged 70 years or older with a BMD (BMD) T-score of -3.0 or less. Based on cost-minimisation with zoledronic acid.
1 June 2010	ALENDRONATE with COLECALCIFEROL and CALCIUM CARBONATE	Listed on PBS for osteoporosis in patients 70 years or older with a BMD T-score of -3.0 or less and for established osteoporosis in patients with fracture due to minimal trauma.
1 November 2010	ALENDRONATE AND COMBINATIONS	Extension for people with corticosteroid-induced osteoporosis in a patient on long-term, high-dose corticosteroid therapy with a BMD (BMD) T-score of -1.5 or less.
1 December 2010	DENOSUMAB	Listed on PBS on cost-minimisation basis with zoledronic acid (with an adjustment to the price to account for the different requirements for administration) for women aged 70 or older with a BMD T-score of -3.0 or less and for established post-menopausal osteoporosis in patients with fracture due to minimal trauma. Listed as Authority Required and changed to STREAMLINED in March 2012.
1 April 2011	RISEDRONATE AND COMBINATIONS	Statutory price reduction.
1 December 2011	ALENDRONATE AND COMBINATIONS	Amend the listing of alendronate for the treatment of osteoporosis for patients aged 70 years and above be changed to include patients with a BMD T score of -2.5 or less.

Date	Drug	Detail
1 March 2012	DENOSUMAB	Changed to Authority Required (Streamlined).
1 April 2012	ALENDRONATE	Price disclosure reduction of 31.84%.
1 July 2012	TERIPARATIDE	Changed from written authority to telephone authority (Authority Required).
1 August 2012	DENOSUMAB	Amend the listing of denosumab for the treatment of osteoporosis for women aged 70 years and above be changed to include patients with a BMD T score of -2.5 or less.
1 September 2012	DISODIUM ETIDRONATE AND COMBINATIONS	Delisted at request of Sponsor.
1 December 2012	RISEDRONATE AND COMBINATIONS	The price was decreased on 1 December 2012, however following a court order on 6 December 2012 the prices were corrected to the 1 November 2012 prices.
1 April 2013	ALENDRONATE	Price disclosure reduction of 31.84%.
1 August 2013	RISEDRONATE AND COMBINATIONS	Amend the listing of risedronate for the treatment of osteoporosis for patients aged 70 years and above be changed to include patients with a BMD T score of -2.5 or less
1 December 2013	DENOSUMAB	Restriction expanded to include males
1 October 2014	STRONTIUM	Restriction narrowed. • The approval type was change from Authority required (STREAMLINED) to Authority Required. • The indication was changed from “Established osteoporosis” to “Severe established osteoporosis” • The following clinical criteria were added; - Patient must be at high risk of fracture; and - Patient must be unable to use other medications for the treatment of osteoporosis due to contraindications or intolerance.
1 May 2015	ALENDRONATE and RISEDRONATE	Changed from Authority Required (STREAMLINED) to Restricted Benefit. Combination items including these drugs remained Authority Required (STREAMLINED).

Date	Drug	Detail
1 August 2016	STRONTIUM RANELATE	Delisted.
1 May 2018	RISEDRONATE AND CALCIUM CARBONATE WITH COLECALCIFEROL	Delisted.
1 April 2021	ROMOSOZUMAB	Listed for the treatment for severe established osteoporosis.
1 January 2022	ROMOSOZUMAB and TERIPARATIDE	'PBS-subsidised treatment' to ensure that patients who previously self-funded their romosozumab or teriparatide treatment were not excluded from initiating PBS treatment
1 October 2022	ALENDRONATE WITH COLECALCIFEROL AND CALCIUM CARBONATE	Delisted.
1 March 2023	ROMOSOZUMAB	Removal of requirement for specialist continuing treatment.
1 September 2023	ALENDRONATE AND COMBINATIONS, CALCITRIOL, RALOXIFENE, RISEDRONATE AND COMBINATIONS	Additional listings due to introduction of the 60 day prescribing measure.