

Denosumab for osteoporosis: utilisation analysis using PBS data

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

Naik-Panvelkar et al. (2020) used MedicineInsight data to examine osteoporosis management in general practice, reporting that 80% of patients who ceased denosumab treatment did not appear to have any record of subsequent bisphosphonate prescription.¹ This is a concern because there is evidence of lower bone mineral density (BMD) and increased risk of multiple vertebral fractures shortly after discontinuation of denosumab. For this reason, it is suggested that denosumab not be discontinued without considering a substitute treatment.²

At its June 2020 meeting, DUSC noted that the findings of Naik-Panvelkar et al. suggest that Australian patients who cease denosumab are at risk of fractures. DUSC requested that the utilisation of denosumab, including use of bisphosphonates or other osteoporosis medicines after denosumab discontinuation, be reviewed in the context of the total osteoporosis market using both PBS dispensing data and MedicineInsight data.

The osteoporosis medicines included in this analysis are:

- denosumab;
- bisphosphonates alone and in combination with colecalciferol and/or calcium carbonate (alendronate, risedronate and zoledronic acid³);
- raloxifene and teriparatide;
- strontium ranelate (delisted in 2016); and
- calcitriol.

Date of first listing on the Pharmaceutical Benefits Scheme (PBS) for the treatment of osteoporosis

- Calcitriol: 1 December 1991

¹ Naik-Panvelkar P, Norman, S, Elgebaly, Z, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. *BMC Fam Pract* 2020; 21(1): 32.

² AMH. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2020.

³ A fourth bisphosphonate, etidronate, has not been included as it was removed from the PBS in 2012 (prior to the study period) and is no longer available in Australia.

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- Disodium etidronate and calcium carbonate: 1 August 1996 (delisted September 2012)
- Alendronate: 1 November 1996
- Raloxifene: 1 November 1999
- Risedronate: 1 February 2001
- Risedronate and calcium carbonate: 1 April 2006
- Alendronate with colecalciferol: 1 August 2006
- Strontium: 1 April 2007 (delisted 1 August 2016)
- Risedronate and calcium carbonate with colecalciferol (1 May 2008)
- Zoledronic acid: 1 December 2008
- Teriparatide: 1 May 2009
- Alendronate with colecalciferol and calcium carbonate: 1 June 2010
- Denosumab: 1 December 2010

Data Source / methodology

PBS Data

Patient counts and patient level analysis data were extracted from the Services Australia PBS 10% sample database for prescriptions supplied from January 2012 to June 2019. Prescription analyses were based on prescriptions supplied from January 2014 to June 2019.

MedicineInsight Data

This paper reports on a retrospective cohort study using MedicineInsight data to explore the use of osteoporosis medicines in general practice, with a particular interest in the use of denosumab. It uses de-identified patient data from the clinical information system (CIS) of 506 participating general practices and provides information on the following patient cohorts:

- 896,548 regularly attending patients aged 50+ years who visited their general practice at least 3 times between January 2018 and December 2019 (**regular patient prevalence study population**)
- 120,388 patients aged 50+ years who visited their general practice at least 3 times between January 2014 and December 2017 and had a recorded diagnosis of osteoporosis prior to 1 January 2018 (**historical osteoporosis study population**);
- 22,256 patients who were started on denosumab between January 2014 and December 2017 regardless of whether they had been prescribed another osteoporosis medicine first (**denosumab initiator population**); and
- 11,122 patients who were started directly on denosumab between January 2014 and December 2017 without having been prescribed another osteoporosis medicine first (**initiated directly on denosumab population**).

Key Findings

PBS Data

- In 2014, 32,277 patients in the 10% PBS sample were dispensed an osteoporosis medicine at least once. In 2018, this number had risen to 49,451 patients – a 50% increase.
- Patterns of dispensing between 2014 and 2018 changed with denosumab accounting for 76.1% of the patients dispensed any osteoporosis medicines in 2018 compared with 36.5% of patients in 2014. Over the same period, the bisphosphonates decreased from being dispensed to 46.5% of all patients dispensed an osteoporosis medicine in 2014 to 18.6% in 2014.
- Initiations to denosumab have driven an increase in the overall number of patients initiating osteoporosis therapy from 7,202 patients initiating in 2014 to 9,514 patients in 2018, representing a 32% increase (PBS 10% sample).
- There has been a 2.8-fold increase in the rate of prevalent prescribing of denosumab. In 2014, the prevalent rate of prescribing was 4.5 per 1,000 persons. In 2018, the prevalent rate was 12.5 per 1,000 persons.
- Females aged 70+ years accounted for almost two-thirds of all patients dispensed denosumab in the 10% PBS sample between January 2014 and June 2019.
- However, between 2014 and 2018 the number of male prevalent denosumab patients increased 4.6-fold compared with 3.0-fold for women and the number of male denosumab initiators increased by 60% compared with 40% for women.
- The number of all patients newly started on denosumab in the 10% PBS sample each year has stabilised in recent years. However, the number of patients who start on denosumab despite not having used any osteoporosis medicine in the prior two years is still increasing. This suggests that denosumab is being used more and more frequently as a first-line therapy for osteoporosis.
- The proportion of patients who were directly initiated on denosumab (without previous osteoporosis therapy) increased from 55% in 2014 to 76% in 2018. However, in the MedicineInsight study, among all patients who had been prescribed denosumab at least once between 2014 and 2017, 50% were directly initiated on denosumab. The lower proportion of patients directly initiated on denosumab in the MedicineInsight study compared with the PBS 10% study could indicate that specialists are more likely to start patients directly on denosumab than GPs. The PBS 10% study may have misclassified (and overestimated) patients as new to denosumab therapy if they had previously used other osteoporosis drugs prior to 2012 which could partly explain the magnitude of the difference between the data sources.
- The median average duration on any initiating osteoporosis medicine was 2.1 years, including breaks or 1.8 years excluding treatment breaks.
- The longest duration of therapy was seen for patients who initiate denosumab with a median average treatment duration (including breaks) of 2.5 years. In the subset of patients with at least 3.5 years of follow-up available (sensitivity analysis), the median average treatment duration, including breaks, was 3.9 years. The MedicineInsight data reported a 3.2-year median treatment duration (including breaks).

- Patients who initiated zoledronic acid had a median average duration of therapy of 1.0 years including or excluding treatment breaks. Alendronate and risedronate had similar treatment durations, at 1.1 years including breaks and 0.7 years excluding breaks. Of the 11,219 patients who experienced a treatment break from the very first osteoporosis medicine they were dispensed, patients on zoledronic acid and denosumab had the longest median time to first treatment break, at approximately 1 year, reflecting one supply of zoledronic acid and two supplies of denosumab.
- Of the 11,533 of the patients who were started on denosumab (regardless of whether they had been dispensed a different osteoporosis medicine beforehand), 35.2% had a treatment break. During this break only 2.5% were covered by another prescription for osteoporosis therapy.
- Just over a third (33.8%) of patients directly initiated on denosumab (without being dispensed a different osteoporosis medicine beforehand) had ceased therapy by the end of the study period and in the MedicineInsight study almost a quarter of patients (24.6%) had ceased denosumab treatment by study end.
- Of the PBS patients who ceased denosumab only 5.0% had a subsequent record of osteoporosis treatment and of the MedicineInsight patients who ceased denosumab only 13.8% had a subsequent record of osteoporosis treatment. Patients who were directly initiated on bisphosphonates were more likely to cease therapy than patients initiated on denosumab. They were also more likely to start treatment with an alternative osteoporosis medicine (probably denosumab) after ceasing their original medicine.

MedicineInsight Data

- The prevalence of osteoporosis among regularly attending MedicineInsight patients, (aged 50+ years, for all analyses), was 13.6% (95% confidence interval [CI] 13.0 to 14.1). As expected, the patient prevalence of osteoporosis was higher in women and rose with increasing age in both sexes.
- 60.5% (95% CI 59.5 to 61.4) of all regularly attending patients with a record of osteoporosis had been prescribed an osteoporosis medicine at least once.
- Just over half (52.7%; 95% CI 51.2 to 54.1) of regularly attending men with recorded osteoporosis had been prescribed an osteoporosis medicine at least once, compared with 62.5% (95% CI 61.5 to 63.5) of regularly attending women, suggesting that men may still be less likely to be treated for osteoporosis than women even when they have a recorded diagnosis.
- The proportion of regularly attending patients who had no record of being prescribed an osteoporosis medicine was higher in this study (39.5%; 95% CI 38.6% to 40.5%) than that reported in the Naik-Panvelkar paper (23.5%). This is most likely due to differences in cohort selection, as the cohort in the Naik-Panvelkar paper was restricted to patients seen at the general practice at least once every year over an 8-year period.
- Among the 22,256 patients in the historical osteoporosis cohort who had been prescribed denosumab at least once, 50.0% were started on denosumab without any record of having been previously prescribed any other osteoporosis medicine.

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- The median duration of treatment of denosumab treatment (including treatment holidays) was 1,154 days or 3.2 years (interquartile range: 887 days [1st quartile] to 1,679 days [3rd quartile]).
- 66.0% (95% CI 64.8 to 67.1) of the patients started on denosumab between January 2014 and December 2017 were still on denosumab treatment on 31 December 2019. Almost a quarter of patients (24.6%; 95% CI 23.6 to 25.6) had ceased denosumab treatment by this date.
- 86.2% of the historical osteoporosis cohort had no record of osteoporosis therapy after denosumab cessation. This is higher than that reported by Naik-Panvelkar et al. (2020) but may be explained by the differences in the study cohorts.

Purpose of analysis

Naik-Panvelkar et al. (2020) used MedicineInsight data to examine osteoporosis management in general practice, reporting that 80% of patients who ceased denosumab treatment did not appear to have any record of subsequent bisphosphonate prescription.¹ This is a concern because there is evidence of lower bone mineral density (BMD) and increased risk of multiple vertebral fractures shortly after discontinuation of denosumab. For this reason, it is suggested that denosumab not be discontinued without considering a substitute treatment.²

At its June meeting, DUSC noted that the findings of Naik-Panvelkar et al. suggests Australian patients who cease denosumab are placed at risk of fractures. DUSC requested that the utilisation of denosumab, including use of bisphosphonates or other osteoporosis medicines after denosumab discontinuation, be reviewed in the context of the total osteoporosis market using both PBS dispensing data and MedicineInsight data.

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.^{4,5,6}

There are a number of modifiable and non-modifiable risk factors that contribute to an individual's likelihood of developing osteoporosis. Non-modifiable risk factors include gender, age, being post-menopausal and family history of osteoporosis. Modifiable risk factors include physical inactivity, inadequate dietary calcium intake, low vitamin D, smoking, excessive alcohol intake and use of some medicines.⁶

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

⁴ Australian Institute of Health and Welfare. Osteoporosis. Canberra: AIHW; 2019.

⁵ 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.

⁶ Expert Group for Bone and Metabolism. Osteoporosis and minimal-trauma fracture [published June 2019]. Melbourne: Therapeutic Guidelines Limited; 2020.

common in older Australians and among women. More than a quarter of Australian women over the age of 75 years report having osteoporosis.⁴

Bisphosphonates (alendronate, risedronate and zoledronic acid) and denosumab are the more commonly used first-line medicines for osteoporosis in Australia.¹ Other osteoporosis medicines include calcitriol, raloxifene and teriparatide and until it was delisted in 2016, strontium ranelate.^{5,6,2}

Concerns have been raised about an increased risk of multiple vertebral fractures shortly after discontinuation of denosumab, a risk not associated with cessation of bisphosphonate therapy. Cessation of denosumab is associated with a rapid decrease of BMD and a steep increase in bone turnover markers.^{2,7,8,9} For this reason, it is suggested that denosumab not be discontinued without considering a substitute treatment.²

Pharmacology

See Appendix A.

Therapeutic Goods Administration (TGA) approved indications

Table 1: TGA approved osteoporosis* indications (as at August 2020)

Alendronate and combinations	<ul style="list-style-type: none"> • Treatment of osteoporosis, including glucocorticoid-induced osteoporosis. • Treatment and prevention of glucocorticoid-induced osteoporosis in those patients on long term corticosteroid therapy.
Calcitriol	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Prevention and treatment of osteoporosis in post-menopausal women.

⁷ Tsourdi E, Langdahl, B, Cohen-Solal, M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone* 2017; 105: 11-17.

⁸ Anastasilakis AD, Polyzos, SA, Makras, P, et al. Clinical Features of 24 Patients With Rebound-Associated Vertebral Fractures After Denosumab Discontinuation: Systematic Review and Additional Cases. *J Bone Miner Res* 2017; 32(6): 1291-1296.

⁹ Cummings SR, Ferrari, S, Eastell, R, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *J Bone Miner Res* 2018; 33(2): 190-198.

Risedronate and combinations	<ul style="list-style-type: none"> • Treatment of osteoporosis. • Treatment of glucocorticoid-induced osteoporosis. • Preservation of bone mineral density in patients on long term corticosteroid therapy.
Strontium ranelate	No longer registered in Australia. Previously used for: <ul style="list-style-type: none"> • Treatment of severe (established) osteoporosis in postmenopausal women at high risk of fracture to reduce the risk of fracture. • Treatment of severe (established) osteoporosis in men at increased risk of fracture.
Teriparatide (RBE)	<ul style="list-style-type: none"> • 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.
Zoledronic acid	<ul style="list-style-type: none"> • 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.

*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

Generic Name	Route and frequency of administration
Alendronate and combinations (alendronate with colecalciferol; alendronate with colecalciferol and calcium carbonate)	Oral; weekly
Calcitriol	Oral; twice daily
Denosumab	Subcutaneous injection; once every six months
Raloxifene	Oral; daily
Risedronate and combinations (risedronate and calcium carbonate)	Oral; daily, weekly or monthly
Strontium ranelate	No longer registered in Australia.
Teriparatide (RBE)	Subcutaneous injection; daily. Max 18 months
Zoledronic acid	IV infusion; once per year

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 August 2020)

Table 3 provides an overview of the PBS restrictions for osteoporosis medicines.

Table 3: Summarised PBS restrictions as at August 2020

Active ingredient	Minimal trauma	BMD -3.0 or less	BMD -2.5 or less	Corticosteroid-induced	Men
Alendronate and combinations	✓	✓	✓	✓	✓
Calcitriol	✓	✗	✗	✗	✓
Denosumab	✓	✓	✓	✗	✓
Raloxifene	✓	✗	✗	✗	✗
Risedronate and combinations	✓	✓	✓	✓	✓
Strontium ranelate (delisted August 2016)	✗	✗	✗	✗	✗
Teriparatide (RBE)*					
Zoledronic acid	✓	✓	✗	✓	✓

* Teriparatide is only listed for severe osteoporosis: when the patient has had a two or more fractures due to minimal trauma and the BMD T-score is -3.0 or less and the patient must have experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses.

Date of listing on PBS and changes to listing

The listing dates and relevant changes to the listing of osteoporosis medicines, such as restriction changes and price reductions, can be found in Appendix B.

Current PBS listing details are available from www.pbs.gov.au

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

At its July 2010 meeting, the PBAC recommended listing of denosumab pre-filled syringe 60 mg in 1 mL for treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a woman aged 70 years of age or older with a BMD T-score of -3.0 or less on a cost-minimisation basis compared with zoledronic acid. Listing was effective from 1 December 2010.

A copy of the Public Summary Document (PSD) from the July 2010 meeting is available at the [Public Summary Document for Denosumab - July 2010](#).

Following this decision the PBAC recommended the following changes:

- the current Authority Required listing for denosumab pre-filled syringe 60 mg in 1 mL for the treatment of osteoporosis be changed to a Streamlined Authority listing (November 2011 meeting)
- the current Authority Required (Streamlined) listing for denosumab 60 mg in 1 mL injection for the treatment of post-menopausal osteoporosis be extended to include women aged 70 years of age or older with a bone mineral density (BMD) T-score of - 2.5 or less ([March 2012 meeting](#))
- the current Authority required (Streamlined) benefit as the sole PBS-subsidised anti-resorptive agent for osteoporosis be extended to include both male and female patients ([July 2013 meeting](#))
- to allow initiation of treatment of osteoporosis by nurse practitioners ([July 2016 meeting](#)).

Previous reviews by the DUSC

In 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.

Methods

PBS Data

This is a descriptive analysis of 5.5 years of dispensing data extracted from the PBS 10% sample (1 January 2014 to 30 June 2019), with an additional 2 year look back period (1 January 2012 to 31 December 2013) to assess initiation of osteoporosis treatment. PBS data for the remainder of 2019 (July to December) was not available in time for this report.

To be eligible for inclusion in the study, patients must have had at least one prescription for an osteoporosis medicine between 1 January 2014 and 30 June 2019. Prescriptions for osteoporosis medicines were identified using PBS item codes as per Table 4. Unless otherwise stated:

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- all results, except for the crude and age-standardised treatment rates, represent 10% of the Australian population with a PBS prescription and have not been extrapolated to the whole population; and
- results for 2019, except for the crude and age-standardised incident treatment rates, include only 6 months of data, without extrapolation to the 12 month calendar year, and should be interpreted with caution.

Table 4: Osteoporosis medicines, associated PBS and ATC codes and restriction dates

Item code	Active ingredient	ATC5	Restriction start date	Restriction end note
08102K	alendronate	M05BA04	01 May 2001	30 Nov 2004
08511Y	alendronate	M05BA04	01 Aug 2001	
09012H	alendronate + colecalciferol	M05BB03	01 Aug 2006	
09183H	alendronate + colecalciferol	M05BB03	01 Aug 2008	
02502Q	calcitriol	A11CC04	01 May 2000	
05457F	denosumab	M05BX04	18 Oct 2009	
08363E	raloxifene	G03XC01	01 May 2000	
08481J	risedronate	M05BA07	01 Aug 2003	
08621R	risedronate	M05BA07	01 Aug 2003	
09391G	risedronate	M05BA07	01 Jul 2009	
08899J	risedronate (&) calcium carbonate	M05BB02	01 Apr 2006	30 Jun 2007
09147K	risedronate (&) calcium carbonate + colecalciferol	M05BB04	01 May 2008	30 Nov 2012
03036T	strontium ranelate	M05BX03	01 Apr 2007	01 Aug 2016
09411H	teriparatide	H05AA02	01 May 2009	
09288W	zoledronic acid	M05BA08	01 Dec 2008	31 Mar 2009
10555M	zoledronic acid	M05BA08		

PBS 10% sample

The 10% PBS sample is a random 10% sample of PBS claims data for Australians that contains patient-level administrative information about each prescription dispensed for medicines listed on the PBS between 2003 and June 2019. The data includes information on patient demographics (year of birth, sex, year of death), information on the medicines dispensed (e.g. type of script – original or repeat, PBS item code, quantity dispensed, concessional status, number of repeats, date of prescribing, date of supply, pharmacy state, prescriber ID, prescriber type). Under patient co-payment prescription data is available from 1 April 2012. The PBS 10% sample does not provide information on diagnoses, outcomes or tests.

Patient count analysis

Prevalent to denosumab and other osteoporosis medicines

The number of prevalent patients who received a supply of any osteoporosis medicine at least once in each calendar year from 2014 to 2019 was determined by counting the number of person specific numbers (non-identifying) in the data for each year. Results are presented overall, and by type of therapy (single agent and combination therapy).

Most PBS prescriptions generally provide one month of therapy, however prescriptions of zoledronic acid and denosumab cover 12 months and six months, respectively. As per previous DUSC reports which selected a 1-year analysis time period, the prevalence of prescription supply should be a good approximation of patients on treatment for all drugs which are expected to be supplied monthly or even 6 monthly. However, the prevalence of prescription supply for zoledronic acid will slightly underestimate the number of patients on treatment as it is expected to be supplied every 12 months and some patients will not be supplied in a calendar year even if they are on therapy. The potential underestimation of zoledronic acid prevalent patients should be kept in mind when considering the results of this analysis.

Initiating on denosumab

The number of new (incident) patients starting denosumab therapy in each calendar year from 2014 to 2019 was calculated in two ways:

- We counted **denosumab initiators** if they were dispensed denosumab that year but were not dispensed denosumab in at least the prior two years, or further back if records permitted (i.e. initiating patient count starts in 2014 with at least a two year look back to January 2012).
- We counted patients who were **directly initiated on denosumab** (a subset of the above) if they were dispensed denosumab that year but were not dispensed any other osteoporosis medicine in at least the prior two years or further back if records permitted.

Initiating on other osteoporosis medicines

The number of new patients first starting osteoporosis medicines in each calendar year from 2014 to 2019 was calculated overall and by type of medicine (single agent or combination therapy). We counted patients who were **directly initiated on osteoporosis medicines** as those who were dispensed an osteoporosis medicine that year but were not dispensed any osteoporosis medicines in at least the prior two years, or further back if records permitted (i.e. initiating patient count starts in 2014 with at least a two year look back to January 2012). Results were presented overall and by type of therapy (single agent and combination therapy). Patients could be included in more than one therapy type in one calendar year if they were co-administered at initiation.

Denosumab treatment rates (patients per 1000 population)

Treatment rates (patients per 1000 population) of patients initiating on, and prevalent to, osteoporosis medicines (nationally) were calculated as the number of initiating or prevalent patients, multiplied by 10 to extrapolate the 10% PBS sample to the whole population, divided by the ABS Estimated Residential Population (ERP) population¹⁰ as of 30 June in the specified year. These (crude) treatment rates were also age adjusted to correct for the effect of an ageing population. As 2019 only included 6 months of dispensing data we multiplied the treatment rates for incident patients by two, as a simple extrapolation to 12 months. No such extrapolation was performed for the prevalent patient treatment rates as we would expect the majority of prevalent patients to be counted in the first six months of the year (particularly if they are on monthly medicines).

The age-standardised prescribing rates for denosumab and all osteoporosis medicines, were calculated using Direct Standardisation¹¹, with the Australian age distribution of the ABS ERP in the reference year (30 June 2001) serving as the reference population. In other words, the age-specific prescribing rates observed in patients in each calendar year were applied to the age structure of the ABS ERP in the reference year 2001.

Treatment duration

The duration of treatment for each initiating osteoporosis medicine was calculated in two ways, using denosumab as an example:

- duration including treatment breaks was defined as the number of days between the date of the first denosumab dispensing and the expected end of the last dispensed prescription or the 30 June 2019 (whichever came first). The expected end date of the last dispensed denosumab prescription was defined as the date of the last dispensing plus the expected duration of treatment (180 days) as defined in Table 7.
- duration excluding treatment breaks was calculated by summing the number of days between the date of the first denosumab dispensing and the expected end of the last dispensed prescription or the 30 June 2019 (whichever came first) and then subtracting the days the patient was considered to be on a treatment break(s).

Treatment break

Treatment breaks were identified for each initiating osteoporosis medicine. Using denosumab as an example, a treatment break was defined as a period of at least 60 days after the expected end of the last dispensed denosumab prescription in which no refill for denosumab was obtained.¹² Treatment breaks ended on the date of the next denosumab dispensing. The expected end of the last prescription for each osteoporosis medicine is

¹⁰ Australian Bureau of Statistics, 2020. http://stat.data.abs.gov.au/Index.aspx?DataSetCode=ERP_QUARTERLY#

¹¹ Principles on the use of direct age-standardisation in administrative data collections, September 2011, AIHW

¹² Brookhart MA, Avorn, J, Katz, JN, et al. Gaps in treatment among users of osteoporosis medications: the dynamics of noncompliance. *Am J Med* 2007;120(3): 251-256.

defined in Table 5. Any gaps between the expected end of one dispensed prescription and the next refill that were less than 60 days were considered continuous therapy.

Table 5: Expected duration of treatment for included osteoporosis medicines

Active ingredient	Expected duration of treatment
Alendronate (including combination products)	28 days
Calcitriol	50 days
Denosumab	180 days
Raloxifene	28 days
Risedronate (including combination products)	28 days
Strontium ranelate	28 days
Teriparatide	28 days
Zoledronic acid	365 days

Treatment cessation

An initiating osteoporosis medicine was considered to have been ceased if the expected end of the last prescription for the medicine type (Table 5) was at least 60 days before the end of the study period. For example, if a patient's last script for alendronate was recorded on the 10 October 2018, this would be considered ceased because 28 days plus 60 days is before 30 July 2019. Whereas if a patient's last script for alendronate is recorded on the 10 May 2019, this would not be considered ceased, because the expected end of therapy is 7 June 2019, which is not 60 days before the end of the study period (30 June 2019) and the patient may still be on continuous therapy.

Management post-medicine cessation

For a patient who had ceased their initiating medicine to be recorded as having been started on another osteoporosis medicine they had to meet both of the following criteria, using denosumab as an example:

- have a prescription for a different medicine on or after the date of the last prescription for denosumab; and
- the expected end of the last prescription for the different medicine is after the expected end of the ceased treatment.

Statistical analysis

Analyses of the data were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), including the use of the SURVEYFREQ procedure. Measures included descriptive statistics, frequencies and proportions as appropriate.

MedicineInsight Data

MedicineInsight is a leading large-scale primary care data set of longitudinal de-identified electronic health records (EHR) in Australia. MedicineInsight was initially established by NPS MedicineWise in 2011, with core funding from the Australian Government Department of Health, to collect general practice data to support quality improvement in Australian primary care and post-market surveillance of medicines. The monthly collation of collected data can be analysed for the purposes of improving patient care, quality improvement and evaluation, performing population health analysis, research and developing health policy.

MedicineInsight utilises third-party data extraction tools which extract, de-identify, encrypt and securely transmit whole-of-practice data from the clinical information systems of over 700 general practices. Patient level data are de-identified 'at source' meaning patients' personal identifiers such as name, date of birth and address are not extracted by the tool (although year of birth and postcode are extracted, enabling the calculation of age and Socio-Economic Indexes for Areas [SEIFA]). The data held in the MedicineInsight database are non-identifiable. However, each patient has a unique identifying number which allows all the records (clinical, prescription, referral etc) held in the database to be linked to the associated patient identifying number. The process of collecting patient data achieves a data collection that meets the definition of non-identified data in the NHMRC National Statement on Ethical Conduct in Human Research. [chapter 3.2, p.27]. Further information is available online: <https://www.nps.org.au/medicine-insight>

Study ethics and approval

In December 2017, NPS MedicineWise was granted ethics approval for the standard operations and uses of the MedicineInsight database by NPS MedicineWise. This program approval was given by the RACGP NREEC (NREEC 17-017).

The use of MedicineInsight data for the purposes of this report was approved by the independent Data Governance Committee (2020–018).

Eligible patients

The MedicineInsight analyses used data from 1 January 2014 to 31 December 2019. There are a number of different study populations in the MedicineInsight study:

- the **regular patient prevalence study population** (to explore the prevalence of osteoporosis among regularly attending patients in general practice);
- the **historical osteoporosis study population** (to explore the history of use of osteoporosis medicines in general practice patients with a diagnosis of osteoporosis);

- the **denosumab initiator population** (to explore patterns of prescribing among patient started on denosumab regardless of whether they had been trialled on another osteoporosis medicine prior); and
- the **initiated directly on denosumab population** (to explore number of patients started directly on denosumab without being trialled on another osteoporosis medicine first).

Information on the eligibility criteria for each study population is show in Table 6.

Table 6: Eligibility criteria for inclusion in MedicinesInsight patients included in the three study populations

Study population	Eligibility criteria
Regular patient prevalence study population	<ul style="list-style-type: none"> • visited a practice site that contributed data to MedicinesInsight and meets specific MedicinesInsight data quality requirements* • have valid information for age and sex • had at least three clinical encounters during the study time period (1 January 2018–31 December 2019) (i.e. regular patients) • aged 50–112 years in 2019
Historical osteoporosis study population	<ul style="list-style-type: none"> • have visited a practice site that contributed data to MedicinesInsight and meets specific MedicinesInsight data quality requirements* • have valid information for age and sex • had at least three clinical encounters during the study time period (1 January 2014–31 December 2017) • aged 50–112 years in 2017 • had a diagnosis of osteoporosis recorded before 1 January 2018
Denosumab initiator population	<ul style="list-style-type: none"> • meet the osteoporosis study population criteria • have evidence of initiating denosumab therapy between 1 January 2014 and 31 December 2017: <ul style="list-style-type: none"> ○ no denosumab recorded prior to 1 January 2014 ○ the patient has at least 14 months attendance at the practice prior to the first prescription of denosumab (i.e.1 clinical encounter 14 months or more prior to the first denosumab prescription). • have at least 2 years of follow-up at the MedicinesInsight practice after initiating denosumab therapy i.e. at least 1 clinical encounter 2 years after initiation of denosumab therapy
Directly initiated on denosumab population	<ul style="list-style-type: none"> • meet the osteoporosis study population criteria • have evidence of using denosumab therapy between 1 January 2014 and 31 December 2017: <ul style="list-style-type: none"> ○ no osteoporosis medicine (bisphosphonates, denosumab, calcitriol, raloxifene, strontium ranelate or teriparatide) recorded prior to the first denosumab

Study population	Eligibility criteria
	<p>prescription recorded between 2014 and 2017 or prior to 1 January 2014</p> <ul style="list-style-type: none"> ○ the patient has at least 14 months attendance at the practice prior to the first prescription of denosumab (i.e. 1 clinical encounter 14 months or more prior to the first denosumab prescription).

*Practices must have been established for at least 2 years before the end of the analysis period and have no interruptions 2 months or longer in practice data in the 2 years to the end of the analysis period.

Osteoporosis definition

Patients in the regular patient prevalence study were defined as having osteoporosis, if they had an osteoporosis flag recorded at any time from the patient's earliest record up until 31 December 2019. Patients in the historical osteoporosis study were defined as having osteoporosis, if they had an osteoporosis flag recorded at any time from the patient's earliest record up until 31 December 2017.

MedicineInsight condition flags are devised using algorithms that analyse coded and free-text information in one of the three diagnosis fields – ‘reason for encounter’ or ‘reason for prescription’ or ‘diagnosis’. The relevant terms for the osteoporosis flag¹³ include osteoporosis (with fracture, no fracture, corticosteroid/steroid induced, disuse, post-menopausal) or steroid osteopathy. It does not include osteopenia, transient osteoporosis, ‘osteoporosis family history’ or ‘osteoporosis prevention’.

We did not use bone mineral density results or T-scores, which are largely unavailable to MedicineInsight, or a record of prescription for osteoporosis medicines as part of our definition of a diagnosis of osteoporosis.

Osteoporosis medicines

Osteoporosis medicines were identified using a combination of ATC codes and active-ingredient terms. Patients were defined as having had a prescription for an osteoporosis medicine if they had at least one record of a medicine provided in Table 7 in either the Prescription table or the Script Item table.

¹³ During a recent in-practice validation study, the MedicineInsight osteoporosis flag had excellent sensitivity, specificity, PPV and NPV (all 0.94 and above) making it a reliable measure of the prevalence of osteoporosis according to general practice records. The MedicineInsight was compared with electronic records at the practice including medical history, reason for visit, reason for prescription, correspondence, bone mineral density test results and progress notes. These findings are being submitted for publication.

Table 7: Osteoporosis medicines and ATC codes

Active ingredient	ATC codes
Alendronate and combinations (alendronate with colecalciferol; alendronate with colecalciferol and calcium carbonate)	M05BA04, M05BA04, M05BB03 and M05BB05
Calcitriol	A11CC04
Denosumab	M05BX04
Raloxifene	G03XC01
Risedronate and combinations (risedronate and calcium carbonate)	M05BA07, M05BA07, M05BA07, M05BB02 and M05BB04
Strontium ranelate	M05BX03
Teriparatide (RBE)	H05AA02
Zoledronic acid	M05BA08

Treatment duration

The duration of denosumab treatment including treatment breaks was defined as the number of days between the date of the first prescription and the expected end of the last prescription or the 31 December 2019 (whichever came first). The expected end date of the last denosumab prescription was calculated as the date of the last prescription plus 180 days multiplied by {the number of repeats + 1}. Referring to Table 8, the expected duration of treatment for each original or repeat prescription for denosumab is 180 days.

Table 8: Expected duration of therapy for included osteoporosis medicines

Active ingredient	Expected duration of treatment
Alendronate (including combination products)	28 days
Calcitriol	50 days
Denosumab	180 days
Raloxifene	28 days
Risedronate (including combination products)	28 days
Strontium ranelate	28 days
Teriparatide	28 days
Zoledronic acid	365 days

Whether denosumab treatment was ongoing or had ceased by study end (31 December 2019) was calculated using the rules described in Table 9. Note that these rules were only applied to determine the status of denosumab treatment at study end. They were not used

to determine the actual duration of denosumab treatment or the expected end-date of treatment for denosumab or any other osteoporosis medicine.

Table 9: Definitions of denosumab treatment status as at 31 December 2019 (study end)

Treatment status	Definition
Ongoing treatment	Denosumab treatment was considered ongoing at 31 December 2019 if the expected end of the last prescription plus 60 days was on or after 31 December 2019. For example, if a patient's last script for denosumab was recorded on 10 January 2019 and had one repeat, the expected duration would be (180 days x 2) + 60 days. (i.e. after 31 December 2019) and this would be considered ongoing treatment
Ceased treatment	Denosumab treatment was considered ceased at 31 December 2019 if the expected end of the last prescription plus 60 days, was before 31 December 2019 and on or before the patient's last visit at the MedicineInsight practice. For example, if a patient's last script for denosumab was recorded on the 10 October 2018 (and there were no repeats), this would be considered ceased if the patient's last visit at the practice was at least 240 days after the 10 October 2018
Lost to follow-up	Denosumab therapy was considered neither ceased nor active (i.e. lost to follow-up) if the expected end of the last prescription plus 60 days was before 31 December 2019 and after the patient's last visit at the MedicineInsight practice. For example, if a patient's last script for denosumab is recorded on the 10 October 2018, this would be considered lost to follow-up if the patient's last visit at the practice was less than 240 days after the 10th October 2018

Management post-denosumab cessation

For a patient who had ceased denosumab to be recorded as having been started on another osteoporosis medicine (bisphosphonate, calcitriol, strontium ranelate, teriparatide or raloxifene), they had to meet both of the following criteria:

- have a prescription for a different medicine on or after the date of the last prescription for denosumab; and
- the expected end of the last prescription for the different medicine is after the expected end of the ceased denosumab therapy (see Table 5 for expected duration of treatment).

Statistical analysis

Analyses were conducted on the February 2020 download using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), including the use of the SURVEYFREQ procedure. Measures included descriptive statistics, frequencies, proportions and odds ratios as appropriate. To indicate the reliability of the estimates of prevalence and proportions, 95% confidence intervals (adjusted for clustering by practice site) and p-values are reported as needed.

Guide to interpreting MedicineInsight data

When interpreting the information presented in this report, readers should note some of the limitations or caveats related to the MedicineInsight data:

- Information in the CIS is collected to provide clinical care to a patient, not for research purposes. All analyses are therefore dependent upon on the accuracy and completeness of data recorded in, and available for extraction from, the general practice CISs.
- Medicine-use information from MedicineInsight relates to records of GP prescribing, and therefore differs in several important ways from national PBS dispensing data. Not all prescriptions and repeats will be dispensed, i.e. prescription counts are an overestimate of dispensed prescription counts. Specialist and hospital prescriptions are not included. There may be a delay of up to 12 months between prescribing and dispensing.
- Practices were recruited to MedicineInsight using non-random sampling, and systematic sampling differences between regions cannot be ruled out.
- Due to confidentiality issues we do not have access to progress notes or access to correspondence, which may contain further information on reasons for prescriptions, reasons for encounters and diagnoses.
- Patients are free to visit multiple other practices. We do not have data on patients from non-MedicineInsight clinics. Currently we cannot identify patients who have attended multiple MedicineInsight practices.

Results

PBS Data

Prevalent denosumab patients

Over the 5.5-year period, the number of unique patients dispensed denosumab at least once a year increased. In 2018, the last full calendar year of data, there were an estimated 37,617 patients from the 10% PBS sample who were using denosumab, representing a 3-fold increase from 2014 (Table 8). While the count of prevalent denosumab patients increased between 2014 and 2018 among all age groups, the largest increase in terms of absolute numbers was seen in patients aged 70+ (3.3-fold increase) and the smallest among patients aged 50–59 years (2.4-fold increase) (Table 10).

Most patients dispensed denosumab in each year were females aged 70+ years (Figure 1; Table 8). Females aged 70+ years accounted for 63–65% of all unique patients dispensed denosumab each year. While significantly more females than males are dispensed denosumab each year the difference has reduced over time; in 2014 the ratio of prevalent denosumab women to men was 7.3:1 and by 2018 it was 4.8:1 indicating that denosumab use in males has increased at a greater rate than in females. In fact, between 2014 and 2018 the number of male prevalent denosumab patients has increased 4.6-fold compared with 3-fold among women (Table 10).

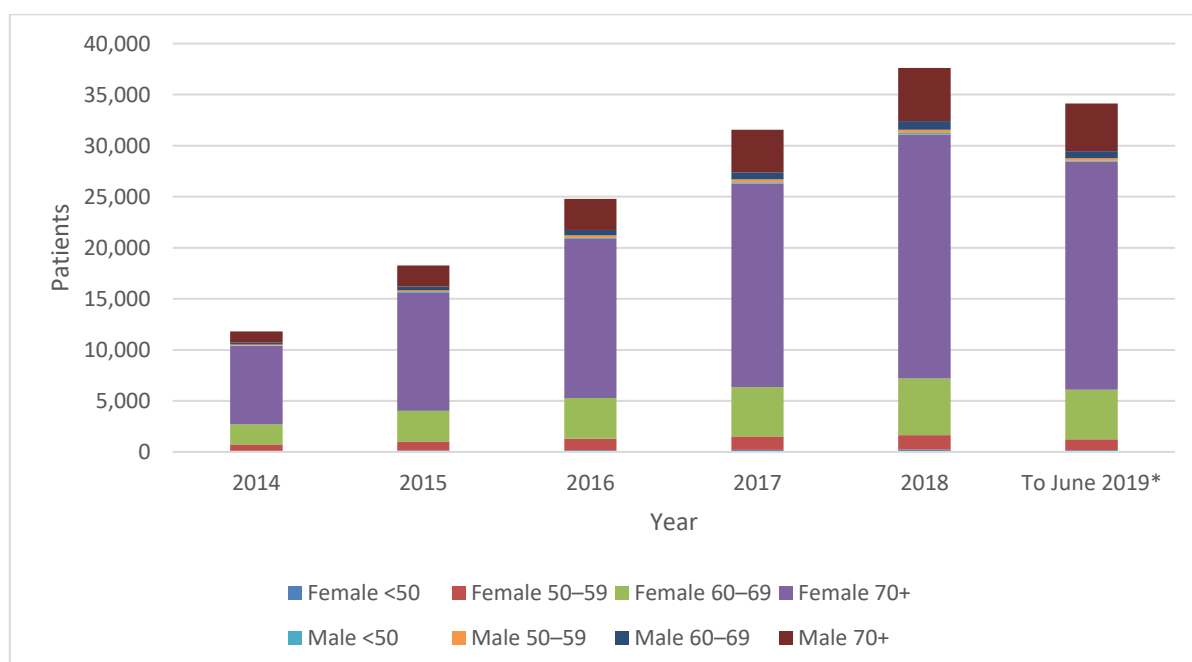


Figure 1: Number of prevalent patients dispensed denosumab at least once between January 2014 and June 2019, by age-sex groups

*Six months of data only

Table 10: Annual count of prevalent denosumab patients overall, by age, sex and age-sex groups (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019*
Total	11,790	18,273	24,778	31,574	37,617	34,123
Age group (10 years)						
<50	144	208	273	331	391	278
50–59	720	1,033	1,379	1,601	1,701	1,290
60–69	2,196	3,394	4,486	5,509	6,412	5,533
70+	8,730	13,638	18,640	24,133	29,113	27,022
Sex						
Female	10,377	15,581	20,878	26,297	31,090	28,433
Male	1,413	2,692	3,900	5,277	6,527	5,690
Sex/age group						
Female <50	101	137	180	203	246	178
Female 50–59	616	858	1,129	1,320	1,385	1,056
Female 60–69	1,999	3,021	3,966	4,810	5,564	4,851
Female 70+	7,661	11,565	15,603	19,964	23,895	22,348
Male <50	43	71	93	128	145	100
Male 50–59	104	175	250	281	316	234
Male 60–69	197	373	520	699	848	682
Male 70+	1,069	2,073	3,037	4,169	5,218	4,674

*Six months of data only

Incident denosumab patients***Denosumab initiators (regardless of whether they had previously been dispensed another osteoporosis medicine)***

The number of patients newly started on denosumab, regardless of whether they had previously used a different osteoporosis medicine, increased from 2014, before stabilising in 2017 and 2018. In 2018, there were an estimated 9,391 patients from the 10% PBS sample who were denosumab initiators – a 40% increase from the number of denosumab initiators in 2014. The number of female denosumab initiators increased by 40% between 2014 and 2018 and the number of male denosumab initiators increased by 60%. Once again, women aged 70+ years were the largest group of patients newly started on denosumab (Figure 2, Table 11).

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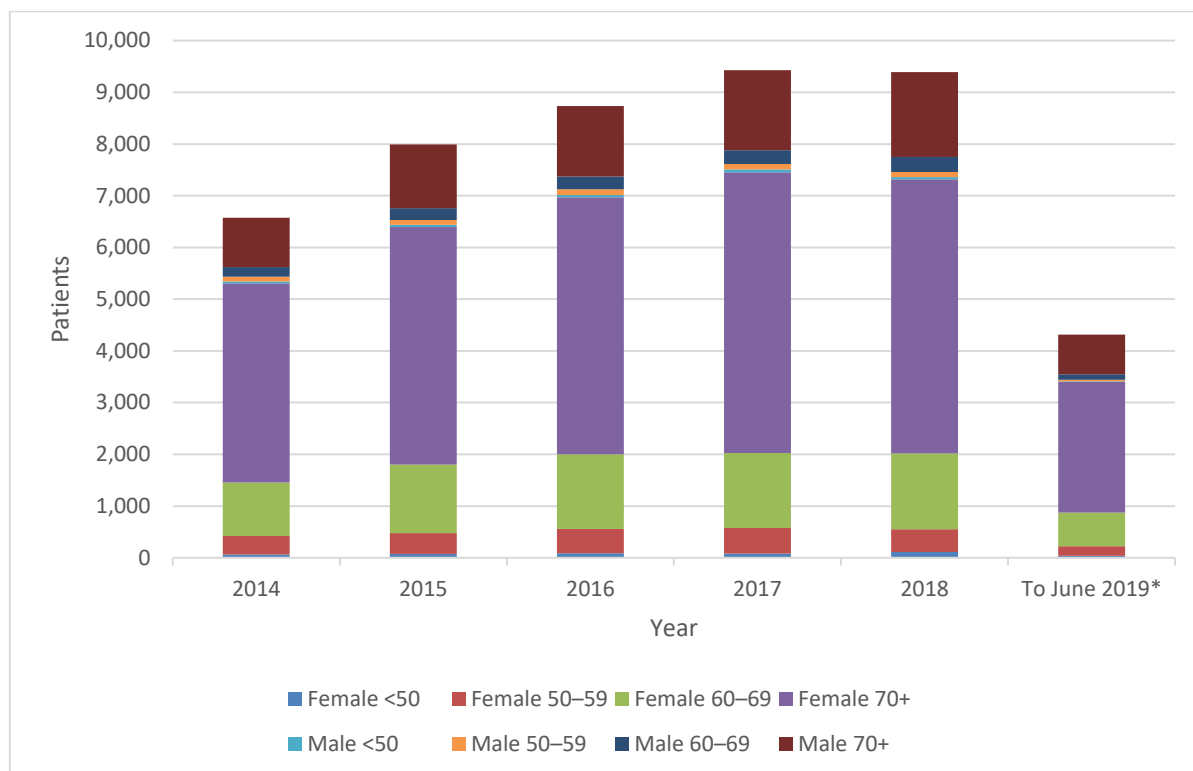


Figure 2: Number of patients newly dispensed denosumab (denosumab initiators) between January 2014 and June 2019 regardless of whether they had previously been dispensed another osteoporosis medicine, by age-sex groups

*Six months of data only

Table 11: Annual count of denosumab initiators overall, by age, sex and age-sex groups (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019*
Total	6,575	7,994	8,733	9,429	9,391	4,315
Age group (10 years)						
<50	103	116	130	143	155	54
50-59	448	496	586	594	544	214
60-69	1,218	1,556	1,686	1,717	1,753	751
70+	4,806	5,826	6,331	6,975	6,939	3,296
Sex						
Female	5,304	6,395	6,969	7,451	7,315	3,400
Male	1,271	1,599	1,764	1,978	2,076	915
Sex/age group						
Female <50	64	73	86	82	109	40
Female 50-59	355	404	473	493	445	186

	2014	2015	2016	2017	2018	To June 2019*
Female 60–69	1,035	1,327	1,439	1,447	1,462	648
Female 70+	3,850	4,591	4,971	5,429	5,299	2,526
Male <50	39	43	44	61	46	14
Male 50–59	93	92	113	101	99	28
Male 60–69	183	229	247	270	291	103
Male 70+	956	1,235	1,360	1,546	1,640	770

*Six months of data only

Directly initiated on denosumab (with no record of being prescribed any osteoporosis medicine prior)

Figure 3 and Table 12 show the number of patients who have been started directly on denosumab between January 2014 and June 2019, without any record of having been dispensed any osteoporosis medicine in at least the two years prior to starting denosumab or further if records were available. The number of patients directly initiated on denosumab has increased steadily since 2014. In 2018, there were an estimated 7,187 patients from the 10% PBS sample who were directly initiated on denosumab – double the number of patients directly started on denosumab in 2014. The scale of the increase was similar for both males and females. Once again, women aged 70+ years were the largest group of patients newly started on denosumab (Figure 3, Table 12).

In 2014, 45% of 6,575 patients initiating denosumab had previously used at least one other osteoporosis drug and 55% were directly initiated on denosumab. By 2018, only 24% of 9,391 patients initiating denosumab had previously used at least one other osteoporosis drug and 76% were directly initiated on denosumab.

Whereas the 2016 DUSC report on osteoporosis therapies found that in 2015, 57% of patients initiating denosumab had previously used at least one other osteoporosis drug, this study found that in 2015, 38% of 7,994 patients initiating denosumab had previously used at least one other osteoporosis drug. One explanation for the discrepancy between these findings is the different data sources used, with this study based on a random 10% PBS sample which might differ from the full PBS dataset. Another explanation is the amount of prior history available for patients; whereas the 2016 DUSC report analysed prescription records from January 2003, this study only analysed prescriptions from January 2012 and may have misclassified (and overestimated) patients as new to osteoporosis therapy if they had previously used other osteoporosis drugs prior to 2012.

In this PBS 10% sample study, between 2014 and 2017 the proportion of patients who were directly initiated on denosumab increased from 55% in 2014 to 76% in 2018. In the MedicineInsight study, among all patients who had been prescribed denosumab at least once between 2014 and 2017, 50% were directly initiated on denosumab. The lower proportion of patients directly initiated on denosumab in the MedicineInsight study

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compared with the PBS 10% study could indicate that specialists are more likely to start patients directly on denosumab than GPs.

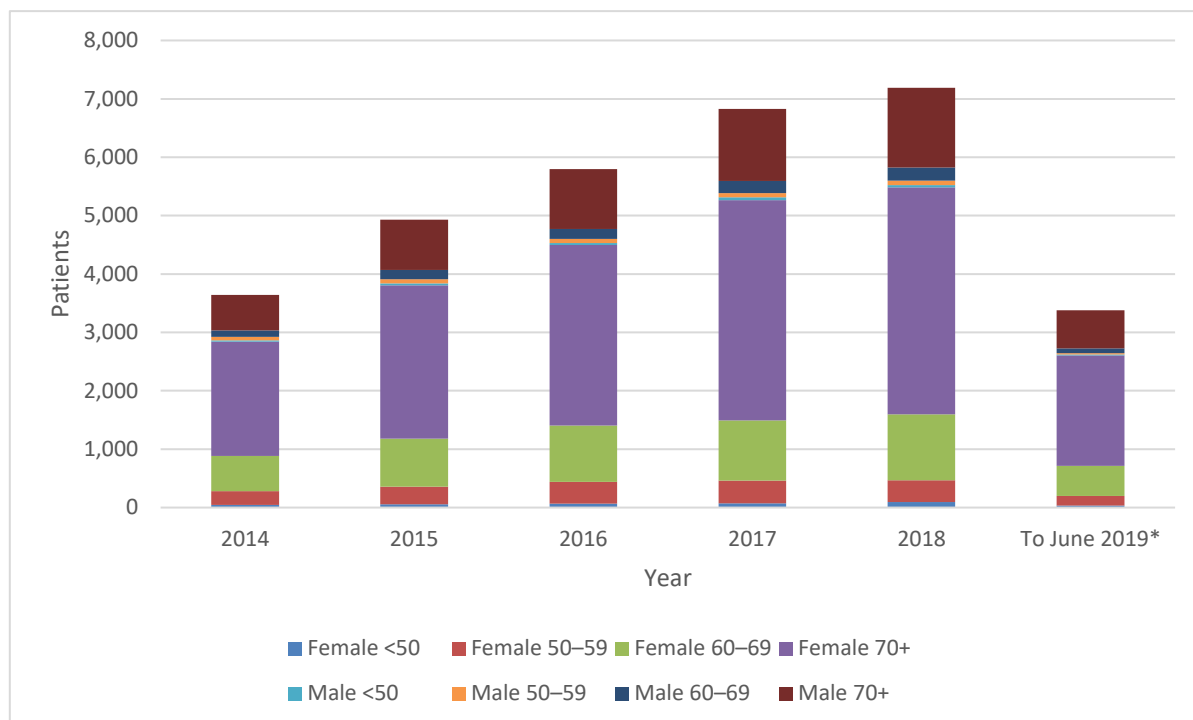


Figure 3: Number of patients directly initiated on denosumab (incident patients with no record of being prescribed any osteoporosis medicine prior) between January 2014 and June 2019, by age-sex groups

*Six months of data only

Table 12: Annual count of patients directly initiated on denosumab overall, by age, sex and age-sex groups (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019*
Total	3,641	4,932	5,797	6,827	7,187	3,381
Age group (10 years)						
<50	67	87	99	120	133	46
50-59	298	373	447	463	451	187
60-69	711	979	1,136	1,239	1,351	598
70+	2,565	3,493	4,115	5,005	5,252	2,550
Sex						
Female	2,842	3,808	4,497	5,266	5,484	2,608
Male	799	1,124	1,300	1,561	1,703	773
Sex/age group						
Female <50	46	57	67	72	96	34
Female 50-59	236	303	372	390	372	165

	2014	2015	2016	2017	2018	To June 2019*
Female 60–69	603	819	966	1,032	1,128	514
Female 70+	1,957	2,629	3,092	3,772	3,888	1,895
Male <50	21	30	32	48	37	12
Male 50–59	62	70	75	73	79	22
Male 60–69	108	160	170	207	223	84
Male 70+	608	864	1,023	1,233	1,364	655

*Six months of data only

Prevalent versus incident denosumab use

Figure 4 shows the total number of people treated with denosumab each year (prevalent) and the number who are new to denosumab therapy (denosumab initiators) and new to osteoporosis therapy (directly initiated on denosumab) between January 2014 and June 2019. While the number of all patients newly started on denosumab each year has somewhat stabilised year on year, the proportion of patients who are started on denosumab despite not having used any osteoporosis medicine in the prior two years is still increasing. This suggests that denosumab is being used more and more frequently as a first-line therapy for osteoporosis.

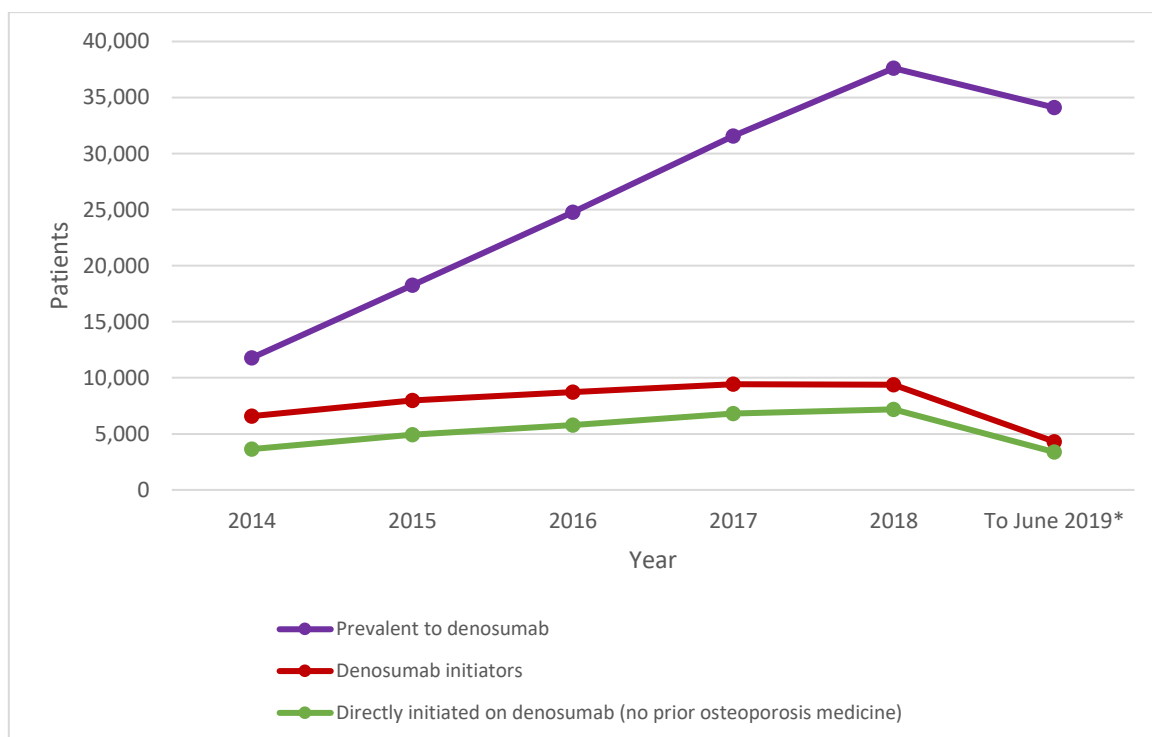


Figure 4: Number of patients newly dispensed denosumab (incident patients) between January 2014 and June 2019 regardless of whether they had previously been dispensed another osteoporosis medicine, by age-sex groups

*Six months of data only

Denosumab treatment rates

Age-standardised treatment rates

The rate at which patients are newly started on denosumab has been stable since 2014, at between 2.8 to 3.8 patients initiating per 1,000 population (Table 13, Figure 5). Consequently, as would be expected with a medicine used for a chronic condition, the prevalence rate has been increasing year on year as more and more patients are started on treatment. Figure 5 shows raw prevalent treatment rates increased between 2014 and 2018 from 5 to 15 patients prevalent to denosumab per 1,000 patients, representing a 3-fold increase over 5 years. After adjusting for the change in the age distribution of the population over the 5 years the increase in the prevalent prescribing rate remained high (2.8-fold increase).

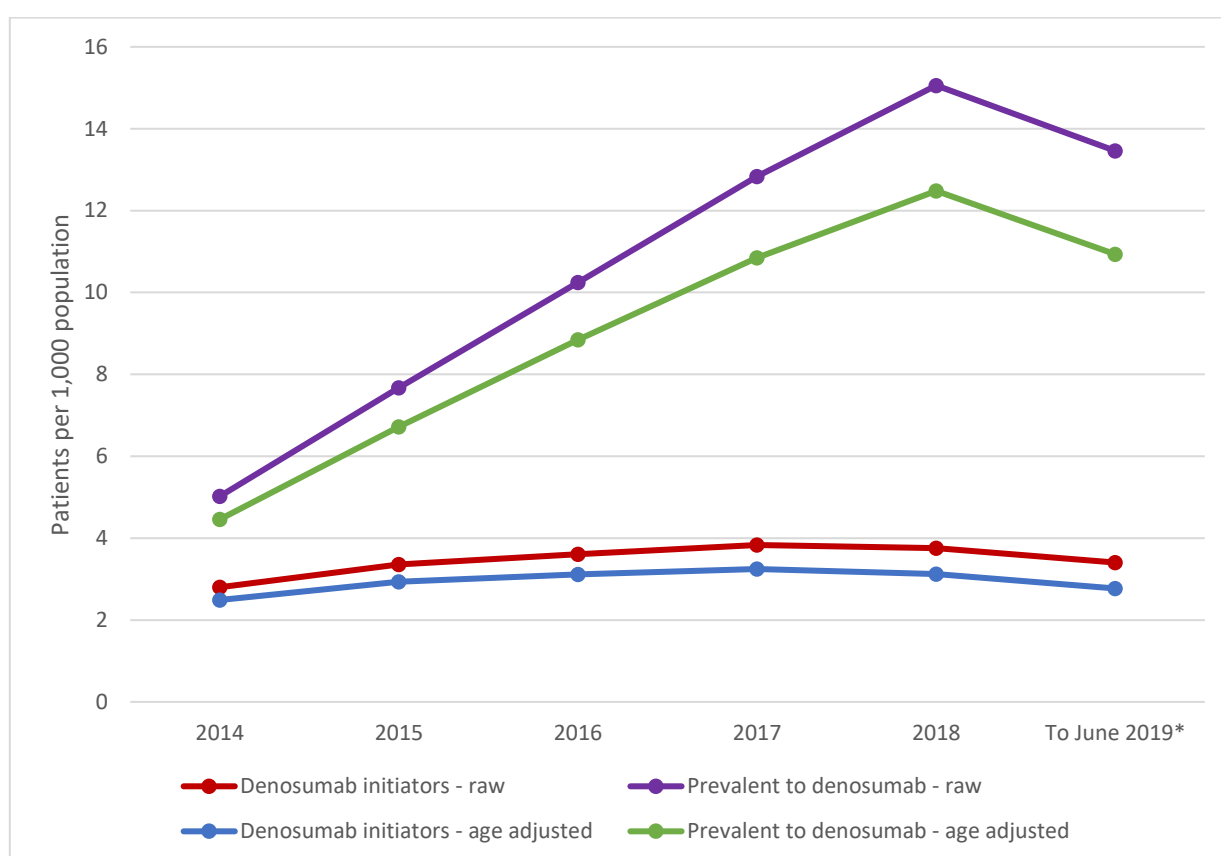


Figure 5: Patients initiating and prevalent to denosumab treatment rates (per 1000 population), raw and age adjusted, PBS 10% sample extrapolated to the whole population.

*Six months of data only; only incident results were extrapolated to the whole year.

Table 13: Crude annual rate of incident to denosumab patients (denosumab initiators) and prevalent denosumab patients per 1000 persons* (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019†
Incident	2.80	3.36	3.61	3.83	3.76	3.40
Prevalent	5.02	7.67	10.24	12.83	15.06	13.46

*Number of patients on denosumab (multiplied by 10) divided by the ABS Estimated Residential Population (ERP) population in the specified year (as at 30 June)

†Six months of data only

Table 14: Age-standardised annual rate of incident to denosumab patients (denosumab initiators) and prevalent denosumab patients per 1000 persons* (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019†
Incident	2.49	2.94	3.12	3.25	3.12	2.77
Prevalent	4.46	6.72	8.84	10.85	12.48	10.93

*Number of patients on denosumab (multiplied by 10) divided by the ABS Estimated Residential Population (ERP) population in the specified year (as at 30 June) age-adjusted to the ABS ERP 2001 reference population using direct standardisation

†Six months of data only; incident results were extrapolated to the whole of 2019 by multiplying by 2.

Prevalence to osteoporosis medicines

Figure 6 shows the number of people treated with each osteoporosis medicine class annually. A patient may be counted in more than one medicine class in a calendar year if they switched treatment or were co administered two medicines.

Figure 6 shows that the number of people treated with any osteoporosis medicine has increased substantially, by 50%, between 2014 and 2018. Additionally, the most commonly administered osteoporosis medicines have changed. In 2014 the most common class was bisphosphonates (alone or in combination with calcium and/or colecalciferol), prescribed to 46.5% of all patients on osteoporosis medicines, followed by denosumab (36.5%). By 2018, denosumab was by far the most common class of medicine, prescribed to 76.1% of all patients on osteoporosis medicines, with bisphosphonates only prescribed to 18.6% of those on osteoporosis medicines.

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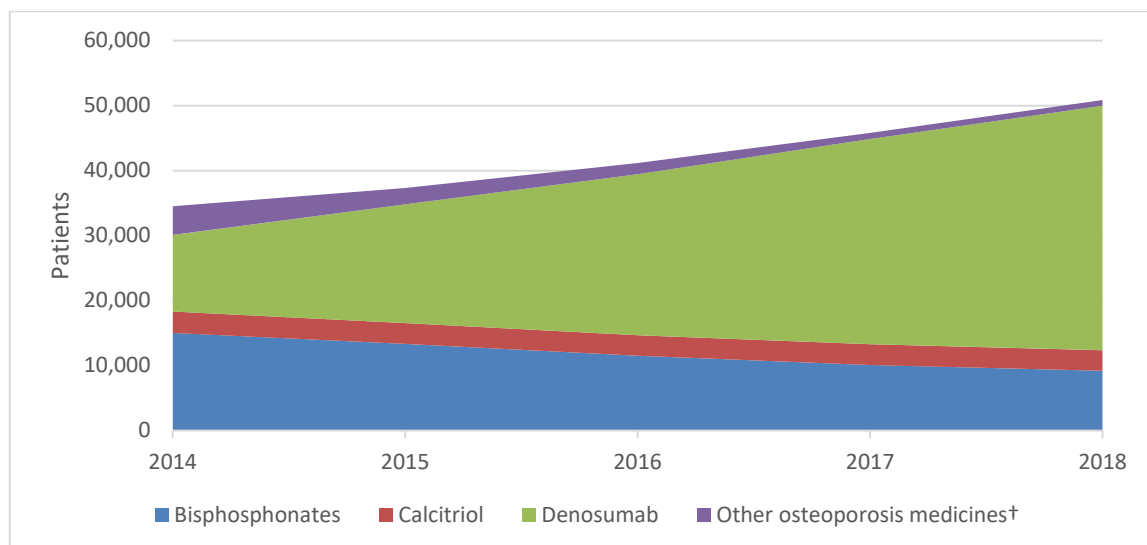


Figure 6: Patients prevalent to osteoporosis therapy by class of medicine

Table 15: Annual count of prevalent patients using osteoporosis medicines by type of treatment and age (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019*
Total	32,277	35,547	39,379	44,307	49,451	44,241
Age group (10 years)						
<50	1,062	1,104	1,127	1,183	1,194	889
50–59	2,497	2,567	2,776	2,852	2,959	2,261
60–69	6,854	7,423	7,982	8,618	9,304	7,842
70+	24,104	26,252	29,264	33,164	37,402	33,873
By group of therapy						
Denosumab	11,790	18,273	24,778	31,574	37,617	34,123
Bisphosphonates	15,031	13,360	11,510	10,088	9,200	7,436
Other osteoporosis medicines†	4,411	2,556	1,690	969	874	707
Calcitriol	3,285	3,157	3,171	3,186	3,168	2,599
<50 years						
Alendronate (incl combination products)	144	122	114	109	86	79
Calcitriol	568	554	565	571	557	425
Denosumab	144	208	273	331	391	278
Raloxifene	<15	<15	<10	5	<10	<5
Risedronate (incl combination products)	94	107	98	104	88	63
Strontium ranelate (delisted August 2016)	32	12	6	-	-	-
Teriparatide	<5	<5	<5	-	<5	-

	2014	2015	2016	2017	2018	To June 2019*
Zoledronic acid	64	84	64	63	63	41
Alendronate (incl combination products)	144	122	114	109	86	79
50–59 year old						
Alendronate (incl combination products)	479	455	428	387	331	264
Calcitriol	459	455	465	438	474	391
Denosumab	720	1,033	1,379	1,601	1,701	1,290
Raloxifene	80	63	59	47	48	40
Risedronate (incl combination products)	300	265	248	240	257	202
Strontium ranelate (delisted August 2016)	190	80	26	-	-	-
Teriparatide	6	8	10	9	7	6
Zoledronic acid	263	208	161	130	141	68
60–69 year old						
Alendronate (incl combination products)	1,503	1,411	1,237	1,108	953	828
Calcitriol	715	679	679	689	662	574
Denosumab	2,196	3,394	4,486	5,509	6,412	5,533
Raloxifene	296	265	219	178	147	123
Risedronate (incl combination products)	901	870	837	734	739	581
Strontium ranelate (delisted August 2016)	654	289	137	-	-	-
Teriparatide	24	32	33	43	39	30
Zoledronic acid	565	483	354	357	352	173
70+ year old						
Alendronate (incl combination products)	6,218	5,357	4,561	3,855	3,327	3,068
Calcitriol	1,543	1,469	1,462	1,488	1,475	1,209
Denosumab	8,730	13,638	18,640	24,133	29,113	27,022
Raloxifene	961	836	715	607	515	427
Risedronate (incl combination products)	3,013	2,822	2,517	2,219	2,188	1,739
Strontium ranelate (delisted August 2016)	2,043	848	389	-	-	-
Teriparatide	109	106	89	80	109	78
Zoledronic acid	1,487	1,176	891	782	675	330

Age of prevalent patients using osteoporosis medicines

Figure 7 shows the number of people treated with any osteoporosis medicine annually by age group. Most of the increase in people treated with any osteoporosis medicine per year

can be attributed to growth in prescribing among patients aged 70+ years. From 2014 to 2018 the number of prevalent patients using osteoporosis medicines aged 70+ years increased by 55%, whereas the number of prevalent patients aged 60–69 years increased by 30% and those aged 50–59 years by only 20% (Figure 7, Table 15).

Figure 8 illustrates the annual count of patients on at least one osteoporosis medicine (prevalent patients) by type of therapy and age group. While trends are similar across the age groups the number of patients on all therapies, and denosumab in particular, has plateaued since 2016 for patients aged 50–59 years but increased year on year for those aged 60–69 and 70+ years. For those aged 60–69 and 70+ years, alendronate and risedronate (including their combination products) are the next most common therapies dispensed, with decreasing use year on year. For patients aged 50–59 years alendronate and calcitriol are the next most common therapies. In patients <50 years calcitriol has remained stable as the most common therapy over the years, followed by denosumab which has increased steadily.

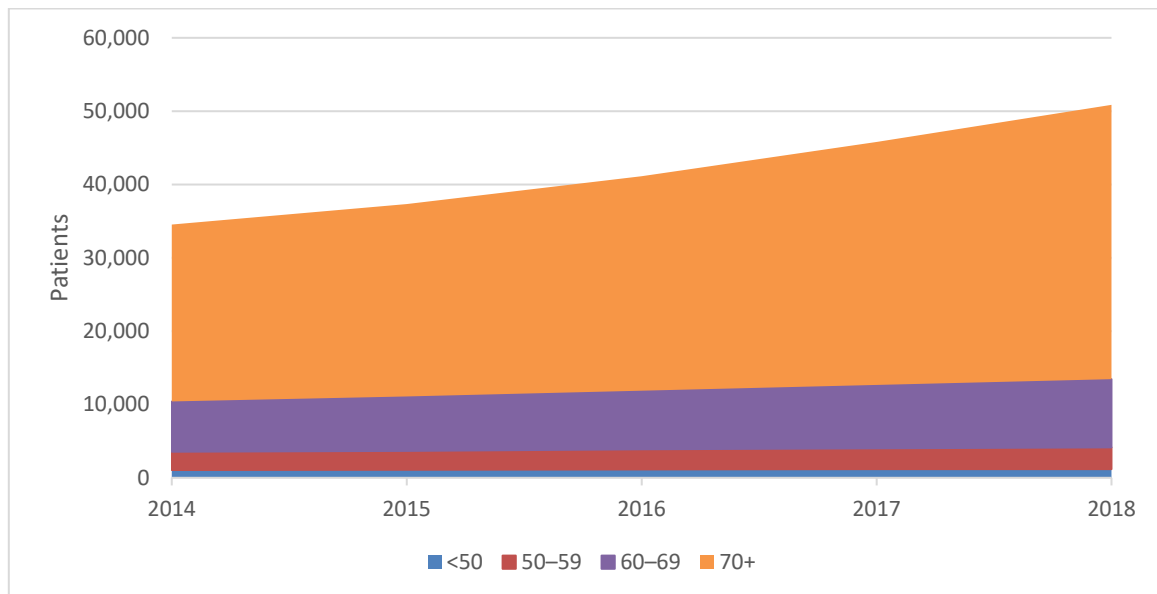


Figure 7: Patients prevalent to any osteoporosis therapy by age group

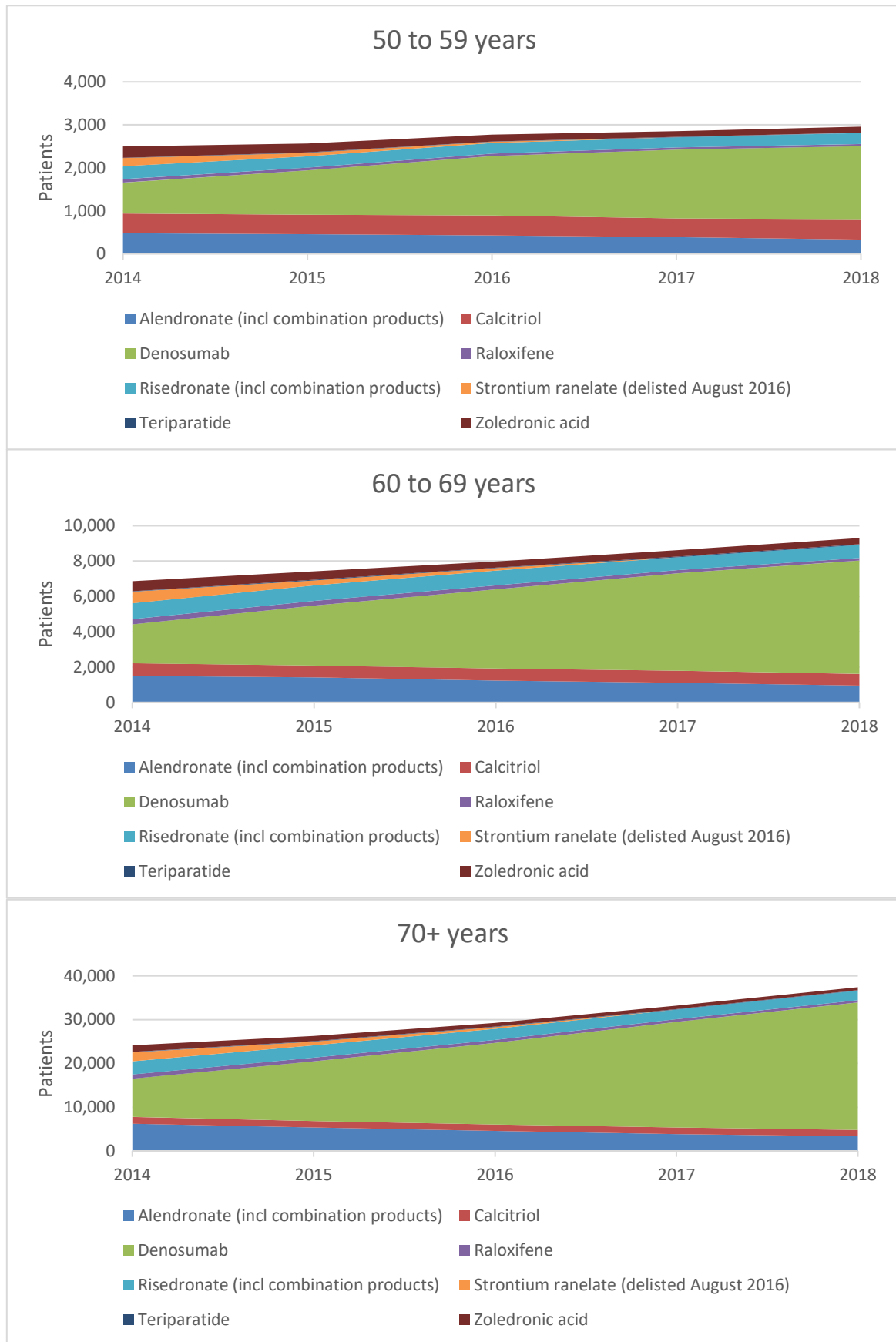


Figure 8: Patients prevalent to osteoporosis therapy by medicine type and age group

Initiation to osteoporosis medicines

Table 16 presents the number of patients in each year who had started an osteoporosis medicine but had not been supplied a prescription for any osteoporosis medicine in at least the prior two years (or longer if history is available). Results are presented by medicine and class. Very few patients were co-dispensed two medicines as initiating therapy (<5 each year) so this information was not presented, however these patients were counted in more than one medicine/class in a calendar year.

Figure 9 shows that denosumab was the most frequently prescribed medicine for patients initiating osteoporosis therapy every year from 2014 to 2019, followed by bisphosphonates (including in combination with calcium and/or colecalciferol). Denosumab use increased steadily year upon year whereas initiation to therapy with bisphosphonates decreased between 2014 and 2017 before plateauing in 2018 (Figure 9). Initiations to denosumab have driven an increase in the overall number of patients initiating osteoporosis therapy from 7,202 patients initiating in 2014 to 9,514 patients in 2018, representing a 32% increase (PBS 10% sample) (Table 16).

Initiation to therapy with calcitriol has been low but stable across the years (Figure 10). Strontium initiations decreased, following a change in the registered indication and PBS restriction in 2014 to specify use in patients with severe established osteoporosis with intolerance or contraindications to other treatments (Table 16). Strontium was delisted in August 2016, due to safety concerns around the risk of cardiovascular events and venous thrombosis.

Initiation to therapy with zoledronic acid has been low and declining between 2014 and 2017 before plateauing in 2018. Raloxifene is infrequently prescribed. Teriparatide, is rarely the first PBS prescribed medicine, restricted to patients at very high risk who have had multiple prior fractures including at least one which occurred after at least 12 months of continuous therapy with an anti-resorptive agent. It is possible that the small number of patients on teriparatide had been dispensed osteoporosis medicines prior to 2012 and have been misclassified as directly initiating in this study, or there could be some potentially inappropriate use (Table 16, Figure 10).

Table 16: Annual count of patients directly initiating osteoporosis medicines overall, by type of treatment (2014 to June 2019)

	2014	2015	2016	2017	2018	To June 2019*
Total	7,202	8,113	8,380	9,139	9,514	4,863
By active ingredient						
Alendronate (incl combination products)	1,267	1,248	984	876	735	726
Calcitriol	591	568	545	553	543	274
Denosumab	3,641	4,932	5,797	6,827	7,187	3,381
Raloxifene	79	73	53	36	40	23
Risedronate (incl combination products)	735	763	651	564	698	292
Strontium ranelate (delisted August 2016)	251	44	14	-	-	-

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	2014	2015	2016	2017	2018	To June 2019*
Teriparatide	11	16	7	8	9	-
Zoledronic acid	630	474	338	282	304	168
By class of medicine						
Denosumab	3,641	4,932	5,797	6,827	7,187	3,381
Bisphosphonates	2,632	2,485	1,973	1,722	1,737	1,186
Other osteoporosis medicines†	341	133	74	44	49	23
Calcitriol	591	568	545	553	543	274

*Six months of data only

†Includes raloxifene, strontium ranelate and teriparatide

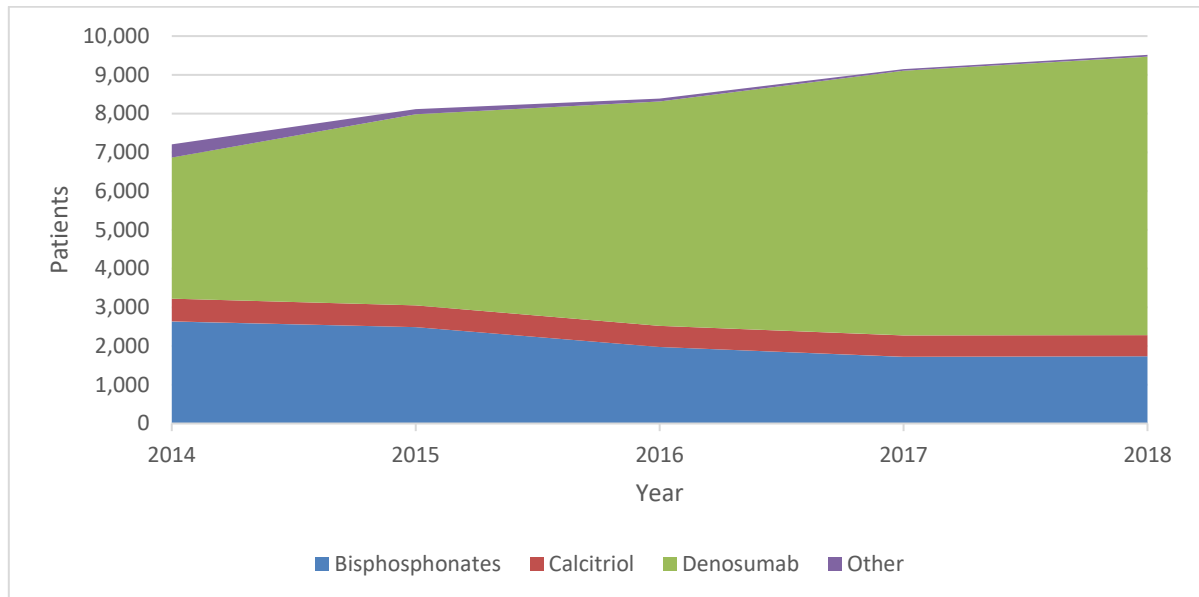


Figure 9: Patients initiating osteoporosis therapy by class of medicine at initiation

*Other medicines include raloxifene, strontium ranelate and teriparatide

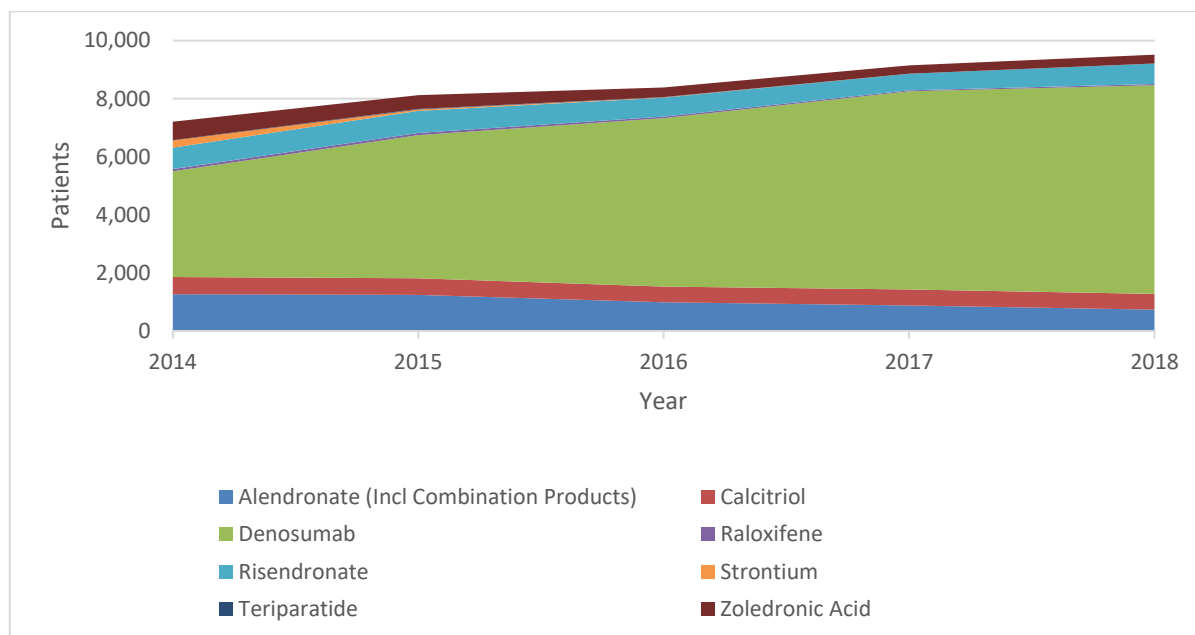


Figure 10: Patients initiating osteoporosis therapy by type of medicine at initiation

Treatment duration

Table 17 presents the average treatment duration on a patient’s initiating therapy, including breaks, for patients who initiated an osteoporosis medicine between 2014 and 2017, noting that some patients only had 18 months of follow-up available and others up to 5.5 years. A sensitivity analysis limited the population to only those who initiated therapy between 2014 and 2015, allowing a longer follow-up period to be assessed before the end of the study time period. Table 18 presents the average treatment duration on a patient’s initiating therapy, excluding breaks, for patients who initiated an osteoporosis medicine between 2014 and 2017. The same sensitivity analysis was applied to Table 16.

The median average duration on any initiating osteoporosis medicine was 769 days or 2.1 years, including breaks (Table 17) and 665 days or 1.8 years excluding treatment breaks (Table 18). This figure was largely attributable to, by far the most initiated therapy, denosumab. The longest duration of therapy was seen for patients who initiate denosumab, with a median average of 2.5 years with breaks or 2.2 years excluding breaks. Patients who initiated zoledronic acid had a median average duration of therapy of 1.0 years. The 6 monthly and 12 monthly administration of denosumab and zoledronic acid, respectively, along with their good tolerability profile might explain their favourable duration on therapy profiles. Alendronate and risedronate had similar treatment durations, at 1.1 years including treatment breaks and 0.7 years excluding breaks.

In the sensitivity analysis, the subset of patients with at least 3.5 years of follow-up available, showed even longer durations of therapy for denosumab, with a median average treatment duration, including breaks, of 3.9 years. This was not the case for zoledronic acid whose results were similar (1 year). Alendronate and risedronate durations increased by around a month in the sensitivity analysis.

In the MedicineInsight study the median duration of denosumab treatment (including treatment breaks) was approximately 7.9 months longer than the PBS study estimated, at 3.2 years. This was despite the limitation that MedicineInsight might underestimate treatment duration for therapies that are initiated by specialists. There are several potential explanations for the differing results between the two studies, including:

- the difference in available follow-up time, with patients in the PBS study having at least 18 months of follow-up compared with at least 2 years in the MedicineInsight study.
- a difference between prescribed versus dispensing information. Patients prescribed a medicine may or may not have the medicine dispensed by a pharmacist. If the script is not dispensed, MedicineInsight data will overestimate the duration of treatment compared with PBS data.
- if denosumab therapy was initiated by specialists but only used once and not continued by the GP, the PBS data will pick this up, drawing the PBS average down.

Interestingly, in the subset of PBS patients with at least 3.5 years of follow-up available in the sensitivity analysis, the median average treatment duration, including breaks, was longer at 3.9 years.

Table 17: Average treatment duration in days (including treatment breaks) for patients initiating osteoporosis medicines between 2014 and 2017, by type of treatment

	Initiators between 2014 and 2017				Sensitivity analysis Initiators between 2014 and 2015			
	Mean	Mode	Median	N	Mean	Mode	Median	N
Total	815.8	180	769	32,834	993.5	180	1197	15,315
Alendronate (incl combination products)	563.8	28	392	4,375	651.7	28	421	2,515
Calcitriol	590	50	421	2,257	723.2	50	511	1,159
Denosumab	946	180	915	21,197	1254.4	180	1416	8,573
Raloxifene	589.2	28	393	241	648.6	28	452	152
Risedronate (incl combination products)	550.3	28	387	2,713	643.7	28	430	1,498
Strontium ranelate (delisted August 2016)	196.7	28	84	309	202.3	28	85	295
Teriparatide	398.9	28	508	42	364.9	28	506	27
Zoledronic acid	713.6	365	365	1,724	774.2	365	365	1,104

Table 18: Average treatment duration in days (excluding treatment breaks) for patients initiating osteoporosis medicines between 2014 and 2017, by type of treatment

	Initiators between 2014 and 2017				Sensitivity analysis Initiators between 2014 and 2015			
	Mean	Mode	Median	N	Mean	Mode	Median	N
Total	716.3	180	665	32,834	856.5	180	843	15,315
Alendronate (incl combination products)	459.0	28	255	4,375	527.3	28	281	2,515
Calcitriol	360.2	50	225	2,257	432.6	50	272	1,159
Denosumab	858.3	180	803	21,197	1121.4	180	1286	8,573
Raloxifene	492.4	28	248	241	542	28	285.5	152
Risedronate (incl combination products)	448.6	28	253	2,713	521.2	28	280	1,498
Strontium ranelate (delisted August 2016)	150.8	28	68	309	154.5	28	69	295
Teriparatide	361.2	28	480.5	42	324.9	28	477	27
Zoledronic acid	645.8	365	365	1,724	689.1	365	365	1,104

Time to first treatment break

Table 19 presents the median time to first treatment break for patients who initiated therapy between 1 January 2014 and 31 December 2017, and who experienced a treatment break, by type of treatment. Of the 11,219 patients who experienced a treatment break from their initiating therapy, patients on zoledronic acid and denosumab had the longest median time to first treatment break, at approximately 1 year, reflecting one supply of zoledronic acid and two supplies of denosumab (Table 19). The median time to first treatment break was approximately 5 months for alendronate and risedronate, just over 6 months for teriparatide, 4 months for raloxifene, and 3 months for calcitriol. The sensitivity analysis, the subset of patients with at least 3.5 years of follow-up available, showed a slightly longer median time to first treatment break for all medicines (Table 20). However, for teriparatide the median time to first treatment break more than doubled in the sensitivity analysis, however these findings should be interpreted with caution due to the small number of patients (n=5) on teriparatide (Table 20).

Table 19 also presents the average (mean and median) duration of the first treatment break by type of therapy. The mean average duration of the first treatment break was highest for patients initiating on zoledronic acid (268 days), followed by alendronate (220 days), denosumab (200 days) and calcitriol and raloxifene (both 190 days). The shortest treatment break was experienced by patients initiating on teriparatide (125 days). In the sensitivity analysis, the subset of patients with at least 3.5 years of follow-up available, showed slightly longer duration of first treatment breaks for all medicines (Table 20).

Table 19: Time to first treatment break and duration of break for patients initiating osteoporosis medicines between 2014 and 2017, by type of treatment

	Time to first treatment break (days)	Duration of first treatment break (days)				N
	Median	Mean	Median	Q1	Q3	
Alendronate (incl combination products)	147	220.3	124	82	237	1,345
Calcitriol	87	190.5	126	78	210	1,207
Denosumab	357	200.4	142	86	218	7,303
Raloxifene	127.5	189.7	123	84	195.5	72
Risedronate (incl combination products)	147	208	127	81	243	849
Strontium ranelate (delisted August 2016)	80	153	115	77	198	59
Teriparatide	190	125.4	117	93	123	9
Zoledronic acid	365	268.6	170	94	368	383
Total	207	204.1	137	85	223	11,219

Table 20: Time to first treatment break and duration of break for patients initiating osteoporosis medicines between 2014 and 2015, by type of treatment (sensitivity analysis)

	Time to first treatment break (days)	Duration of first treatment break (days)				N
	Median	Mean	Mode	Q1	Q3	
Alendronate (incl combination products)	165	228.6	120	81	235	826
Calcitriol	97	205.3	126	79	216	657
Denosumab	374	222.3	149	87	236	3,736
Raloxifene	122	200.5	112	84	212	47
Risedronate (incl combination products)	150	221.9	127	84	265	497
Strontium ranelate (delisted August 2016)	81	154.3	115	78	198	58
Teriparatide	356	146.6	120	117	153	5
Zoledronic acid	365	301.1	204.5	97.5	392.5	268
Total	309.5	223.7	140	85	241	6,092

Treatment breaks while on denosumab

For 32,731 patients who initiated therapy with denosumab (regardless of whether they had been dispensed a different osteoporosis medicine beforehand) between 1 January 2014 and 31 December 2017, 11,533 (35.2%) experienced a treatment break¹⁴. Of the denosumab initiators who experienced a treatment break, only 2.5% were covered by another prescription for osteoporosis therapy during that treatment break (Table 21). In the sensitivity analysis, the subset of patients with at least 3.5 years of follow-up available, patients were slightly more likely to be prescribed another medicine while on a treatment break from denosumab (Table 21).

Table 21: Evidence of alternative treatment during breaks in denosumab treatment for patients who initiated denosumab between 2014 and 2017, or between 2014 and 2015 (sensitivity analysis)

	Pts who initiated denosumab	Pts who had a treatment break	Pts who had another treatment during treatment break	
	N	N1 (% N1/N)	Yes	No
2014–2017	32,731	11,533 (35.2%)	289 (2.5%)	11,244 (97.5%)
2014–2015	14,569	6,347 (43.6%)	192 (3.0%)	6,155 (97.0%)

Treatment cessation

For 21,197 patients who were directly initiated on denosumab, without being dispensed any other osteoporosis medicine, between 1 January 2014 and 31 December 2017, 7,157 (33.8%) ceased therapy. Of the patients directly initiated on denosumab who ceased therapy, only 5.0% had another treatment after cessation (Table 22). In the sensitivity analysis, the results for denosumab were not significantly different among the subset of patients with at least 3.5 years of follow-up available (Table 23).

Patients who were directly initiated on bisphosphonates and other osteoporosis medicines were much more likely to cease therapy than patients initiated on denosumab and were also much more likely to start treatment with an alternative osteoporosis medicine after ceasing their original medicine. Around three quarters of patients who first started osteoporosis therapy on alendronate, risedronate, zoledronic acid or raloxifene, ceased their initiating therapy during the time period assessed and around a third to two fifths of those that ceased had an alternative therapy after cessation (Table 22). Presumably, the majority of these patients were switched to denosumab which was dispensed to three quarters of all patients on an osteoporosis medicine in 2018.

¹⁴ Note that this group of patients includes all patients started on denosumab regardless of whether they had been dispensed another osteoporosis medicine prior to starting denosumab or not. This differs from the analyses provided in Table 19 and 20, in which the data on denosumab only applies to patients who were directly started on denosumab without being dispensed another osteoporosis medicine beforehand.

Table 22: Treatment cessation for patients who initiated osteoporosis medicines 2014 and 2017

	Pts who initiated osteoporosis medicines	Pts who ceased initiated treatment	Pts who had another treatment after cessation	
	N	N1 (% N1/N)	Yes	No
Alendronate (incl combination products)	4,375	3,326 (76.0%)	1,328 (39.9%)	1,998 (60.1%)
Calcitriol	2,257	1,720 (76.2%)	119 (6.9%)	1,601 (93.1%)
Denosumab	21,197	7,157 (33.8%)	355 (5.0%)	6,802 (95.0%)
Raloxifene	241	180 (74.7%)	74 (41.1%)	106 (58.9%)
Risedronate (incl combination products)	2,713	2,101 (77.4%)	834 (39.7%)	1,267 (60.3%)
Strontium ranelate (delisted August 2016)	309	309 (100.0%)	178 (57.6%)	131 (42.4%)
Teriparatide	42	42 (100.0%)	29 (69.0%)	13 (31.0%)
Zoledronic acid	1,724	1,350 (78.3%)	461 (34.1%)	889 (65.9%)
Total	32,858	16,185 (49.3%)	3,378 (20.8%)	12,807 (79.2%)

Table 23: Treatment cessation for patients who initiated osteoporosis medicines 2014 and 2015 (sensitivity analysis)

	Pts who initiated osteoporosis medicines	Pts who ceased initiating treatment	Pts who had another treatment after cessation	
	N	N1 (% N1/N)	Yes	No
Alendronate (incl combination products)	2,515	2,040 (81.1%)	844 (41.4%)	1,196 (58.6%)
Calcitriol	1,159	921 (79.5%)	74 (8.0%)	847 (92.0%)
Denosumab	8,573	3,329 (38.8%)	177 (5.3%)	3,152 (94.7%)
Raloxifene	152	125 (82.2%)	59 (47.2%)	66 (52.8%)
Risedronate (incl combination products)	1,498	1,227 (81.9%)	524 (42.7%)	703 (57.3%)
Strontium ranelate (delisted August 2016)	295	295 (100.0%)	172 (58.3%)	123 (41.7%)
Teriparatide	27	27 (100.0%)	21 (77.8%)	6 (22.2%)
Zoledronic acid	1,104	940 (85.1%)	346 (36.8%)	594 (63.2%)
Total	15,323	8,904 (58.1%)	1,907 (21.4%)	6,997 (78.6%)

MedicineInsight Data

Baseline population

There were 896,548 regularly attending patients from 445 practice sites¹⁵, comprising 506 active practices, who were eligible for inclusion in the regular patient prevalence study (study period January 2018 to December 2019).

There were 1,073,261 patients from 444 practice sites, comprising 505 active practices, who were eligible for inclusion in the historical osteoporosis study (had had least three clinical encounters during the study period January 2014 to December 2017).

Prevalence of osteoporosis in general practice patients

Among eligible regularly attending patients aged 50 years or older in the Jan 2018–Dec 2019 period (regular patient prevalence study), 13.6% had a record of osteoporosis at some point in their medical record (Table 24). This is similar to that reported by Naik-Panvelkar (12.4%).

As expected, the patient prevalence of osteoporosis was higher in women with an estimated prevalence ratio in general practice of 3.1:1 for people over 50 years (6.3% of men and 19.5% of women).

Patient prevalence of osteoporosis rose with increasing age in both sexes (Table 24; Figure 11). Just over a third of female patients aged 70+ years had a recorded diagnosis of osteoporosis compared with 13.2% of men of the same age.

Table 24: Patient prevalence of recorded osteoporosis in the Jan 2018–Dec 2019 (prevalence study population) and the Jan 2014–Dec 2017 (osteoporosis study population) by age and sex

	Regular patient prevalence study (3 visits between Jan 2018–Dec 2019)			Historical osteoporosis study (3 visits between Jan 2014–Dec 2017)		
	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)
Total	896,648	121,598	13.6 (13.0–14.1)	1,073,261	120,388	11.2 (10.7–11.7)
Age group (10 years)						
50–59	283,869	9,119	3.2 (3.0–3.4)	358,297	9,515	2.7 (2.5–2.8)
60–69	269,443	23,586	8.8 (8.3–9.2)	318,719	23,692	7.4 (7.1–7.8)
70+	343,336	88,893	25.9 (25.0–26.7)	396,245	87,181	22.0 (21.2–22.8)

¹⁵ The term practice site is used to describe one or more practices that share the same installation of the clinical information system (CIS). For example, one organisation may consist of a number of geographically diverse general practices who all share the same CIS, or a site may be a single GP practice.

	Regular patient prevalence study (3 visits between Jan 2018–Dec 2019)			Historical osteoporosis study (3 visits between Jan 2014–Dec 2017)		
	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)
Sex						
Female	492,759	96,255	19.5 (18.8–20.3)	590,008	96,229	16.3 (15.7–17.0)
Male	403,889	25,343	6.3 (5.9–6.6)	483,253	24,159	5.0 (4.7–5.3)
Sex/age group						
Female 50–59	158,865	7,597	4.8 (4.5–5.1)	199,306	7,910	4.0 (3.7–4.2)
Female 60–69	145,310	20,195	13.9 (13.2–14.6)	171,652	20,238	11.8 (11.2–12.4)
Female 70+	188,584	68,463	36.3 (35.3–37.3)	219,050	68,081	31.1 (30.1–32.1)
Male 50–59	125,004	1,522	1.2 (1.1–1.3)	158,991	1,605	1.0 (0.9–1.1)
Male 60–69	124,133	3,391	2.7 (2.6–2.9)	147,067	3,454	2.3 (2.2–2.5)
Male 70+	154,752	20,430	13.2 (12.5–13.9)	177,195	19,100	10.8 (10.1–11.4)

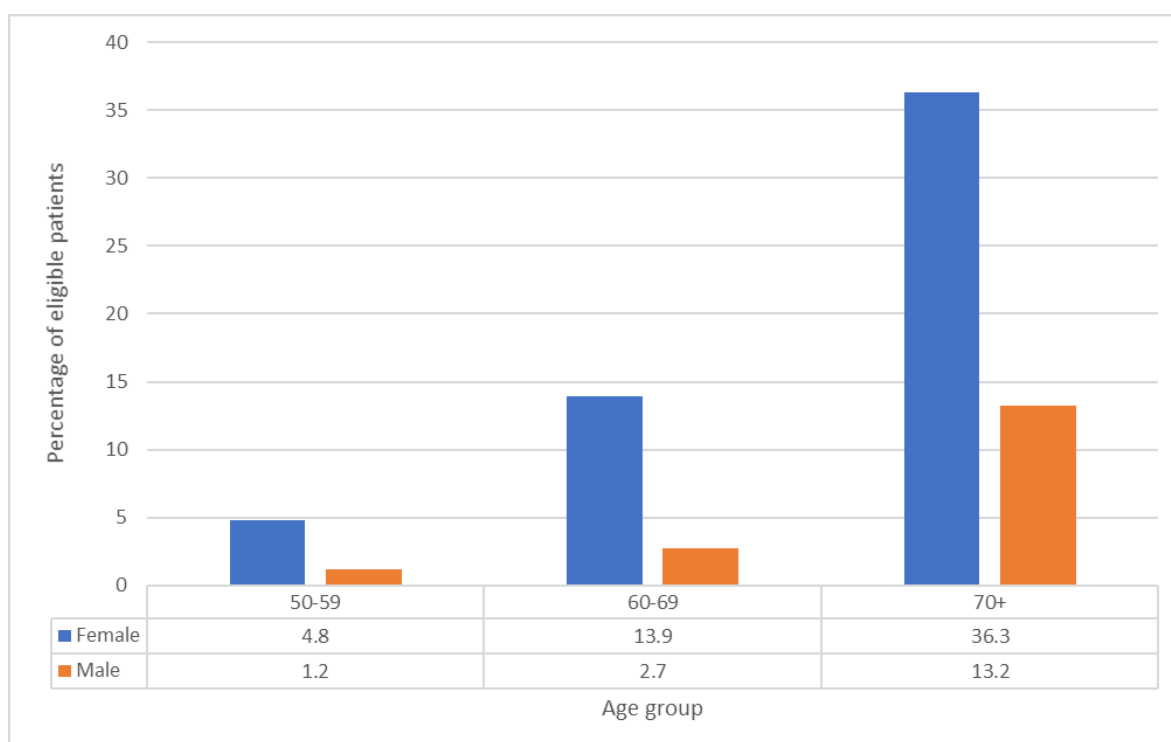


Figure 11: Proportion of eligible regularly attending patients between Jan 2018–Dec 2019 (prevalence study population) who have a recorded diagnosis of osteoporosis by age and sex

The patient prevalence of recorded osteoporosis among eligible patients aged 50 years or older in the Jan 2014–Dec 2017 period (historical osteoporosis study) was slightly lower than that reported in the prevalence study population for almost all groups, with the exception of men aged 50–59 (Table 8). This may be because:

- the historical osteoporosis study population includes patients who visit their general practice less frequently than the prevalence study. To be eligible for inclusion in the historical osteoporosis study, patients had to visit at least three times over the 4-year study period, rather than at least three times over the 2-year study period as in the prevalence study. Infrequent attending patients are more likely to be healthier than regularly attending patients; or
- GPs may be more likely to identify patients at risk, diagnose and record osteoporosis in recent years.

Comparisons with national population estimates of prevalence

The patient prevalence of osteoporosis among regular patients was compared to national population estimates published by the Australian Institute of Health and Welfare (AIHW) and taken from the ABS NHS. In order to allow direct comparison, the age categories for the regular patient prevalence study were amended to correspond with the age categories used by the AIHW and ABS (55–64, 65–74 and 75+ years).

Among MedicineInsight patients aged 55–64, the patient prevalence of osteoporosis in regularly attending patients is lower than the population prevalence estimates in both women and men (Table 25; Figure 12). Patient prevalence and population prevalence estimates are similar in women aged 65–69. However, in men aged 65–69 and in both women and men aged 75+ years, the patient prevalence of osteoporosis is higher than the population estimates.

Table 25: Patient prevalence of recorded osteoporosis among regular attendees between Jan 2018–Dec 2019 (prevalence study population) compared with Australian population prevalence

	Regular patient prevalence study (3 visits between Jan 2018–Dec 2019)			AIHW estimates of osteoporosis population prevalence
	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)	% (95% CI)
Age group (10 years)				
50–54	139,389	2,994	2.1 (2.0–2.3)	na
55–64	282,919	16,109	5.7 (5.4–6.0)	8.2 (7.3–9.2)
65–74	252,747	36,041	14.3 (13.7–14.8)	12.4 (10.9–13.9)
75+	221,593	66,454	30.0 (29.0–31.0)	20.5 (18.0–23.0)
Sex/age group				

	Regular patient prevalence study (3 visits between Jan 2018–Dec 2019)			AIHW estimates of osteoporosis population prevalence
	No. eligible patients	No. patients with record of osteoporosis	% (95% CI)	% (95% CI)
Female 50–54	78,928	2,414	3.1 (2.8–3.3)	na
Female 55–64	155,090	13,774	8.9 (8.4–9.4)	13.0 (11.4–14.6)
Female 65–74	134,181	29,406	21.9 (21.2–22.7)	21.1 (18.3–24.0)
Female 75+	124,560	50,661	40.7 (39.6–41.8)	29.2 (25.2–33.3)
Male 50–54	60,461	580	1.0 (0.9–1.1)	na
Male 55–64	127,829	2,335	1.8 (1.7–2.0)	3.2 (1.9–4.4)
Male 65–74	118,566	6,635	5.6 (5.3–5.9)	3.2 (2.3–4.2)
Male 75+	97,033	15,793	16.3 (15.4–17.2)	10.1 (7.3–12.8)

AIHW – Australian Institute of Health and Welfare

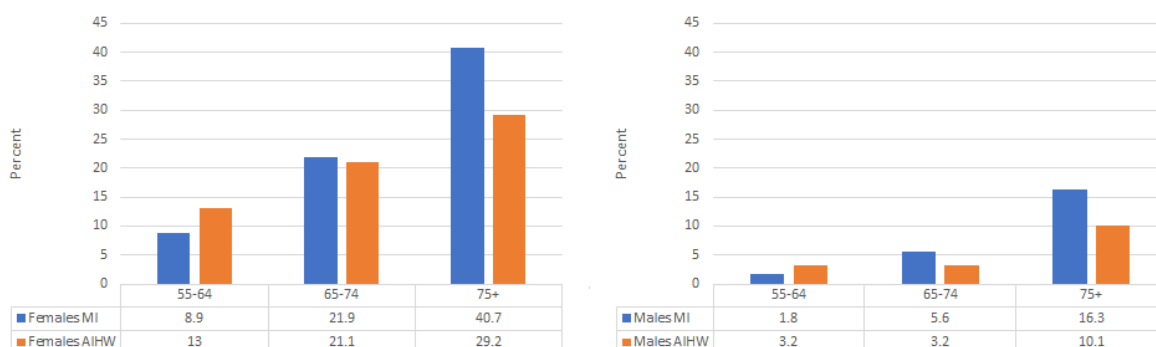


Figure 12: Patient prevalence of recorded osteoporosis among regular attendees between Jan 2018–Dec 2019 (prevalence study population) compared with national population estimates (by age and sex)

Osteoporosis medicines ever prescribed to regular patient population

As can be seen in Table 26, 60.5% (95% CI 59.5 to 61.4) of all regularly attending patients with a record of osteoporosis had been prescribed an osteoporosis medicine at least once. This may be an underestimate as, depending on recording practices, specialist and hospital prescriptions are not always captured in the CIS of a general practice. Therefore, some patients, prescribed an osteoporosis medicine by a specialist, may be missed.

Just over half of men (52.7%) had been prescribed an osteoporosis medicine at least once, compared with 62.5% of women, suggesting that men may still be less likely to be treated than women even when they have been diagnosed with osteoporosis.

The likelihood that a patient with a record of osteoporosis had been prescribed an osteoporosis medicine rose with increasing age for all patients and for women. However, the proportion of men with diagnosed osteoporosis prescribed an osteoporosis medicine was similar in both the 60–69 age group and the 70+ age group.

Table 26: Proportion of patients with a record of osteoporosis who have ever been prescribed an osteoporosis medicine at least once (by age and sex)

	Regular patient prevalence study (3 visits between Jan 2018–Dec 2019)		
	No. patients with recorded osteoporosis	No. patients with at least one record of osteoporosis medicine script ever	% (95% CI)
Total	121,598	73,510	60.5 (59.5–61.4)
Age group (10 years)			
50–59	9,119	3,473	38.1 (36.4–39.8)
60–69	23,586	12,398	52.6 (51.2–53.9)
70+	88,893	57,639	64.8 (63.9–65.8)
Sex			
Female	96,255	60,162	62.5 (61.5–63.5)
Male	25,343	13,348	52.7 (51.2–54.1)
Sex/age group			
Female 50–59	7,597	2,790	36.7 (35.0–38.5)
Female 60–69	20,195	10,564	52.3 (50.9–53.7)
Female 70+	68,463	46,808	68.4 (67.5–69.2)
Male 50–59	1,522	683	44.9 (42.0–47.7)
Male 60–69	3,391	1,834	54.1 (52.0–56.1)
Male 70+	20,430	10,831	53.0 (51.4–54.6)

NB: These figures should not be compared with those in Table 27. Figures in Table 26 refer to 'ever' prescriptions whereas figures in Table 27 refer only to scripts prescribed in Jan 2014–Dec 2017

The proportion of patients who had no record of being prescribed an osteoporosis medicine was higher in this study (39.5%; 95% CI 38.6% to 40.5%) than that reported in the Naik-Panvelkar study (23.5%). This is most likely due to differences in cohort selection. This analysis included patients who had attended at least 3 times over the 2-year study period, but the Naik-Panvelkar study only included patients who had been seen at the general practice at least once every year over an 8-year period. This highly selected group are very likely to see a single GP and because they have been attending the same practice over a long time period are likely to have very complete records. In contrast, the patients in this study may have less complete records and data from other prescribers (such as specialists or GPs from other general practices) may not be captured as well.

Osteoporosis medicines prescribed to the historical osteoporosis study population in Jan 2014–Dec 2017

Prescribing of osteoporosis medicines between January 2014 and December 2017 in the historical osteoporosis study population was more common in women and older patients.

Please note that while prescribing patterns are similar, these figures should not be directly compared with those in Table 26. Figures in Table 26 refer to ‘ever’ prescriptions whereas figures in Table 27 refer only to scripts prescribed in Jan 2014–Dec 2017.

Table 27: Proportion of patients in the historical osteoporosis study population prescribed an osteoporosis medicine at least once in Jan 2014–Dec 2017

	Historical osteoporosis study population (3 visits between Jan 2014–Dec 2017 and osteoporosis recorded before 1 Jan 2018)		
	No. patients with recorded osteoporosis	No. patients with at least one record of osteoporosis medicine script between Jan 2014 and Dec 2017	% (95% CI)
Total	120,388	61,603	51.2 (50.1–52.3)
Age groups (10 years)			
50–59	9,515	3,177	33.4 (31.7–35.1)
60–69	23,692	10,553	44.5 (43.2–45.9)
70+	87,181	47,873	54.9 (53.8–56.1)
Sex			
Female	96,229	50,529	52.5 (51.4–53.6)
Male	24,159	11,074	45.8 (44.3–47.4)
Age/Sex			
Female 50–59	7,910	2,575	32.6 (30.8–34.3)
Female 60–69	20,238	8,993	44.4 (43.1–45.8)
Female 70+	68,081	38,961	57.2 (56.1–58.3)
Male 50–59	1,605	602	37.5 (34.6–40.4)
Male 60–69	3,454	1,560	45.2 (43.1–47.2)
Male 70+	19,100	8,912	46.7 (45.0–48.3)

NB: These figures should not be compared with those in Table 10. Figures in Table 10 refer to ‘ever’ prescriptions whereas figures in Table 11 refer only to scripts prescribed in Jan 2014–Dec 2017.

Denosumab treatment duration

Among the 22,256 patients in the historical osteoporosis study who were started on denosumab between January 2014 and December 2017 (with or without trialling another osteoporosis medicine first), less than 8% of patients had a treatment duration of 180 days (range 180–2,189 days; Table 28, Figure 13). Most were prescribed at least two denosumab prescriptions.

The median duration of treatment (including treatment breaks or ‘holidays’, when no relevant prescription was recorded) was 1,154 days or 3.2 years. Figure 13 shows the duration of treatment with denosumab (including breaks) graphically.

Table 28: Treatment duration including ‘treatment holidays’ in 26,444 patients initiated on denosumab between Jan 2014–Dec 2017 (with or without prior osteoporosis medicine)

Treatment duration (including breaks) up until 31 December 2019	Days	Years
Mean	1,175	3.22
Mode	180	0.49
Median	1,154	3.16
First quartile	887	2.43
Third quartile	1,679	4.60

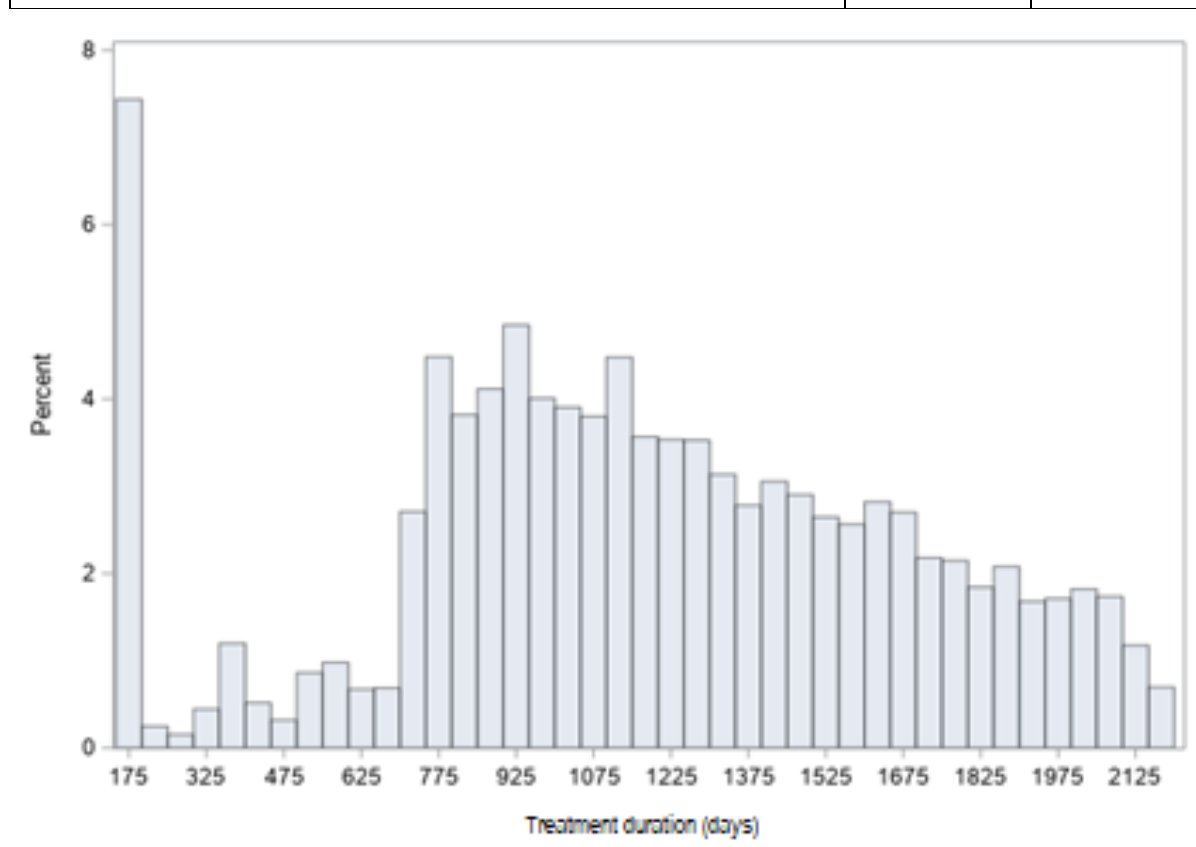


Figure 13: Treatment duration in days (including breaks) for patients initiated on denosumab between Jan 2014–Dec 2017

Denosumab cessation

Two thirds of the 22,256 patients who were started on denosumab between January 2014 and December 2017 were still on denosumab treatment on 31 December 2019 (Table 29). Almost a quarter of patients (24.6%; 95% CI 23.6 to 25.6) had ceased denosumab treatment.

Table 29: Status of denosumab treatment on 31 December 2019 among patients initiated on denosumab between Jan 2014–Dec 2017 (with or without prior osteoporosis medicine)

	No. of patients	% (95% CI)
Ongoing denosumab treatment	14,680	66.0 (64.8–67.1)
Ceased denosumab treatment	5,482	24.6 (23.6–25.6)
Lost to follow-up	2,094	9.4 (8.8–10.0)
Total	22,256	100

As can be seen in Table 30, only 13.8% (95% CI 12.7% to 14.8%) of patients who had ceased denosumab therapy by 31 December 2019, had a record of having been prescribed another osteoporosis medicine after cessation. Therefore 86.2% had no record of osteoporosis therapy after denosumab cessation. This is higher than that reported by Naik-Panvelkar but once again may be explained by the differences in the study cohorts.

Patients aged 70+ years were significantly less likely to have a record of being prescribed another osteoporosis medicine than patients aged 60–69 years.

Table 30: Follow-on therapy for patients who had ceased denosumab treatment prior to 31 December 2019 among patients initiated on denosumab between Jan 2014–Dec 2017 (with or without prior osteoporosis medicine)

Age group	No. of patients ceased	No. prescribed another osteoporosis medicine	% (95% CI)
50–59	392	61	15.6 (12.2–18.9)
60–69	995	191	19.2 (16.7–21.7)
70+	4,095	502	12.3 (11.1–13.4)
Total	5,482	754	13.8 (12.7–14.8)

Qualitative interviews undertaken with Australian GPs suggested that uncertainty about what to do when stopping denosumab meant many referred their patients to specialists for advice about stopping.¹⁶ As the CIS in general practice may not capture specialist prescribing this may explain the low recorded rates of ongoing osteoporosis medicine treatment seen in both studies. Other explanations could include:

- inadequate reminder and recall systems (particularly given denosumab only needs to be prescribed and administered every 6 months)¹⁴;
- patient reluctance to use bisphosphonates due to intolerance or unacceptable side effects;

¹⁶ Naik-Panvelkar P, Norman, S, Elgebaly, Z, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. *BMC Fam Pract* 2020; 21(1): 32.

- short follow-up among patients who ceased denosumab in late 2019 given no data was collected after 31 December 2019; or
- death: 468 (8.5%) of the patients who had no record of follow-up osteoporosis medicines after ceasing denosumab were recorded in the CIS as having died. Of these, 437 patients were aged 70+ years compared with 27 patients in the 60–69 age group and 4 patients in the 50–59 age group.

Patients initiated on denosumab without trialling another osteoporosis medicine

Among the cohort of 120,388 patients included in the historical osteoporosis study, 9.2% (95% CI 8.7 to 9.7%) were started on denosumab with no prior record of any other prescribed osteoporosis treatment.

Among the 22,256 patients who had been prescribed denosumab at least once, 50.0% were started on denosumab without any record of having been previously prescribed any other osteoporosis medicine. In 2015, DUSC reported 42.7% of patients initiating denosumab had not used at least one other osteoporosis drug.

The overwhelming majority (99.1%) of patients who were directly initiated on denosumab had no record of any other osteoporosis medicines being prescribed on the same day (Table 31). Only 88 patients were prescribed both denosumab and a bisphosphonate on the same day. Thirteen patients had a record of being prescribed both denosumab and a non-bisphosphonate osteoporosis medicine on the same day. No patients were initiated on denosumab plus a bisphosphonate plus an ‘other osteoporosis medicine’.

Table 31: Patients initiated on denosumab with no prior osteoporosis medicine in the historical osteoporosis study population (N = 120,388) between Jan 2014–Dec 2017

Analysis	No. of patients initiated on denosumab	% (95% CI)
Denosumab only	11,021	99.1 (98.9–99.3)
Denosumab plus bisphosphonate	88	0.8 (0.6–1.0)
Denosumab plus ‘other osteoporosis medicine’*	13	0.1 (0.1–0.2)
All patients initiated on denosumab	11,122	100

*The ‘other osteoporosis medicine’ category includes raloxifene, strontium ranelate, teriparatide and calcitriol.

CI: confidence interval

DUSC consideration

DUSC commented that osteoporosis was a serious health concern, noting that it affected an estimated 924,000 Australians (National Health Survey 2017-18) and more than a quarter of Australian women over the age of 75 years.

DUSC noted its previous considerations of denosumab:

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- In September 2016, DUSC noted the very high uptake of denosumab and declining use of bisphosphonates, and its concerns at that time of potential adverse events from a greater uptake of denosumab.
- In February 2020, DUSC considered a report commissioned by the department to explore persistence to the various forms of osteoporosis medicines. DUSC noted that increasing numbers of people were receiving osteoporosis therapy and persisting on that therapy; predominantly denosumab. DUSC noted that persistence to treatment appeared to be better for denosumab compared to other osteoporosis medicines. DUSC noted the difference in long-term effects of bisphosphonates and denosumab, where denosumab is associated with bone loss on discontinuation while there is some bone maintenance for bisphosphonates. DUSC considered that the longer pharmacodynamic half-life of bisphosphonates makes bisphosphonates more 'forgiving' if there are breaks in therapy. DUSC considered that clinicians are aware of the ongoing need to encourage adherence to treatment with denosumab due to the early onset of loss of clinical benefit when ceasing denosumab therapy and risk for fracture. DUSC recalled that following PBAC consideration of the 2016 DUSC report on osteoporosis, educational messages were circulated to alert clinicians to the need for ongoing six-monthly treatment with denosumab. DUSC considered the higher persistence with treatment and higher treatment cost of denosumab compared to oral bisphosphonates may affect the cost-effectiveness of denosumab achieved in practice.
- At its June 2020 meeting, DUSC noted QUM issues highlighted by Naik-Panvelkar et al. (2020)¹⁷ which used MedicineInsight data to examine osteoporosis management in general practice. DUSC noted there is evidence of lower bone mineral density (BMD) and increased risk of multiple vertebral fractures shortly after discontinuation of denosumab. Based on the findings of Naik-Panvelkar et al., DUSC requested a further review of the utilisation of denosumab for osteoporosis to investigate patient management following discontinuation from denosumab. DUSC suggested that NPS MedicineWise could be engaged to analyse the use of denosumab for osteoporosis using MedicineInsight data.

DUSC considered the utilisation reports prepared by NPS Medicinewise for the October 2020 meeting using its MedicineInsight data and a 10% PBS sample. DUSC considered that the addition of MedicineInsight data to the reporting gave a useful perspective about patient management through primary care. The data limitation of some loss to follow-up of patients who are treated in settings outside the MedicineInsight sample and cannot be identified from probabilistic matching was acknowledged.

¹⁷ Naik-Panvelkar P, Norman, S, Elgebaly, Z, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. *BMC Fam Pract* 2020; 21(1): 32.

DUSC noted that a lower proportion of patients were directly initiated on denosumab in the MedicineInsight study compared with the PBS 10% study. DUSC considered that this could indicate that specialists are more likely to start patients directly on denosumab than GPs.

DUSC noted that only a low proportion of patients were identified as being treated with another osteoporosis drug during treatment breaks from denosumab therapy. Of the 11,533 patients from the PBS study who were started on denosumab (regardless of whether they had been dispensed a different osteoporosis medicine beforehand), 35.2% had a treatment break. During this break only 2.5% were covered by another prescription for osteoporosis therapy.

DUSC noted that around one-third of patients in the PBS study and one-quarter of patients in the MedicineInsight study who were directly initiated on denosumab had ceased therapy by the end of the study period. DUSC noted that for both the PBS and MedicineInsight studies, only a low proportion of patients recommenced osteoporosis treatment. Of the PBS patients who ceased denosumab only 5.0% had a subsequent record of osteoporosis treatment and of the MedicineInsight patients who ceased denosumab only 13.8% had a subsequent record of osteoporosis treatment.

The duration of denosumab treatment including treatment breaks was defined as the number of days between the date of the first prescription and the expected end of the last prescription or the 31 December 2019 (whichever came first). The expected end date of the last denosumab prescription was calculated as the date of the last prescription plus 180 days multiplied by {the number of repeats + 1}. DUSC considered this method may overestimate the time on longer acting therapy compared to bisphosphonates where there is the addition of 30 days compared to 180 days.

The PBS study examined the average treatment duration on a patient's initiating therapy including breaks for patients who initiated an osteoporosis medicine between 2014 and 2017, noting that some patients only had 18 months of follow-up available and others up to 5.5 years. A sensitivity analysis limited the population to only those who initiated therapy between 2014 and 2015, allowing a longer follow-up period to be assessed before the end of the study time period. DUSC considered that the discontinuation rate may have been overestimated by only including patient initiation up to 2017. DUSC commented that discontinuation rates may be different in more recent initiators, particularly with the trend towards a greater use of denosumab. DUSC further considered that it would be informative to separate the discontinuation analysis into different decades of life which may show differing ceasing patterns between age groups.

DUSC considered that both the PBS and MedicineInsight studies confirm the prior research by Naik-Panvelkar et al. (2020) that a concerning proportion of patients discontinued denosumab without subsequent antiresorptive therapy, placing them at risk of further fractures. DUSC advised that consultation with consumers should be undertaken to better understand patient choices to cease their osteoporosis treatment. In particular whether discontinuation relates to drug interactions, if multiple medicines are taken for several comorbidities, or if there is aversion to having injections. DUSC also considered that prescriber education needed to further emphasize the importance of continuing

osteoporosis treatment and to consider other treatment choices during breaks from denosumab therapy rather than having a gap in treatment.

DUSC actions

- DUSC requested that the report be provided to the PBAC for consideration.
- DUSC requested that the consumer representatives of DUSC engage with relevant consumer organisations about the QUM issues raised from the review.

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: Osteoporosis remains an underdiagnosed and undertreated condition in Australia. The availability of denosumab has made a positive impact on osteoporosis care with improved treatment rates and persistence to therapy as noted in the DUSC analyses. Amgen is committed to quality of care and continues to provide education and programs to address the QUM finding from this review.

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.

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The Department of Health (DoH) 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, DoH 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 DoH nor any DoH 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.

Appendix A: Pharmacology as per Australian Product Information and the Australian Medicine Handbook²

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 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.

Strontium ranelate acts by uncoupling bone resorption and formation.

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
1/12/1991	CALCITRIOL	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
1/08/1996	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
1/11/1996	ALENDRONATE	Listed on PBS on a cost-effectiveness basis with calcitriol for established post-menopausal osteoporosis in patients with fracture due to minimal trauma
1/11/1999	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

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1/02/2001	RISEDRONATE	Listed on PBS on a cost-minimisation basis with alendronate for established post-menopausal osteoporosis in patients with fracture due to minimal trauma
1/12/2005	CALCIUM	Delisting of calcium for patients other than those with chronic renal failure
1/04/2006	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
1/04/2006	RISEDRONATE and CALCIUM CARBONATE	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
1/08/2006	ALENDRONATE with COLECALCIFEROL	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
1/04/2007	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
1/04/2007	ALENDRONATE	Extension to patients 70 years or more at risk of fracture based on BMD test (-3.0 or less)
1/07/2007	ALENDRONATE AND COMBINATIONS, RISEDRONATE AND COMBINATIONS, DISODIUM ETIDRONATE and CALCIUM CARBONATE, CALCITRIOL, RALOXIFENE HYDROCHLORIDE and STRONTIUM RANELATE	STREAMLINED process was introduced
1/08/2007	RISEDRONATE and COMBINATIONS	Extension to patients 70 years or more at risk of fracture based on BMD test (-3.0 or less)
1/11/2007	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
1/12/2007	ALENDRONATE	Statutory price reduction
1/12/2007	ALENDRONATE with COLECALCIFEROL	Partial 12.5% price reduction to alendronate component

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1/05/2008	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
1/12/2008	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
1/02/2009	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.
1/04/2009	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.
1/05/2009	TERIPARATIDE	Listed on PBS on a cost-effectiveness basis over alendronate for patients as the sole PBS subsidised treatment of severe 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.
1/04/2010	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
1/04/2010	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.

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1/06/2010	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
1/11/2010	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
1/12/2010	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.
1/04/2011	RISEDRONATE AND COMBINATIONS	Statutory price reduction
1/12/2011	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
1/3/2012	DENOSUMAB	Changed to Authority Required (Streamlined)
1/04/2012	ALENDRONATE	Price disclosure reduction of 31.84%
1/07/2012	TERIPARATIDE	Changed from written authority (Complex Authority Required to telephone authority (Authority Required)
1/08/2012	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
1/09/2012	DISODIUM ETIDRONATE AND COMBINATIONS	Delisted at request of Sponsor
1/12/2012	RISEDRONATE AND COMBINATIONS	The price was decreased on 1 December 2012, however following a court order on

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		6 December 2012 the prices were corrected to the 1 November 2012 prices
1/04/2013	ALENDRONATE	Price disclosure reduction of 31.84%
1/08/2013	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
1/12/2013	DENOSUMAB	Restriction expanded to include males
1/10/2014	STRONTIUM	<p>Restriction narrowed.</p> <ul style="list-style-type: none"> • 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; <ul style="list-style-type: none"> - 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.
1/5/2015	ALENDRONATE and RISEDRONATE	Changed from Authority Required (STREAMLINED) to Restricted Benefit. Combination items including these drugs remained Authority Required (STREAMLINED)
1/08/2016	STRONTIUM RANELATE	Delisted because the medicine was not cost-effective at the price proposed by the sponsor.