

Osteoporosis medicines

Drug utilisation sub-committee (DUSC)

September 2016

Abstract

Purpose

To review the utilisation of medicines for the treatment of osteoporosis including an assessment of the predicted and actual use of denosumab.

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

- Calcitriol: 1 December 1991
- 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

Patient counts and patient level analysis data were extracted from the Department of Human Services (DHS) prescription database for prescriptions supplied from January 2003 to March 2016. Prescription and expenditure analyses were based on prescriptions supplied from January 1990 to March 2016.

Key Findings

- Rates of treatment with osteoporosis medicines declined by 15% between 2007 and 2014 despite reports of increasing prevalence of osteoporosis. In 2015 the treatment rate increased. Further data will be needed to confirm if this increase is sustained.
- In 2015, 471,497 patients were treated with osteoporosis medicines through the PBS, and 15% of these people (72,132) commenced osteoporosis treatment for the first time.

- The average age when starting osteoporosis medicines was 71 years. This was similar between men and women.
- 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.

Purpose of analysis

To review the utilisation of medicines for the treatment of osteoporosis including an assessment of the predicted and actual use of denosumab.

Background

At its June 2016 meeting DUSC requested that utilisation of denosumab be reviewed in the context of the total osteoporosis market noting that use of denosumab had increased rapidly. DUSC recommended that the review include an assessment of the extent that denosumab has grown the overall osteoporosis market, extent of switching from other agents, frequency of administration, co-administration, and age at initiation.

DUSC also considered that uptake in residential aged care facilities, and relationships between rates of bone mineral density (BMD) testing and initiation on denosumab and other agents by geographic region may be informative in interpreting utilisation patterns. Rates of BMD testing are included in the current review. Use of medicines in residential aged care facilities (RACF) cannot be distinguished in the PBS prescription data. Additional data sources and/or data linkage would be required.

The osteoporosis medicines included in this analysis are:

- Bisphosphonates: alendronate, risedronate, etidronate and zoledronic acid.
- Bisphosphonate combinations including with colecalciferol and/or calcium carbonate.
- Raloxifene, strontium and teriparatide.
- Calcitriol.

A brief overview of the pharmacology of these medicines is provided in Appendix A.

Therapeutic Goods Administration (TGA) approved indications¹

Table 1: TGA approved osteoporosis* indications

| | |
|------------------------------|---|
| Alendronate and combinations | <ul style="list-style-type: none">• Treatment of osteoporosis, including glucocorticoid-induced osteoporosis.• Prevention of osteoporosis in postmenopausal women with low bone mass.• 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 osteopaenia receiving androgen deprivation therapy for non-metastatic prostate cancer.• Treatment to increase bone mass in men with osteoporosis at increased risk of fracture. |

¹ <https://www.tga.gov.au/product-information-pi>

| | |
|------------------------------|--|
| Etidronic acid + calcium | <ul style="list-style-type: none"> • Treatment of osteoporosis. Osteoporosis must be confirmed by the finding of low bone mass (at least two standard deviations below the gender-specific mean for young adults) or by the presence or history of osteoporotic fracture. • Prevention of bone loss in patients for whom long-term treatment with high-dose corticosteroids is either about to be commenced or has been recently initiated. |
| Raloxifene | <ul style="list-style-type: none"> • Prevention and treatment of osteoporosis in post-menopausal women. |
| 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 | <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.

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; daily or weekly |
| Calcitriol | Oral; twice daily |
| Denosumab | Subcutaneous injection; once every six months |
| Raloxifene | Oral; daily |
| Risedronate and combinations (risedronate and calcium carbonate; risedronate and calcium carbonate with colecalciferol) | Oral; daily, weekly or monthly |
| Strontium ranelate | Granules for oral suspension; daily at bedtime |
| 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 <https://www.tga.gov.au/product-information-pi> and <http://www.tga.gov.au/consumers/information-medicines-cmi.htm> respectively.

Clinical situation

Osteoporosis causes bones to become thin, weak and fragile, and is a major cause of fractures.² Often people do not know that they have osteoporosis because the condition lacks overt symptoms. The factors that increase your likelihood of developing osteoporosis are³:

- Gender – development of osteoporosis is more common in females, however one in three fractures occur in men.
- Post-menopause.
- Family history of osteoporosis.
- Limited physical activity and inadequate dietary calcium intake.
- Limited exposure to sunlight resulting in low vitamin D intake.

² Australian Institute of Health and Welfare 2011. A snapshot of osteoporosis in Australia 2011. Arthritis series no. 15. Cat. no. PHE 137. Canberra: AIHW

³ Garvin Institute of Medical Research, <http://www.garvan.org.au/research/diseases-we-research/osteoporosis>, accessed 17/8/2016.

- Cigarette smoking and excessive alcohol intake.
- Prolonged use of some medicines such as high dose cortisone.
- Some diseases including hyperparathyroidism and intestinal malabsorption.

The Australian Institute of Health and Welfare (AIHW) reported⁴ that one of the larger and more recent studies of measured BMD (the Geelong Osteoporosis Study) estimates prevalence of osteoporosis to be 6% of men and 23% of women over the age of 50.⁵ This estimate is higher than the self-reported estimate of diagnosed cases from the ABS Australian Health Survey⁶ (3% of men and 15% of women), as would be expected for a condition that may not be diagnosed due to an absence of overt symptoms.

In 1994, the World Health Organization (WHO) defined osteoporosis operationally in terms of bone mineral density (BMD) according to a standard deviation (SD) difference between a patient's BMD and that of a young adult reference population.⁷ This value is expressed as a T-score (Table 3).

Table 3: WHO classification of osteoporosis

| Classification | BMD T-score |
|-----------------------------------|--|
| Normal | ≥ -1.0 |
| Osteopaenia (low bone mass) | Between -1.0 and -2.5 |
| Osteoporosis | ≤ -2.5 |
| Severe (established) osteoporosis | T-score < -2.5 with fragility fracture |

BMD is only one component of fracture risk. Absolute fracture risk can be calculated using calculators such as the WHO Fracture Risk Assessment Tool⁸ and the Garvan Institute Fracture Risk Calculator.⁹

While osteoporosis is rarely a direct cause of death, osteoporotic hip fractures are linked to premature deaths in the years following the event.¹⁰ Fracture rates attributable to osteoporosis can be reduced by preventing and treating osteoporosis, and identifying and managing risk factors for falls.³

Lifestyle factors and ensuring adequate calcium and vitamin D intake are important in preventing and treating osteoporosis.¹¹ Australian clinical guidelines¹², as summarised by Bell,¹³ recommend pharmacological treatments in the following patients:

⁴ Australian Institute of Health and Welfare (2014), Estimating the prevalence of osteoporosis in Australia

⁵ Henry MJ, Pasco JA, Nicholson GC & Kotowicz MA. 2011. Prevalence of osteoporosis in Australian men and women: Geelong Osteoporosis Study. Medical Journal of Australia 195(6):321–322.

⁶ ABS (Australian Bureau of Statistics) 2012. Australian Health Survey: first results, 2011–12. ABS cat. no. 4364.0.55.001. Canberra: ABS.

⁷ Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of WHO Study Group. Geneva, WHO, 1994 (WHO Technical Report Series, No 843).

⁸ <https://www.shef.ac.uk/FRAX/>

⁹ <http://www.garvan.org.au/bone-fracture-risk>

¹⁰ Bliuc D et.al., Accelerated bone loss and increased post-fracture mortality in elderly women and men, Osteoporosis Int. 2015 Apr;26(4):1331-9. doi: 10.1007/s00198-014-3014-9. Epub 2015 Jan 20.

¹¹ Osteoporosis treatment: a missed opportunity. Frances Milat and Peter R Ebeling. Med J Aust 2016; 205 (4): 185-190. doi: 10.5694/mja16.00568

- patients with minimal trauma fracture
- patients aged 70 years or over with a T-score of -3.0 or lower
- patients currently on prolonged high dose corticosteroids and who have a T-score of -1.5 or lower.

These clinical guidelines were last updated in February 2010.

PBS listed medicines are available for treatment of these patients, and some medicines are also available to patients aged 70 years or over with a T-score of -2.5 or lower.

Guidelines and PBS restrictions for osteoporosis medicines in primary prevention are largely based on BMD T-score because low BMD was an entry criterion in clinical trials of the drugs.

PBS listing details (as at July 2016)

Restriction (Abridged)

Table 4 provides an overview of the PBS restrictions for osteoporosis medicines. Full wording of the restrictions, including notes, can be found at www.pbs.gov.au. Appendix B contains a PBS listing history and also a history of restriction changes.

Oral bisphosphonates are Restricted benefits; zoledronic acid, denosumab, raloxifene and oral bisphosphates in combination with calcium or colecalciferol are Authority Required (STREAMLINED), and teriparatide is Authority Required (telephone).

¹² The Royal Australia College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in post-menopausal women and older men. February 2010. Available at http://www.racgp.org.au/download/documents/Guidelines/Musculoskeletal/racgp_osteo_guideline.pdf (Accessed 14 July 2016)

¹³ Bell et al. Australian Family Physician, Volume 41 Number 3, March 2012

Table 4: Summarised PBS restrictions

| | 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 | ✓ | ✗ | ✗ | ✗ | ✓ |
| 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.

Note: Etidronic acid was delisted September 2012. Strontium was delisted 1 August 2016.

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)

The basis of PBAC recommendations to list osteoporosis medicines is provided in Appendix B. Most medicines have been recommended on a cost-minimisation basis to existing therapies, and have taken into account the different administration costs where applicable (for example for zoledronic acid and denosumab).

Denosumab

At the July 2010 meeting, the PBAC recommended the listing of denosumab for the treatment of osteoporosis in women aged 70 years of age or older with a BMD T score of -3.0 or less, and the treatment of established post-menopausal osteoporosis in patients with fracture due to minimal trauma on a cost minimisation basis compared with zoledronic acid. PBAC also recommended that pricing should take account of the two doctor's visits required for the administration of denosumab, as well as the administration costs for zoledronic acid.

At the March 2012 meeting, the PBAC recommended that 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 on a cost-minimisation basis compared with alendronate 70 mg once weekly tablets.

At the July 2013 meeting, the PBAC recommended the listing of denosumab as an Authority Required (STREAMLINED) benefit as the sole PBS-subsidised anti-resorptive agent for osteoporosis to include both male and female patients.

For further details refer to the Public Summary Documents from the July 2010, March 2012 and July 2013 PBAC meetings.

At the July 2016 meeting the PBAC recommended a change to the PBS listing for denosumab to allow initiation of treatment of osteoporosis by nurse practitioners. Prior to this denosumab was for prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. This change has not yet been implemented in the PBS Schedule (as at 18 August 2016).

Previous reviews by DUSC

Medicines for the treatment of osteoporosis were reviewed by DUSC at its October 2012 and October 2013 meetings. A key consideration at the October 2012 DUSC meeting was that the observed apparent plateau in the number of PBS prescriptions for osteoporosis medicines may not indicate a plateau in the number of patients treated. DUSC considered that further assessment was needed to account for use in public hospitals, the longer duration of therapy provided by injectable agents compared to oral therapies, and cessation or breaks in therapy for patients who have been treated with these medicines for extended periods.

A subsequent review in October 2013 confirmed that utilisation of osteoporosis medicines had stabilised, and that use of the injectable therapies (denosumab and zoledronic acid) has increased market share with respect to other osteoporosis treatments. DUSC noted the convenience of injectable over oral bisphosphonates in some settings, including residential aged care, and noted the need for vigilant monitoring of adverse effects in at risk groups such as the elderly.

DUSC also noted that 57% of use of the oral bisphosphonates was in combination products which contain calcium and colestiferol, and considered that there is a risk of over-supplementation with calcium. DUSC suggested moving the listings of single component bisphosphonates, including zoledronic acid, from Authority Required (STREAMLINED) listings to Restricted Benefit listings in order to encourage prescribing of single agents. The PBAC subsequently recommended that the single component oral bisphosphonates, alendronate and risedronate, change from Authority Required (STREAMLINED) to Restricted Benefit. This change was implemented on 1 May 2015.

A predicted versus actual analysis of denosumab (presented as an addendum to the October 2013 report) was considered by DUSC in February 2014. Key findings were that:

- denosumab is used for both patients who are new to osteoporosis therapy and in patients who have been on prior osteoporosis medicines.

- Most patients on denosumab have switched from another medicine. The number of patients switching to denosumab from other osteoporosis treatments more than doubled from 2011 to 2012 (8,099 to 16,946).
- The proportion of patients initiating osteoporosis therapy on denosumab (compared to the proportion of patients switching from other osteoporosis treatments) appears to be increasing.
- It appears the age distribution of patients initiating denosumab is similar to the age distribution of patients initiating other osteoporosis treatments.

In addition to noting the key findings, DUSC commented that there have been adverse events related to denosumab reported, for example osteonecrosis of the jaw, atypical femoral fractures and brittle bones. However, DUSC commented these adverse events are not dissimilar to other osteoporosis agents and are reflective of antiresorptive agents in general. The adverse event of particular interest with denosumab is the increased risk of infection.

Methods

The number of patients for dispensed prescriptions were determined from data extracted from the Department of Human Services (DHS) PBS prescription claim database for prescriptions supplied from January 2003 to March 2016, inclusive.

Data for the number of prescriptions and government expenditure for all osteoporosis medicines listed on the PBS were extracted from the same source. A difference from the data used to count patients was that the period was extended back to January 1990. This data source was only used after checking that under co-payment prescriptions were complete for this group of drugs in this data source. All osteoporosis PBS items were priced (ie. DPMQ) above the general patient co-payment before 1 April 2012, thus there was complete capture of PBS prescriptions dispensed. From April 2012 the price of some osteoporosis medicines began to fall below the general patient copayment however at the same time collection of under co-payment prescription information by DHS commenced and there was no loss of PBS prescription data.

Osteoporosis medicines listed on the PBS were defined as the osteoporosis specific item codes for zoledronic acid (ie. 9288W and 10555M) and denosumab (ie. 5457F) and all PBS items in the following WHO or PBS ATC codes; M05BA04, M05BA07, M05BB01, M05BB02, M05BB03, M05BB04, M05BB05, M05BX03, A11CC04, D05AX03, G03XC01 or H05AA02.

Patient count analysis

The number of patients who received a supply of any osteoporosis medicine in each year from 2003 to 2015 was determined by counting the number of person specific numbers (non-identifying) in the data for each year.

Most PBS prescriptions generally provide one month of therapy, however prescriptions of zoledronic acid and denosumab are designed to be supply annually and six monthly respectively. The difference between prevalence on treatment and prevalence of prescription supply in a given time period is dependent on the expected frequency of supply within the period. For this difference to be approximately equal across all drugs (thus making the prevalent patient counts comparable across drugs), the time period needs to be at least the expected frequency of supply of the drug with the longest expected time between supplies. Thus the 1 year analysis time period chosen for this analysis was a compromise. The prevalence of prescription supply should be a good approximation of patients on treatment for all drugs which are expected to be supplied monthly and even denosumab which is expected to be supplied 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 (eg. one supply on 31 December 2014 and next supply on 1 January 2016). Changing the analysis period to 18 months or 2 years was considered, but this was thought to be too infrequent to be able track trends in the time series. Thus the slightly underestimation of zoledronic acid prevalent patients should be kept in mind when considering the results of this analysis.

In addition, the number of new patients starting osteoporosis treatment was estimated by counting the number of patients in each year who had not been supplied a prescription for any osteoporosis medicine in at least the prior two years (ie. initiating patient count starts in 2005 with at least a two year look back to January 2003).

A further analysis counted the number of patients starting on each individual medicine in each calendar year, defined as no prior prescriptions for the specific medicine in at least the prior two years. For this analysis a patient may be counted in more than one medicine in a calendar year if they switched treatment or were co-administered two medicines.

Treatment rates (patients per 1000 population) of patients initiating on and prevalent to osteoporosis medicines (nationally and by State) were calculated as the number of initiating or prevalent patients divided by the ABS Estimated Residential Population (ERP) population¹⁴ in the specific year (as at 30 June) and State. These treatment rates were also age adjusted to correct for the effect of an ageing population and the differences in age distributions between States. The age adjusted rates use the Direct Method¹⁵ and are based on the Australian age distribution of the ABS ERP in the reference year 2011.

The analyses by state were based on the Medicare enrolment postcode of the patient at the time that the prescription was processed.

Time to re-supply analysis

This analysis used the same data as for the patient count analysis (ie. prescriptions supplied from January 2003 to March 2016). Prescriptions were defined as being re-supplied by supply of a subsequent prescription of the same drug for an osteoporosis indication (not necessarily the same item). Prescriptions supplied near the end of the data analysis period (ie. the end of March 2016) were excluded from the analysis as they had limited time for re-supply. These prescriptions were only excluded from the role of being the re-supplied script, not the role of being the re-supplying script. "Near the end of the data analysis period" was defined as being within three times the median days to re-supply (for that drug) of the end to the data analysis period.

¹⁴ Quarterly Population Estimates (ERP), by State/Territory, Sex and Age, extracted from [ABS.Stat](#)

¹⁵ [Principles on the use of direct age-standardisation in administrative data collections](#), September 2011, AIHW

Results

Patient counts

Osteoporosis therapy

Figure 1 shows the total number of people treated with PBS listed medicines each year (prevalent) and the number of these who are new patients starting osteoporosis treatment (initiating).

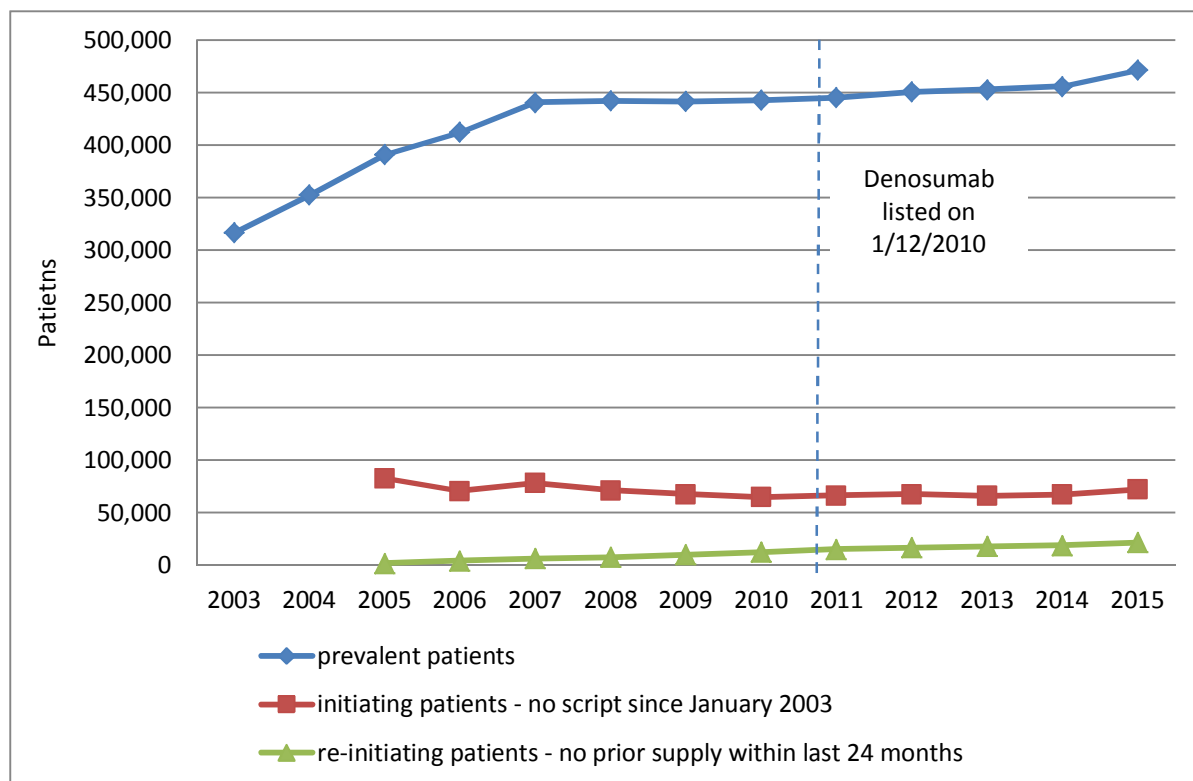


Figure 1: Patients initiating and prevalent to osteoporosis therapy by year of initiation

Note: re-initiators had previously initiated therapy, had a gap of at least 24 months in script supply and are counted in the year of re-initiation.

The number of patients initiating therapy declined between 2007 and 2010 and then remained stable until 2014. In 2015 the initiating patient numbers have increased slightly (ie. from 67,092 in 2014 to 72,132 in 2015, an increase of 7.5%).

Similarly, prevalent patients were increasing strongly up until 2007, after which the numbers plateaued until 2010. After this the prevalent patients started increasing slowly and then more rapidly between 2014 and 2015.

Figure 1 also shows an increasing number of patients who have had a break in treatment for at least 2 years and have returned to treatment. In 2015 there were 21,346 people who recommenced osteoporosis medicines.

The patient counts in Figure 1 can be converted to treatment rates (patients per 1,000 population) to adjust for the effect of an increasing population, and these rates can be age

adjusted to correct for the effect of an ageing population. These rates are shown in Figure 1b.

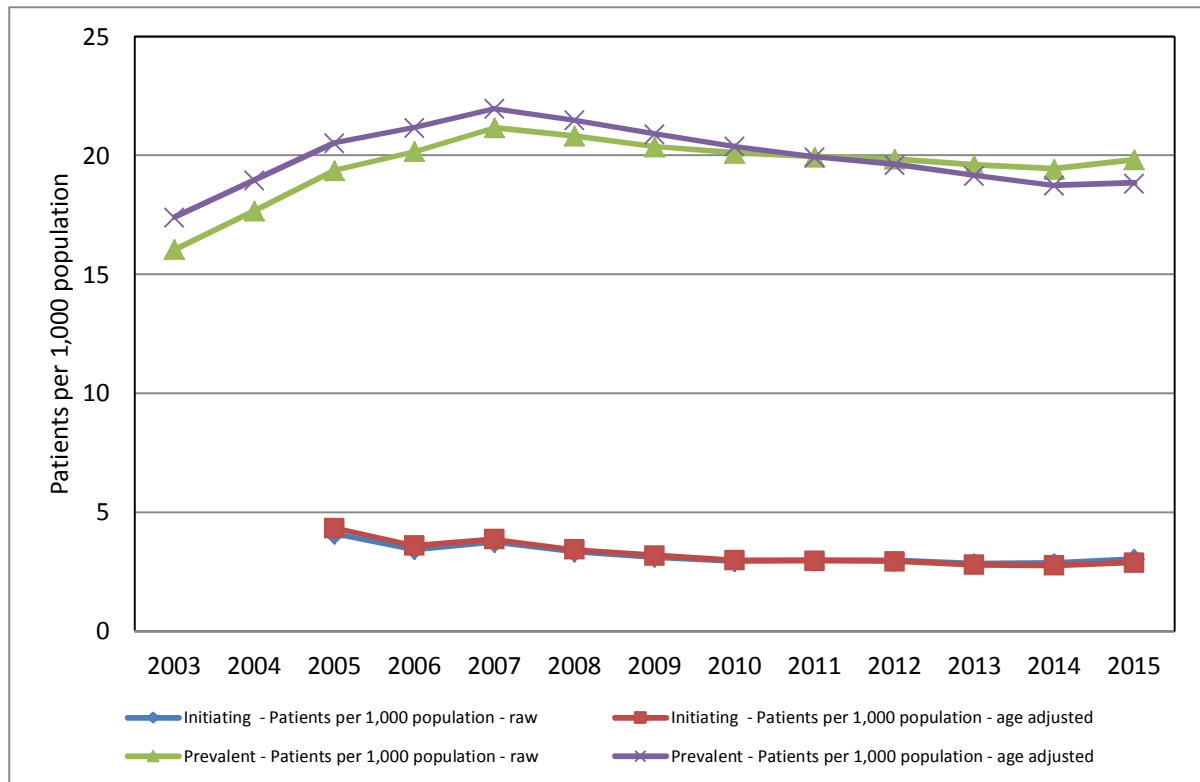


Figure 1b: Patients initiating and prevalent to osteoporosis treatment rates (per 1000 population), raw and age adjusted.

Note: The age adjusted rates use the Direct Method¹⁶ and are based on the Australian age distribution of the ABS Estimated Residential Population in the reference year 2011.

Figure 1b shows that prevalent treatment rates (both raw and age adjusted) decreased between 2007 and 2014. The peak treatment rate was 22.0 patients per 1,000 population (or 2.20% of the population) in 2007 and the trough in 2014 was 18.7 (or 1.87% of the population). This was a decline of 15% over 7 years.

The increasing number of prevalent patients treated in 2015 (Figure 1, 3.4% increase) only translates to a 0.5% higher treatment rate after adjustments for the change in the size and age distribution of the population over time.

Figure 2 shows that the choice of first osteoporosis medicine prescribed has changed over time.

¹⁶ [Principles on the use of direct age-standardisation in administrative data collections](#), September 2011, AIHW

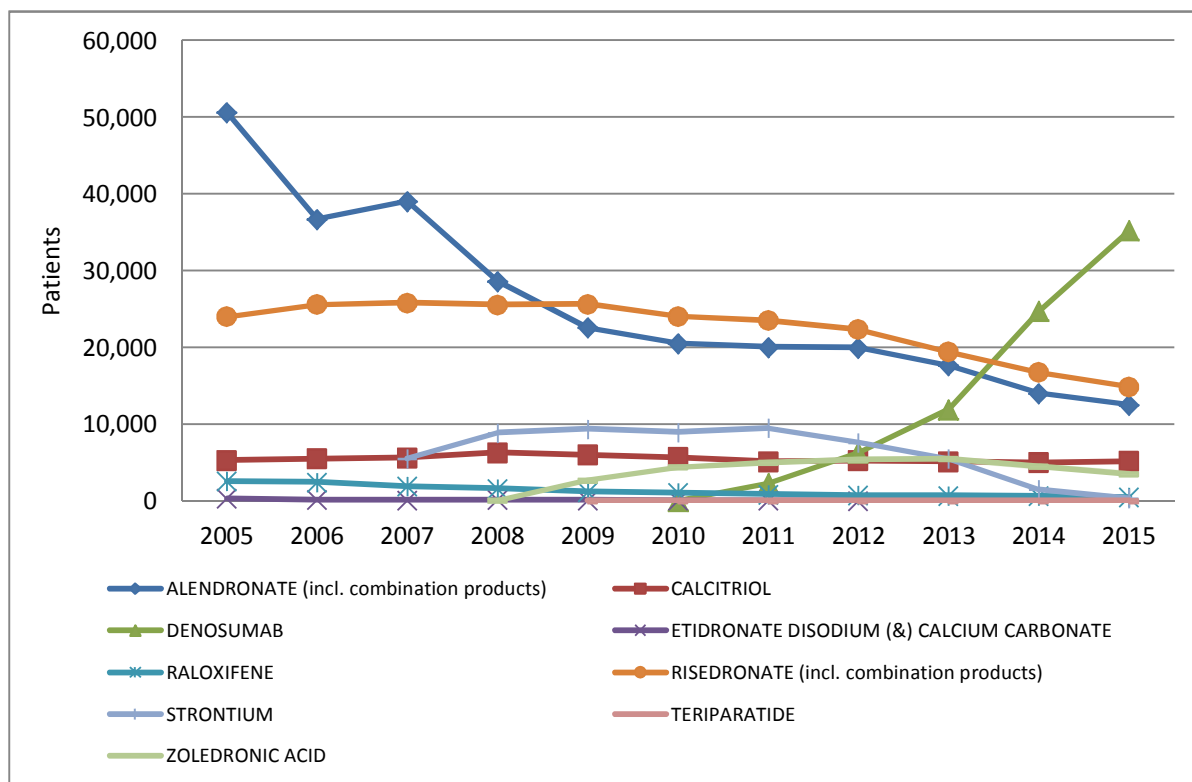


Figure 2: Patients initiating osteoporosis therapy by drug at initiation

The oral bisphosphonates were the most commonly prescribed medicines until 2013. Prescribing of oral bisphosphonates in combination with calcium and/or colestiferol has varied over time with a trend toward a lower proportion of people prescribed the PBS listed combination items between 2010 and 2015 (data not shown). Further assessment of combination prescribing is not presented because calcium and colestiferol can be purchased over the counter and this use is not captured the PBS dataset, and because some patients prescribed combination items through the PBS may not take all components of the co-packaged medicines.

Use of zoledronic acid has been low and stable with some decline in use in 2015. Raloxifene is infrequently prescribed. Teriparatide, 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 is rarely the first PBS prescribed medicine.

The number of patients starting treatment with strontium declined rapidly 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. The change was made due to safety concerns around the risk of cardiovascular events and venous thrombosis associated with strontium.

Denosumab use increased gradually in the first two years of listing and then much more rapidly from 2013 to 2015. Denosumab became the most frequently prescribed medicine for patients initiating osteoporosis therapy in 2014. The strong uptake of denosumab has driven a major change in the prescribing pattern of osteoporosis medicines with injection

becoming the most common mode of treatment for patients starting osteoporosis treatment in 2015 (see Figure 3).

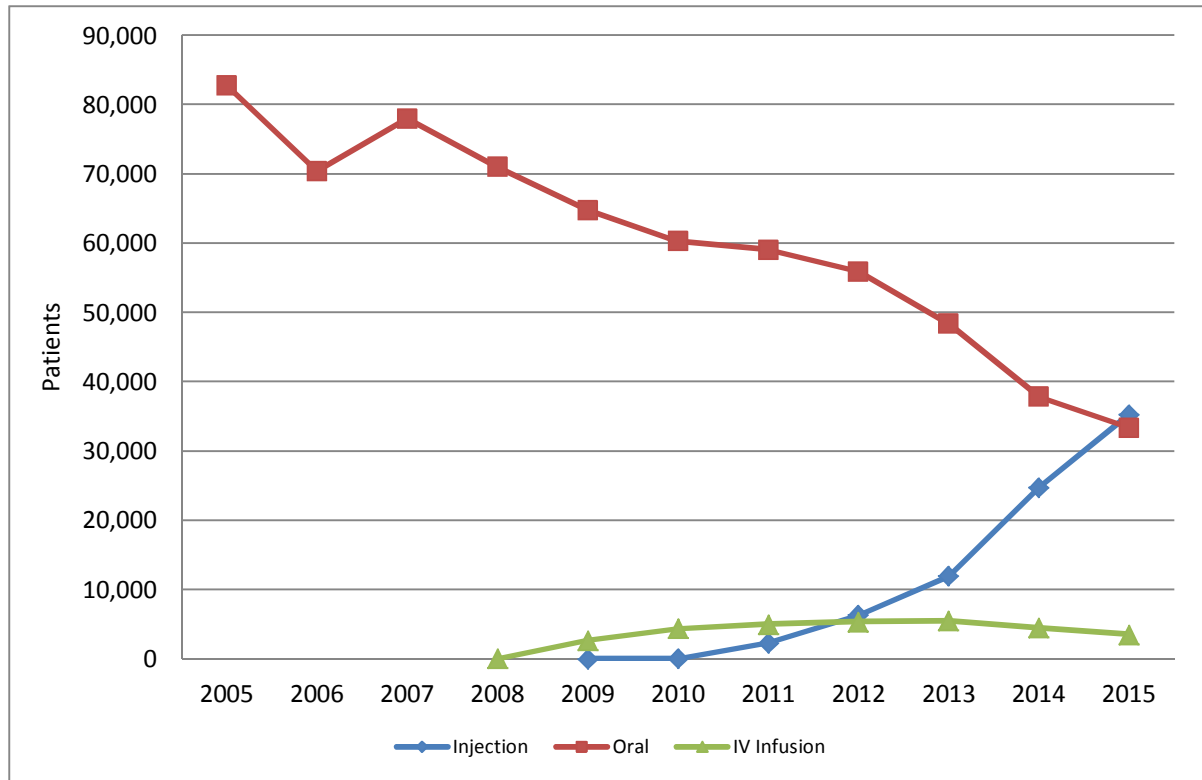


Figure 3: Patients initiating osteoporosis therapy by drug mode of administration

Note: IV infusion = zoledronic acid, subcutaneous injection = denosumab and teriparatide, oral = all other drugs

Initiation to osteoporosis drugs

Figure 4 presents the number of initiations to each medicine each year. The difference between the number of initiations to each drug (Figure 4) and the number of patients starting osteoporosis treatment for the first time by drug (Figure 2) indicates the extent of switching between medicines (ie. the number of patients who were not initiating therapy when they initiated the medicine).

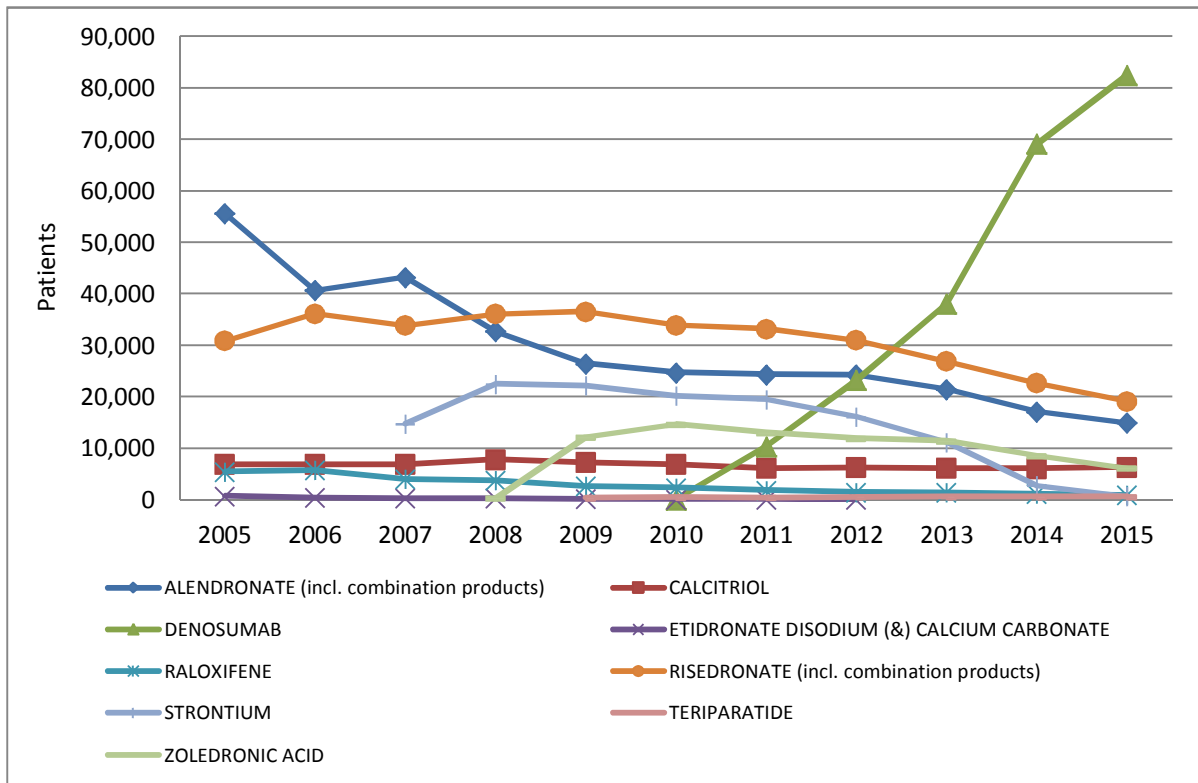


Figure 4: Patients initiating osteoporosis drugs

Comparing Figure 4 with Figure 2 shows that there are many more patients initiating denosumab in 2015 (82,563) than initiating osteoporosis therapy on denosumab (35,260). This indicates that $82,563 - 35,260 = 47,303$ patients (57.3%) had previously been treated with at least one other drug before initiating denosumab in 2015.

For people starting on oral bisphosphonates (plain or combination) the majority (80%) were new to osteoporosis therapy with a smaller proportion switching from another drug. In comparison 57% of people starting zoledronic acid and 45% of people starting strontium in 2015 had received previous osteoporosis therapy. As expected, the vast majority of initiations to teriparatide were in treatment experienced patients.

Prevalence to osteoporosis drugs

Figure 5 shows the number of people treated with each osteoporosis medicine annually. A patient may be counted in more than one medicine in a calendar year if they switched treatment or were co administered two medicines.

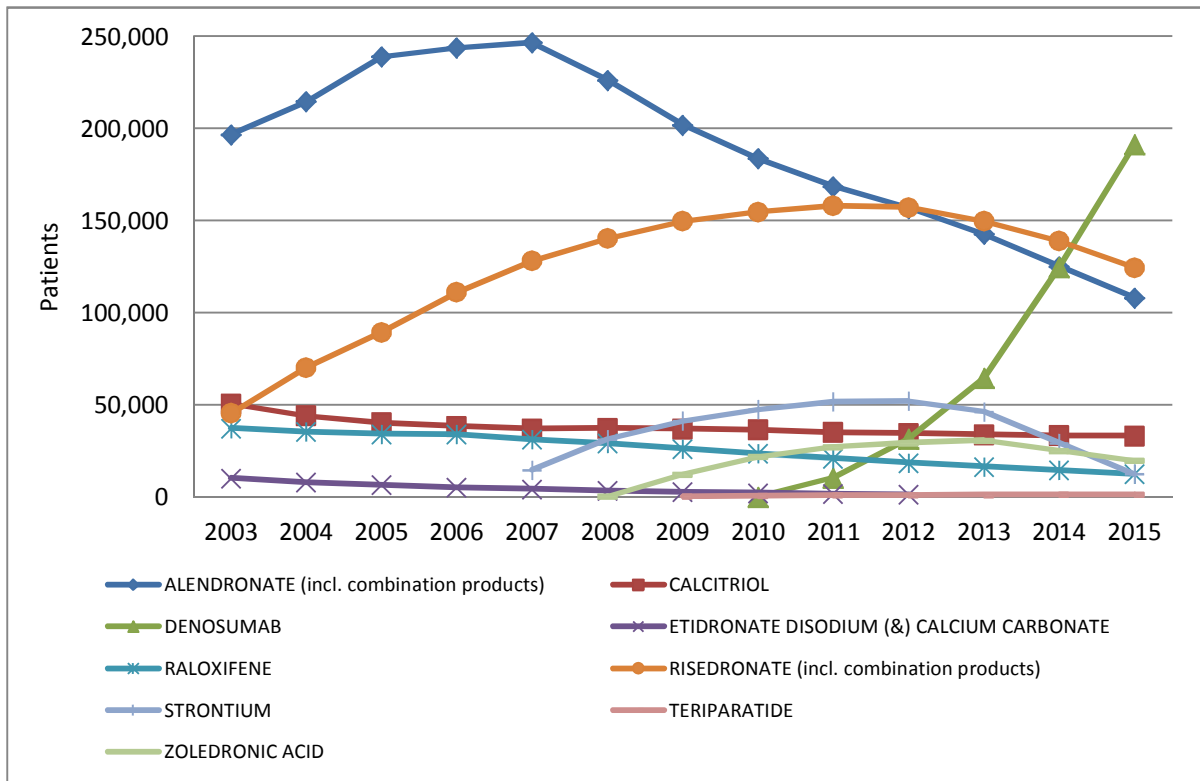


Figure 5: Patients prevalent to osteoporosis drugs

Note: prevalence data starts 2 years prior to incidence data.

Figure 5 shows that denosumab became the drug with the most prevalent patients in 2015. This was a result of strong growth in the number of denosumab patients and a strong decline in the number of patients on alendronate, risedronate and strontium. There were also moderate declines in the number of zoledronic acid and raloxifene patients, whilst the number of calcitriol patients has been relatively constant over the past few years.

Age and gender analysis

Osteoporosis is more prevalent in women than men, with an estimated prevalence ratio in Australia of 3.8:1 for people over 50 years (6% of men and 23% of women¹⁷). Figure 6 shows the prevalence of men and women treated with osteoporosis medicines.

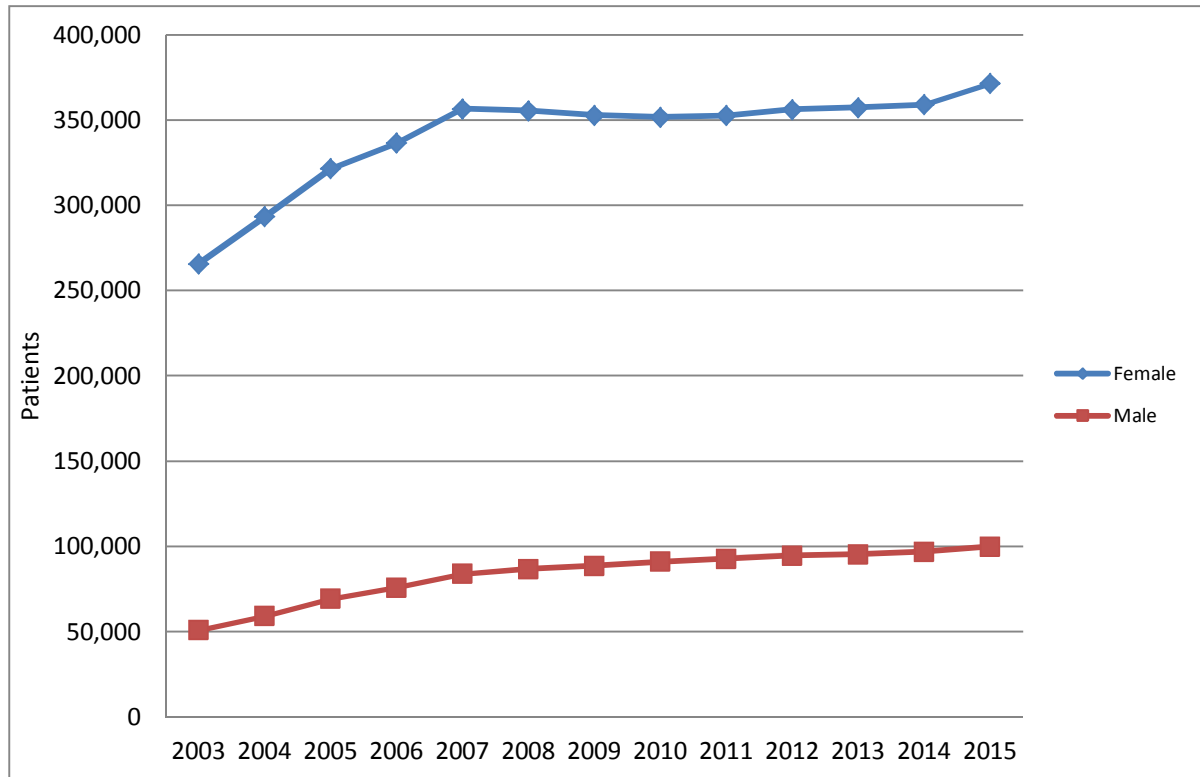


Figure 6: Patients prevalent to osteoporosis therapy by gender

Males prevalent to osteoporosis therapy have increased gradually over the period. In contrast, female prevalent patient numbers plateaued abruptly starting in 2007.

The ratio of women to men aged 50 years or older treated with PBS osteoporosis medicines in 2015 was 3.9:1.

¹⁷ Henry MJ, Pasco JA, Nicholson GC & Kotowicz MA. 2011. Prevalence of osteoporosis in Australian men and women: Geelong Osteoporosis Study. *Medical Journal of Australia* 195(6):321–322.

Table 5 presents the mean and median age of patients when they start taking a PBS subsidised medicines for the first time.

The mean and median age at initiation is similar for men and women and has remained relatively constant over the period 2005 to 2015.

Table 5: Age (years) at initiation to osteoporosis therapy by gender and year

| Year | | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|--------|--------|------|------|------|------|------|------|------|------|------|------|------|
| Female | Mean | 70.9 | 70.6 | 71.5 | 71.3 | 70.7 | 70.4 | 70.7 | 70.7 | 70.7 | 70.6 | 70.3 |
| | Median | 72 | 72 | 73 | 73 | 72 | 72 | 72 | 72 | 72 | 71 | 71 |
| Male | Mean | 70.6 | 70.8 | 71.3 | 71.5 | 70.8 | 70.6 | 70.8 | 71.1 | 71.2 | 71.4 | 71.5 |
| | Median | 73 | 73 | 74 | 74 | 73 | 73 | 73 | 73 | 73 | 74 | 74 |

There was no noticeable change in the age of patients initiating therapy when the PBS listings for some medicines were extended to include primary prevention of fracture in patients aged 70 years or more with a BMD T-score of -3.0 or less (from April 2007) and subsequently for patients with a BMD T-score of -2.5 or less (from December 2011). See Appendix B for details of the extensions to listing. As validation of the streamlined codes for osteoporosis medicines has not been undertaken the age of patients by indication was not determined.

Location (State) analysis

DUSC (October 2012) had noted that there may be lower use of osteoporosis medicines in states where patients may not have ready access to medical facilities for diagnosis and treatment. Figure 7 show osteoporosis therapy initiation rates in each state. In Figure 8 these rates are adjusted for age.

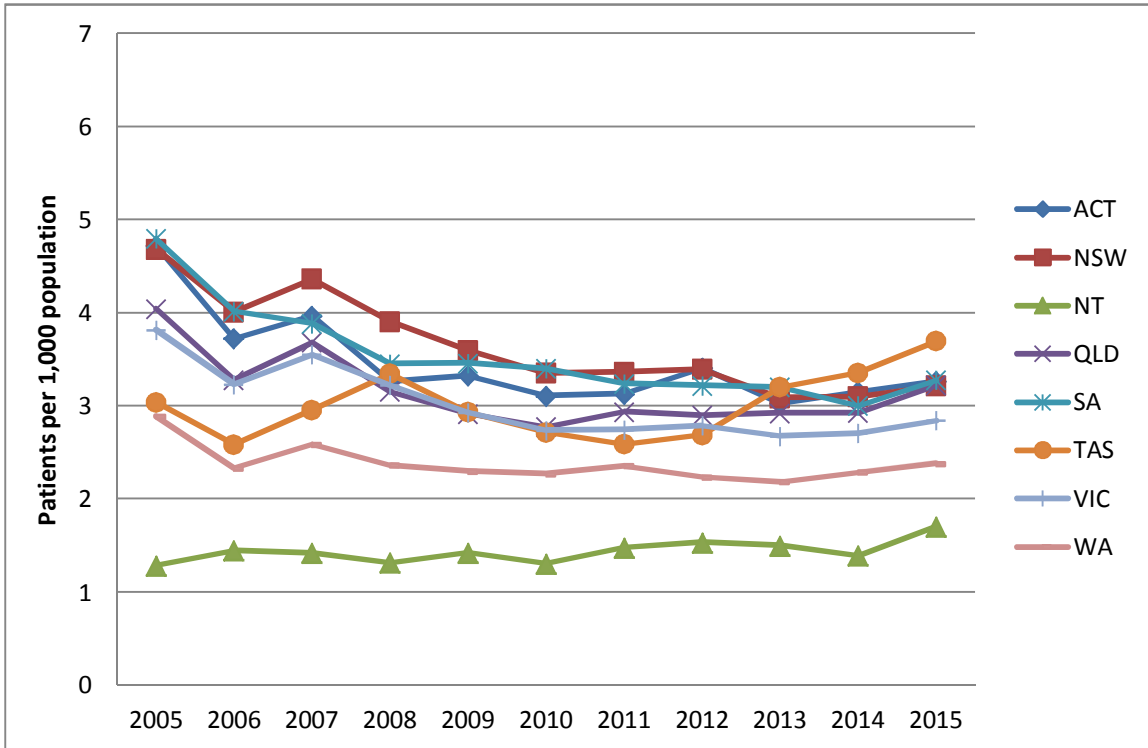


Figure 7: Patients per 1000 population (raw rate) initiating to osteoporosis therapy by State. Note: State is the patients Medicare enrolment State at the time of DHS processing of the initiating prescription.

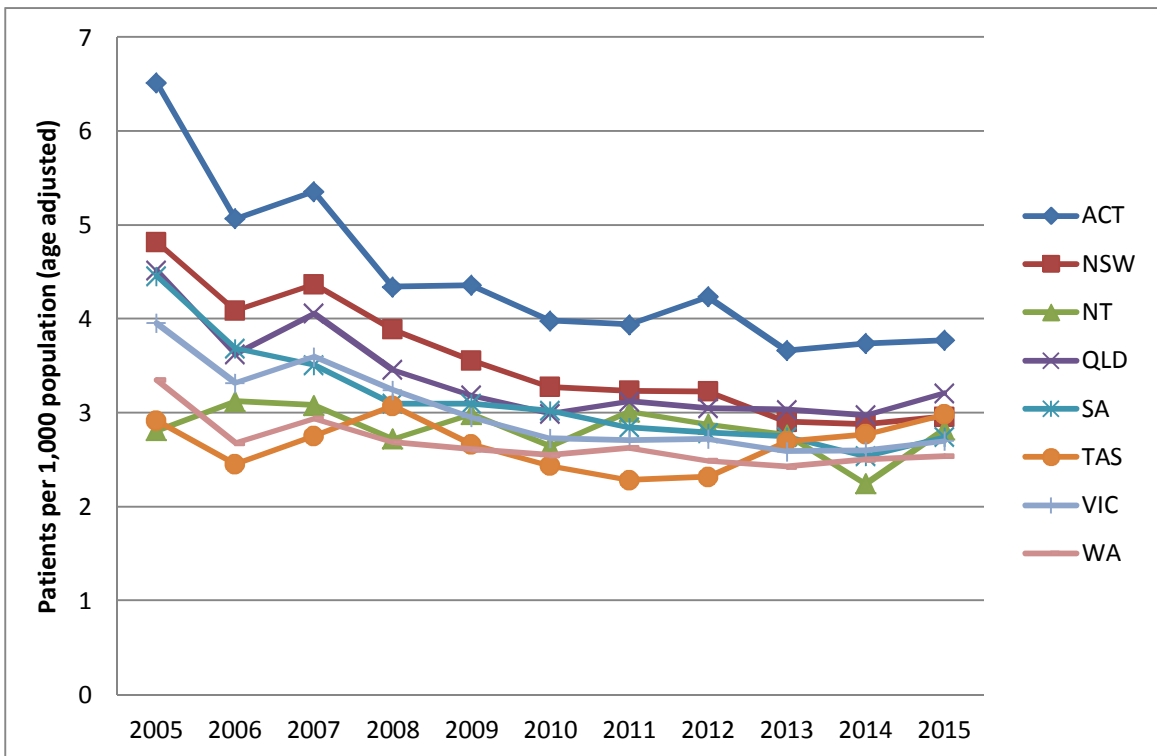


Figure 8: Patients per 1000 population (age adjusted rate) initiating to osteoporosis therapy by State.

Note: The age adjusted rate uses the Direct Method¹⁸ and is based on the Australian age distribution of the ABS Estimated Residential Population in the reference year 2011.

Comparing Figures 7 and 8 shows the effect of the age adjustment. The jurisdictions affected most by the adjustment are NT and ACT (adjusted upwards because of younger populations) and TAS and SA (adjusted downwards because of older populations). There is also a slight increase in the downward trend of the age adjusted rate compared to the raw rate because of the overall ageing of the population over the 11 year period.

Figure 8 shows that the age adjusted rate is highest in the ACT with all other jurisdictions being approximately similar. The rate of initiation to osteoporosis therapy declined in most jurisdictions from 2005, but this trend started to reverse in approximately 2013.

Figure 9 shows prevalent treatment rates in each state adjusted for age.

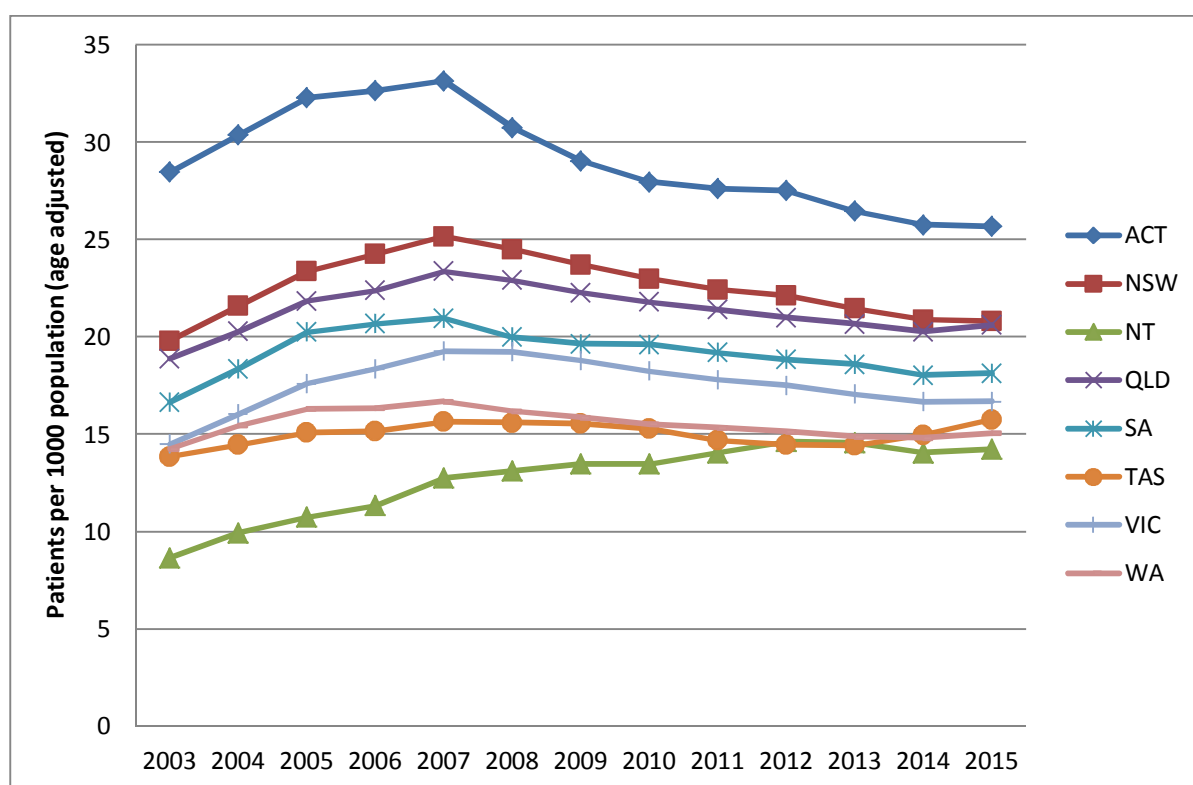


Figure 9: Patients per 1000 population (age adjusted rate) prevalent to osteoporosis therapy by State.

The prevalent patients show a similar picture to the initiating patients, with ACT being the highest. A difference is that NSW and QLD are slightly higher than the other jurisdictions. The decline in prevalent patients has flattened out, but has not yet reversed in most jurisdictions (with the possible exception of QLD and TAS).

Noting the very high uptake of denosumab nationally, Figure 10 shows rates of initiations to denosumab in each state.

¹⁸ [Principles on the use of direct age-standardisation in administrative data collections](#), September 2011, AIHW

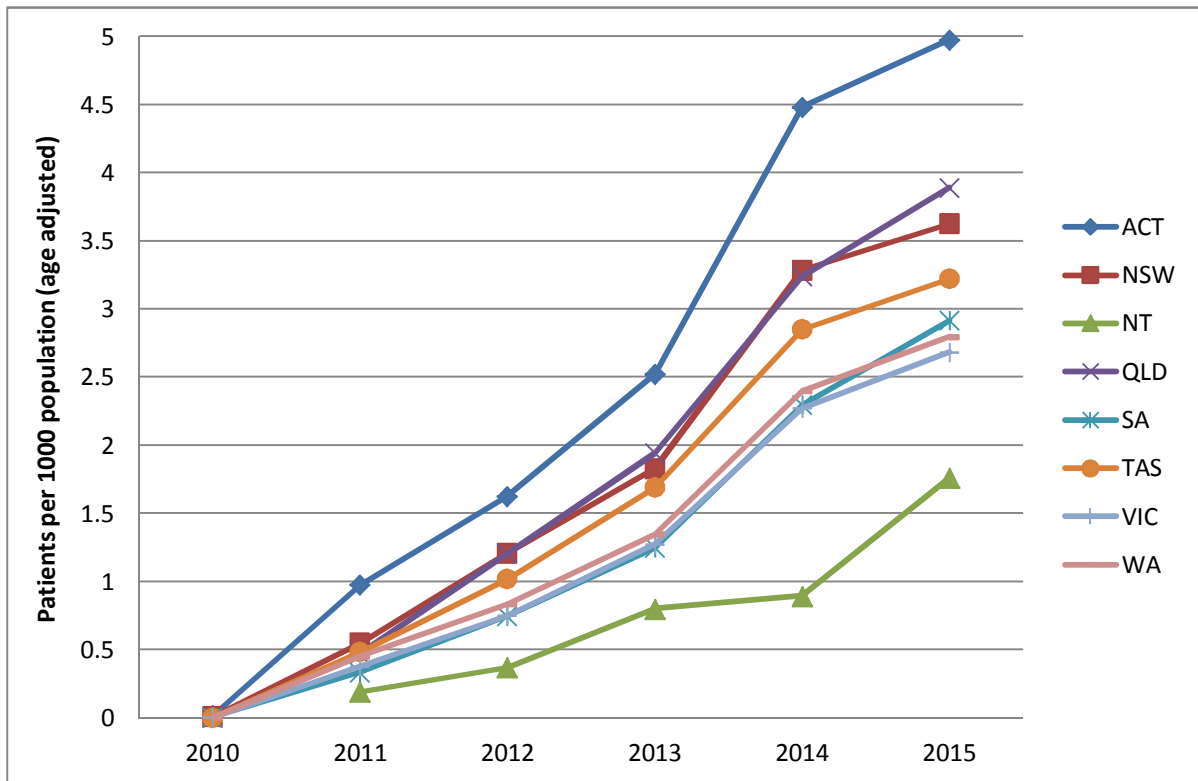


Figure 10: Patients per 1000 population (age adjusted rate) initiating denosumab by State. Note: this measure is patients initiating denosumab, not necessarily initiating osteoporosis therapy on denosumab.

Comparing Figures 8 and 10 shows that even though NT has a similar rate of initiation to osteoporosis therapy to other jurisdictions, this is not the case for initiations to denosumab (ie. NT has a comparatively low rate).

Supply of medicines via Remote Area Aboriginal Health Services (RAAHS) are not captured in the above data and so use may be underestimated in States with this service to a very small extent. Appendix C shows packs of osteoporosis medicines supplied to RAAHS by State and processed between 2010 and 2015. The number of denosumab packs supplied to RAAHS in the NT was very low (i.e. 6 packs in 2015), so inclusion of this data would have negligible impact on the rates reported in Figure 10.

Prescribers

The majority of osteoporosis therapy is initiated by GPs. Of the 72,132 patients initiated to therapy in 2015, 59,735 were initiated by GPs (82.8%). Other frequent prescribers of osteoporosis medicines include endocrinologists and rheumatologists.

Prescriptions

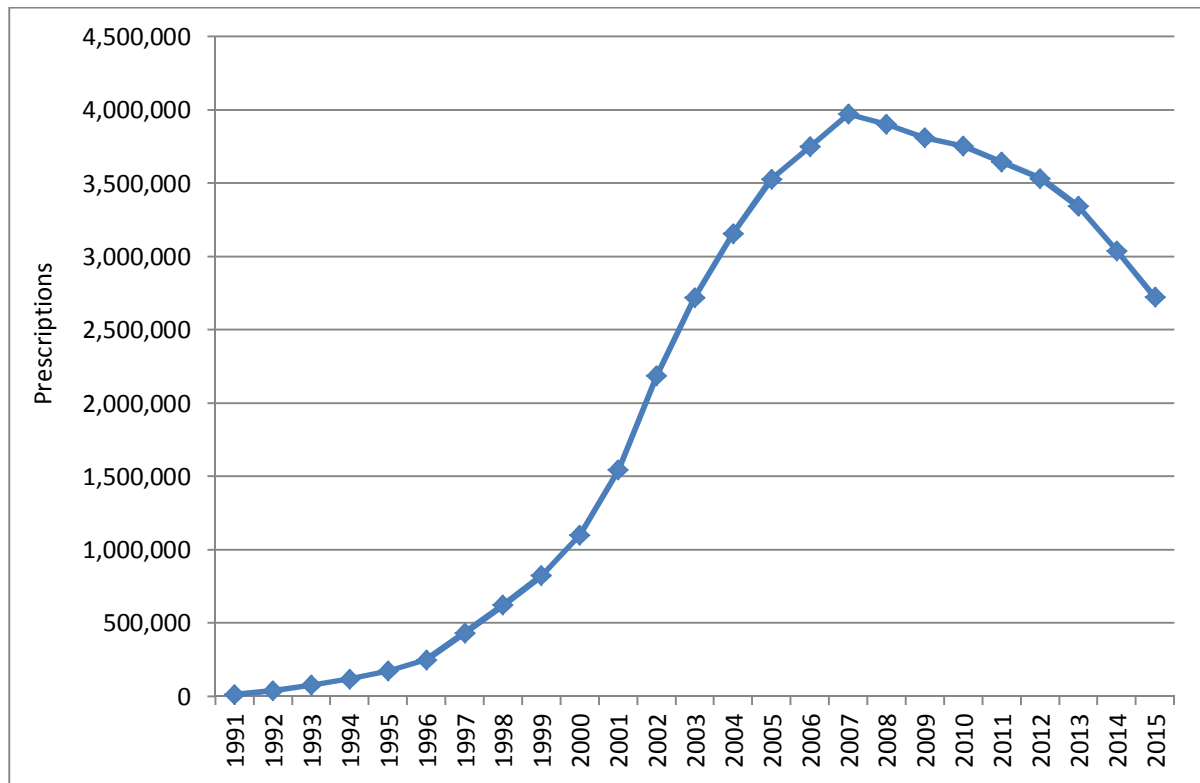


Figure 11: PBS & RPBS prescriptions for osteoporosis drugs

Figure 11 shows that prescription supply peaked in 2007 and has been decreasing since. This is despite that fact that prevalent patient numbers are increasing slightly (see Figure 1) and is a reflection of patients using denosumab and zoledronic acid which have lower frequency of supply (see the days to re-supply analysis below).

Prescriptions by drug

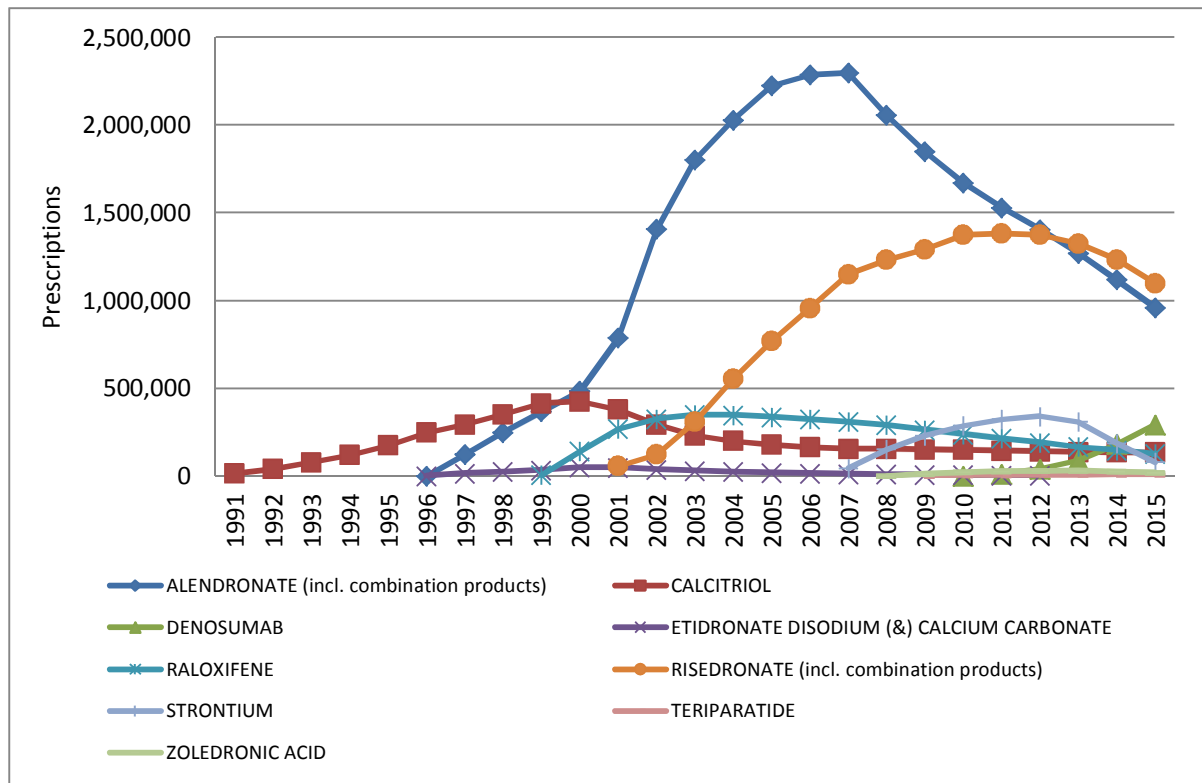


Figure 12: Prescriptions by drug

Figure 12 shows that despite the recent dominance of denosumab in the market (see initiating and prevalent patients in Figures 2 and 4 respectively) this is not reflected in the prescription count because of the low frequency of supply (ie. one prescription every 6 months, see “Days to re-supply” analysis below).

Days to re-supply by drug

The dose regimens for the osteoporosis medicines vary widely (Table 2). The PBS maximum quantities for the parenteral medicines provide sufficient supply (based on the dose in the Product Information) for 28 days of teriparatide, 6 months of denosumab and 12 months of zoledronic acid.

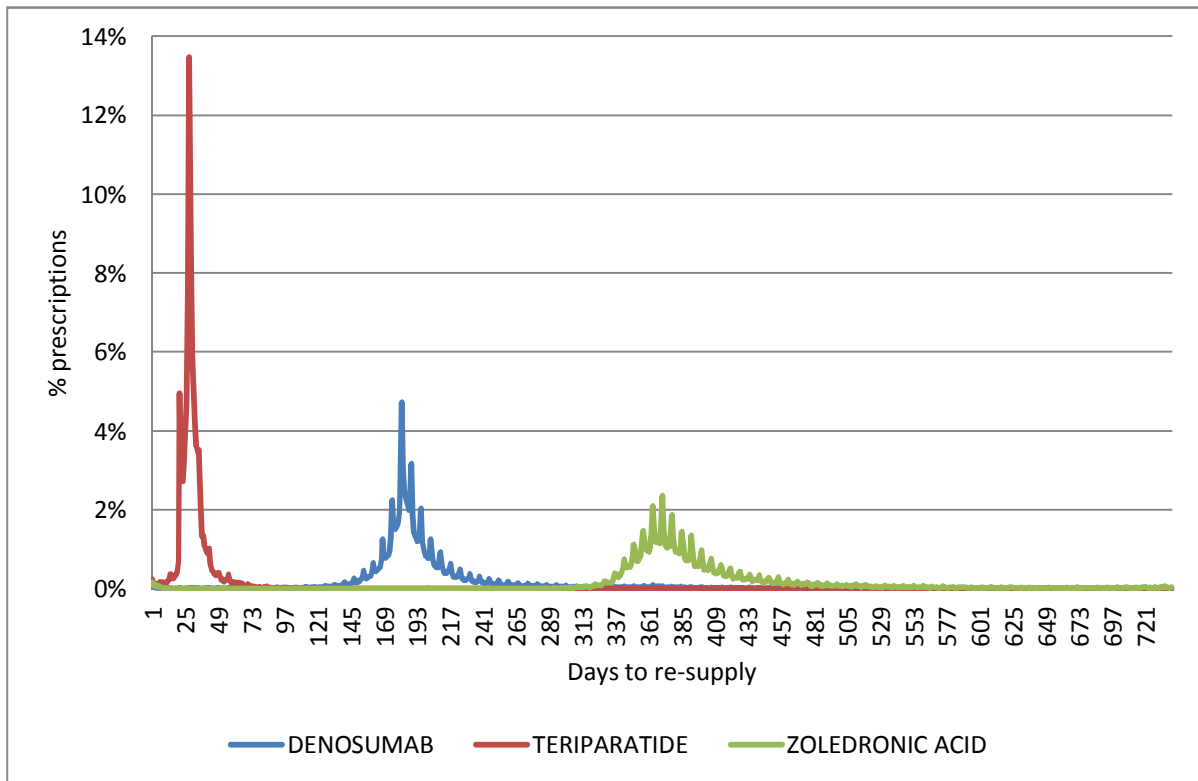


Figure 13: Percentage distribution of prescriptions for each injectable or IV infusion drug by the number of days to re-supply. Note: Scripts can be re-filled by any item of the same drug with an osteoporosis indication. See Methods section for details. The distributions are expressed as % of scripts for each drug, rather than raw script counts to make the distributions more easily comparable

Figure 13 shows that number of days to re-supply for the subcutaneous and IV infusion drugs corresponds with the expected frequency of supply. The most common number of days to re-supply are 28, 182 and 371 for teriparatide, denosumab and zoledronic acid respectively.

Figure 14 presents the time to re-supply distribution for the oral medicines. The PBS maximum quantities of the oral medicines provide sufficient supply (based on the dose in the Product Information) for 28 days of oral alendronate and risedronate (and combination items), raloxifene and strontium; 50 days for calcitriol and 90 days for etidronate with calcium (See listing details at www.pbs.gov.au).

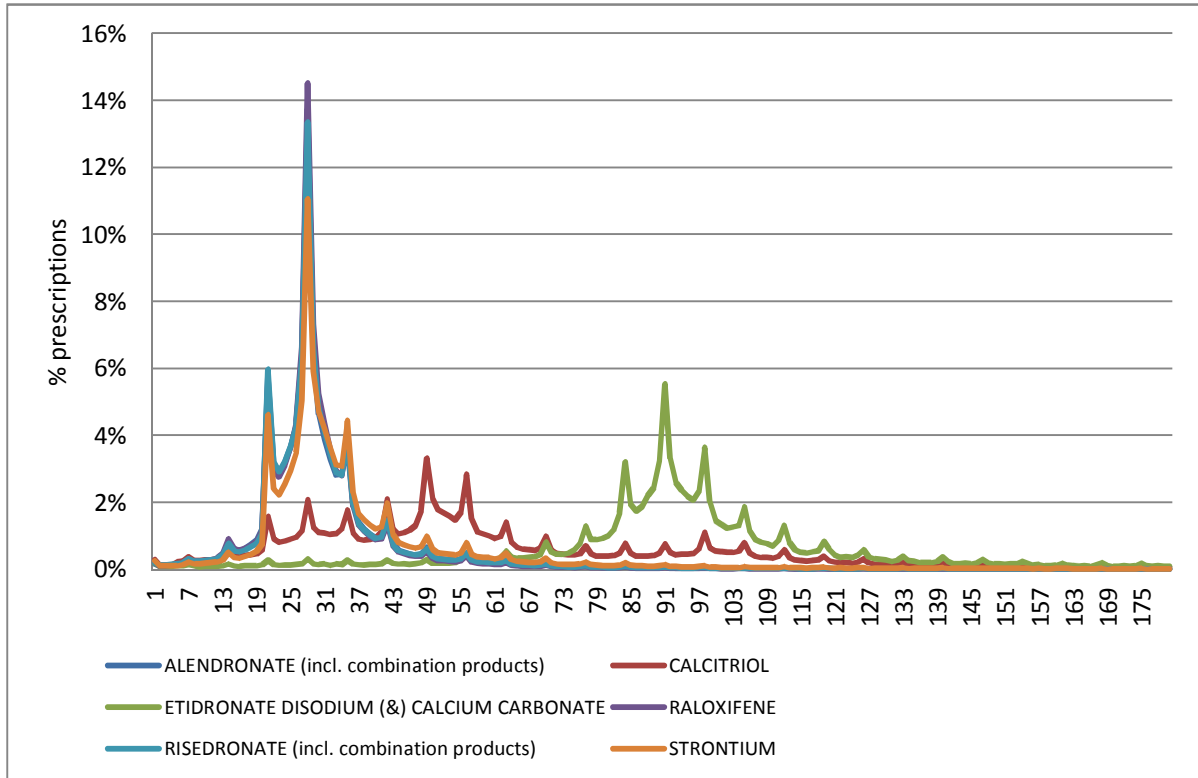


Figure 14: Percentage distribution of prescriptions for each oral drug by the number of days to re-supply. Note: Scripts can be re-filled by any item of the same drug. See Methods section for details. The distributions are expressed as % of scripts for each drug, rather than raw script counts to make the distributions more easily comparable.

The most common number of days to re-supply are 49 and 91 for calcitriol and the etidronate co-pack respectively. For all other oral drugs the most common number of days to resupply is 28 days.

Mode and median days to resupply for each medicine are presented in Table 6. Overall, it appears that osteoporosis medicines are dispensed at time intervals consistent with the recommended dose regimens and may indicate good adherence.

Table 6: Summary statistics for days to re-supply

| Drug | Days to re-supply | | |
|---|-------------------|--------|------------|
| | Mode | Median | n |
| ALENDRONATE (incl. combination products) | 28 | 28 | 21,375,651 |
| RISEDRONATE (incl. combination products) | 28 | 28 | 13,278,362 |
| RALOXIFENE | 28 | 28 | 3,175,606 |
| CALCITRIOL | 49 | 55 | 1,900,771 |
| STRONTIUM | 28 | 31 | 1,778,766 |
| DENOSUMAB | 182 | 188 | 257,357 |
| ETIDRONATE DISODIUM (&) CALCIUM CARBONATE | 91 | 93 | 128,669 |
| ZOLEDRONIC ACID | 371 | 383 | 66,566 |
| TERIPARATIDE | 28 | 29 | 41,951 |

Government Expenditure

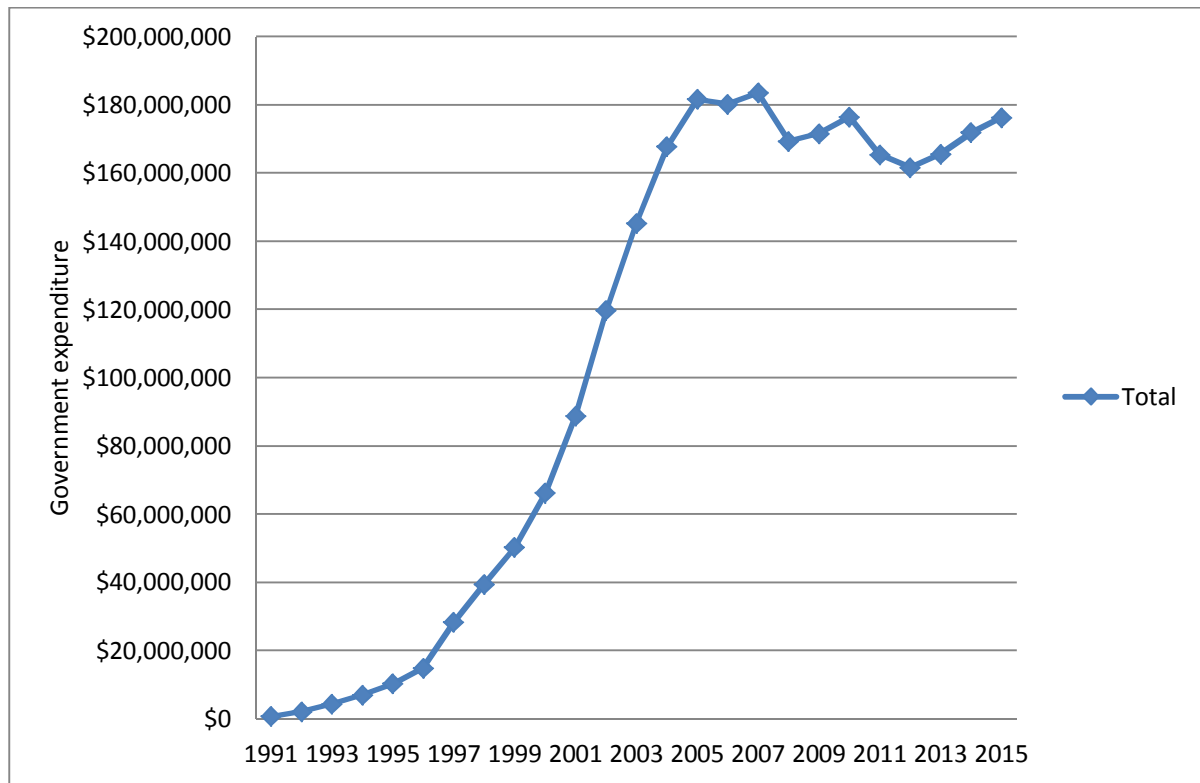


Figure 15: Government expenditure on osteoporosis drugs

Figure 15 shows that total government expenditure peaked in 2007 (the same year as prescription utilisation). It then declined until 2012, after which it increased and is currently at a similar level to the peak in 2007. The price of bisphosphonates has reduced significantly since 2012 however total government expenditure for osteoporosis medicines has not declined to a similar extent because during the same period there has been high uptake of denosumab which is in the F1 formulary.

Table 7: Expenditure, prevalent patients (from Figure 1), and expenditure per patient

| Year | Government PBS expenditure | Prevalent patients | Average annual government PBS expenditure per patient |
|------|----------------------------|--------------------|---|
| 2003 | \$145,381,057 | 316,691 | \$459 |
| 2004 | \$167,778,503 | 352,553 | \$476 |
| 2005 | \$181,668,831 | 391,036 | \$465 |
| 2006 | \$180,298,735 | 412,611 | \$437 |
| 2007 | \$183,607,637 | 440,958 | \$416 |
| 2008 | \$169,446,744 | 442,473 | \$383 |
| 2009 | \$171,618,104 | 441,798 | \$388 |
| 2010 | \$176,528,610 | 442,952 | \$399 |
| 2011 | \$165,706,661 | 445,529 | \$372 |
| 2012 | \$162,641,747 | 450,983 | \$361 |
| 2013 | \$167,544,423 | 452,945 | \$370 |
| 2014 | \$175,242,583 | 455,957 | \$384 |
| 2015 | \$180,910,066 | 471,497 | \$384 |

Table 7 shows that expenditure per patient decreased until 2008 and has remained relatively constant since.

Government Expenditure by drug

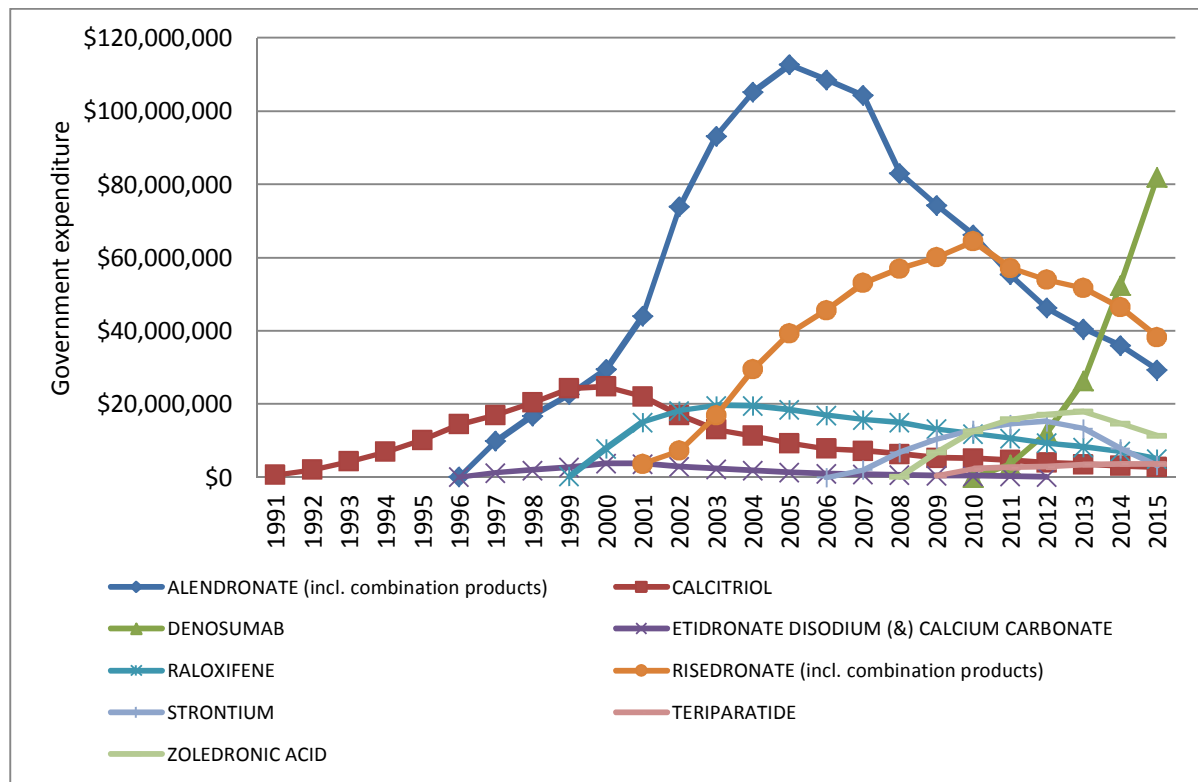


Figure 16: Government expenditure by drug

Predicted vs Actual utilisation for Denosumab333

Denosumab was first listed in December 2010 and the number of patients initiating in that month was relatively low (129 compared to 10,514 in 2011). As calendar year prevalent and initiating patient counts had already been calculated previously in this analysis, it was decided that calendar year 2011 was a reasonable approximation to the first year of listing for the purpose of comparing predicted and actual utilisation.

Approaches taken to estimate utilisation of denosumab

First recommended submission (July 2010 PBAC)

Listed on the PBS on a 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 in December 2010 and changed to STREAMLINED in March 2012. The osteoporosis market was assumed to grow by 3% and a denosumab uptake rate of ■% to ■% of the market was assumed in listing years 1 to 5.

First listing extension (March 2012 PBAC)

The listing of denosumab was extended to the treatment of osteoporosis for women aged 70 years and above with a BMD T score of -2.5 or less.

The submission used the Medicare Australia website, a report titled 'The Burden of Brittle Bones' (Osteoporosis Australia 2007) and a 10% sample of the PBS dispensing data to establish the size of the existing osteoporosis market and inform future growth rates. The submission used the Geelong Osteoporosis Study to estimate the size of the new PBS population (ie. those patients with BMD between -3.0 and -2.5). The DUSC report, Anti-resorptive drugs for the treatment of osteoporosis (February 2009) was used to estimate the BMD testing rate. The submission estimated minimal expansion of the market due to the extension of listing. That is, ■% to ■% in years 1 to 5 post listing respectively. The expected denosumab uptake rate in this expanded market was ■% to ■% in years 1 to 5 post listing respectively. The listing was changed in August 2012.

Second listing extension (July 2013 PBAC)

The restriction was expanded to include males and the listing was changed in December 2013. This extension was expected to expand the potential denosumab market by 17%. However the predicted uptake rates were ■% in year 1 to ■% in year 5, so after incorporating these uptake rates the predicted denosumab market expansion was ■% in year 1 to ■% in year 5.

This submission also estimated the effect of both the extensions to listing on denosumab utilisation. The predicted number of prescriptions for postmenopausal osteoporosis in this submission was actually less than that in the original submission (except in Year 5, see Table 8) even though the restriction was extended to include women with a BMD T score of

-2.5 or less on 1/8/2012. This was because the updated prediction had regard to the slower than expected uptake rate. This submission did not estimate patient numbers.

The original and updated estimates are shown in Table 8.

Table 8: Predicted vs Actual utilisation of denosumab

| | | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|----------------------|---|--------------------------|--------------|--------------|--------------|--------------|
| | | 2011 | 2012 | 2013 | 2014 | 2015 |
| Prescriptions | Predicted – original | ████ | ████ | ████ | ████ | ████ |
| | Predicted - Updated Postmenopausal Osteoporosis (in 2 nd listing extension submission) | ████ | ████ | ████ | ████ | ████ |
| | Predicted - Male Osteoporosis (in 2 nd listing extension submission) | █ | | ████ | ████ | ████ |
| | Predicted - Updated Total (P) | ████ | ████ | ████ | ████ | ████ |
| | Actual (A) | 13,460 | 45,666 | 97,679 | 194,337 | 309,811 |
| | % Difference (A-P)/P | ████ | ████ | ████ | ████ | ████ |
| | Prevalent Patients | Predicted – original (P) | ████ | ████ | ████ | ████ |
| Predicted – updated* | | na | na | na | na | na |
| Actual (A) | | 10,514 | 31,816 | 64,690 | 124,931 | 191,439 |
| % Difference (A-P)/P | | ████ | ████ | ████ | ████ | ████ |
| R/PBS expenditure | Predicted - original** | ████████ | ████████ | ████████ | ████████ | ████████ |
| | Predicted - Updated Total (P) | ████████ | ████████ | ████████ | ████████ | ████████ |
| | Actual (A) | \$3,859,383 | \$13,249,014 | \$28,313,153 | \$55,800,359 | \$86,621,284 |
| | % Difference (A-P)/P | ████ | ████ | ████ | ████ | ████ |

Source of predicted use: Original estimates are from the submission to the July 2010 PBAC. Updated estimates are from the submission to the July 2013 PBAC.

* Patients numbers estimates were not included in the submission to the July 2013 PBAC.

** based on listing DPMQ of \$304.87 rather than submission value.

Table 8 shows that actual prescriptions and expenditure exceeded the updated predictions because market share had been greater than anticipated. In 2015 prescriptions and expenditure were approximately double that predicted. A key assumption in the original submission was that denosumab would take █████% of the osteoporosis market by year 5 (ie. 2015). Figure 4 shows that denosumab had 40.6% (191,439 / 471,497) of prevalent patients in 2015. Also Figure 2 shows that denosumab had 48.9% (35,260 / 72,132) of incident patients in 2015.

The previous predicted versus actual analysis of denosumab considered by DUSC in February 2014 found that denosumab was used both for patients who are new to osteoporosis therapy and in patients who have been on prior osteoporosis medicines. At the time of the last review most patients on denosumab had switched from another medicine but the proportion of patients initiating osteoporosis therapy on denosumab was increasing. Table 9 shows how the proportion of new and previously treated patients

commencing denosumab has varied over time. The number of prior therapies is also presented.

Table 9: Number of osteoporosis drugs initiated prior to initiating denosumab

| % of Patients | Year of initiation to denosumab | | | | |
|--|---------------------------------|-------|-------|-------|-------|
| | 2011 | 2012 | 2013 | 2014 | 2015 |
| Number of drugs initiated prior to denosumab | | | | | |
| None | 22% | 27% | 31% | 36% | 43% |
| 1 | 40% | 40% | 40% | 39% | 37% |
| 2 | 26% | 23% | 21% | 19% | 15% |
| 3 | 9% | 7% | 6% | 5% | 4% |
| 4 | 2% | 2% | 1% | 1% | 1% |
| 5 | 0.5% | 0.2% | 0.2% | 0.2% | 0.1% |
| 6 | 0.03% | 0.04% | 0.03% | 0.02% | 0.02% |
| Total | 100% | 100% | 100% | 100% | 100% |

Note: Alendronate and Risedronate combination products are counted under the plain drug names. Prior initiations are counted back to Jan 2005.

Quality Use of Medicines

A large number of patients had switched from other osteoporosis medicines to denosumab over the past 5 years. With denosumab being a six monthly subcutaneous injection there is possibility of confusion if patients switched to denosumab are not advised to cease taking other osteoporosis medicines. This is also relevant for zoledronic acid and could also occur when transitioning between other osteoporosis medicines.

Table 10 shows prescription supply sequences for patients supplied bisphosphonates (plain or combination), teriparatide, raloxifene or strontium in the 5 months following their first script of denosumab. Only initiations to denosumab from the first listing date (December 2010) to the end of October 2015 are included so that each patient can have the full 5 month follow-up. There were 209,542 patients in this analysis cohort. The results show that a total of 9,537 patients (4.6%) were supplied at least one script of a bisphosphonate, strontium, raloxifene or teriparatide within 5 months of initiating denosumab, thus potentially co-administering denosumab with one of these drugs.

Table 10: Supplies of other osteoporosis medicines within 5 months after initiation to denosumab for osteoporosis

| Prescription supply sequence | Patients | % Patients | Rank |
|---|----------------|--------------|------|
| DENOSUMAB->RISEDRONATE | 1,435 | 0.68% | 1 |
| DENOSUMAB->ALENDRONATE | 1,363 | 0.65% | 2 |
| DENOSUMAB->STRONTIUM | 599 | 0.29% | 3 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE | 477 | 0.23% | 4 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE | 462 | 0.22% | 5 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE->RISEDRONATE | 321 | 0.15% | 6 |
| DENOSUMAB->RISEDRONATE(sd) | 316 | 0.15% | 7 |
| DENOSUMAB->ALENDRONATE(sd) | 284 | 0.14% | 8 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE | 260 | 0.12% | 9 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE->ALENDRONATE | 255 | 0.12% | 10 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE | 232 | 0.11% | 11 |
| DENOSUMAB->RALOXIFENE | 197 | 0.09% | 12 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE | 191 | 0.09% | 13 |
| DENOSUMAB->STRONTIUM->STRONTIUM | 177 | 0.08% | 14 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE | 169 | 0.08% | 15 |
| DENOSUMAB->STRONTIUM(sd) | 155 | 0.07% | 16 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE | 119 | 0.06% | 17 |
| DENOSUMAB->STRONTIUM->STRONTIUM->STRONTIUM | 94 | 0.04% | 18 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE | 87 | 0.04% | 19 |
| DENOSUMAB->RISEDRONATE->DENOSUMAB | 81 | 0.04% | 20 |
| DENOSUMAB->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE | 80 | 0.04% | 21 |
| DENOSUMAB->ALENDRONATE->DENOSUMAB | 75 | 0.04% | 22 |
| DENOSUMAB->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM | 67 | 0.03% | 23 |
| DENOSUMAB->RALOXIFENE(sd) | 64 | 0.03% | 24 |
| DENOSUMAB->RALOXIFENE->RALOXIFENE | 58 | 0.03% | 25 |
| DENOSUMAB->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM | 58 | 0.03% | 26 |
| DENOSUMAB->RISEDRONATE(sd)->RISEDRONATE | 51 | 0.02% | 27 |
| DENOSUMAB->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE | 49 | 0.02% | 28 |
| DENOSUMAB->RALOXIFENE->RALOXIFENE->RALOXIFENE->RALOXIFENE | 48 | 0.02% | 29 |
| DENOSUMAB->ALENDRONATE(sd)->ALENDRONATE | 48 | 0.02% | 30 |
| DENOSUMAB->RALOXIFENE->RALOXIFENE->RALOXIFENE | 46 | 0.02% | 31 |
| DENOSUMAB->RISEDRONATE->RISEDRONATE(sd) | 40 | 0.02% | 32 |
| DENOSUMAB->ALENDRONATE->ALENDRONATE(sd) | 39 | 0.02% | 33 |
| DENOSUMAB->STRONTIUM->DENOSUMAB | 32 | 0.02% | 34 |
| DENOSUMAB->TERIPARATIDE | 31 | 0.01% | 35 |
| DENOSUMAB->ALENDRONATE(sd)->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE->ALENDRONATE | 28 | 0.01% | 36 |
| DENOSUMAB->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM->STRONTIUM | 28 | 0.01% | 37 |
| DENOSUMAB->RISEDRONATE(sd)->RISEDRONATE->RISEDRONATE->RISEDRONATE | 28 | 0.01% | 38 |
| DENOSUMAB->RISEDRONATE(sd)->RISEDRONATE->RISEDRONATE->RISEDRONATE->RISEDRONATE | 27 | 0.01% | 39 |
| Other sequences including bisphosphonates, teriparatide, raloxifene or strontium | 1,304 | 0.65% | |
| Total sequences including bisphosphonates, teriparatide, raloxifene or strontium | 9,537 | 4.55% | |
| Other sequences not including bisphosphonates, teriparatide, raloxifene or strontium | 200,005 | 95.4% | |
| Total | 209,542 | 100% | |

Note: (sd) after a drug indicates that it was supply on the same day as the drug before it in the sequence.

DUSC also requested an assessment of the frequency of administration of denosumab. The time to re-supply analysis indicates that most often resupply of denosumab occurs at 182 days (Table 6 and Figure 13). However there may be a QUM concern if patients are having denosumab injections more frequently than 6 months or if there is wastage of medicine dispensed but never administered.

An assessment of the number of denosumab supplies in the 5 months following a first script of denosumab (same cohort as presented in Table 10) is presented in Table 11.

Table 11: Number of denosumab supplies within 5 months of initiating denosumab

| Number of denosumab supplies | Patients | % Patients |
|------------------------------|----------|------------|
| 1 | 200,023 | 95.4 |
| 2 | 9,342 | 4.45 |
| 3 | 152 | 0.07 |
| 4 | 12 | 0.005 |
| 5 | 10 | 0.004 |
| 6 | 2 | 0.0009 |
| 7 | 1 | 0.0004 |
| Total | 209,542 | 100 |

The vast majority of patients (95.4%) appropriately did not receive a subsequent supply in this time period. A very small number of patients had a frequency of resupply that could indicate that denosumab is being administered more frequently than 6 monthly or that patients are having more prescriptions filled than are needed.

Analysis of utilisation of MBS items for bone densitometry

There are 7 MBS items for bone densitometry listed in the MBS Schedule. An analysis of the restrictions for these items showed they can be summarised into the following indication groups.

- Items 12306, 12309 & 12321 - 1 or more fractures after minimal trauma, or monitoring of low BMD
- Items 12312, 12315 & 12318 - diagnosis and monitoring of bone loss associated with various conditions
- Item 12323 - for a person aged 70 years or over

Figure 17 shows the utilisation of these MBS items grouped by these indications.

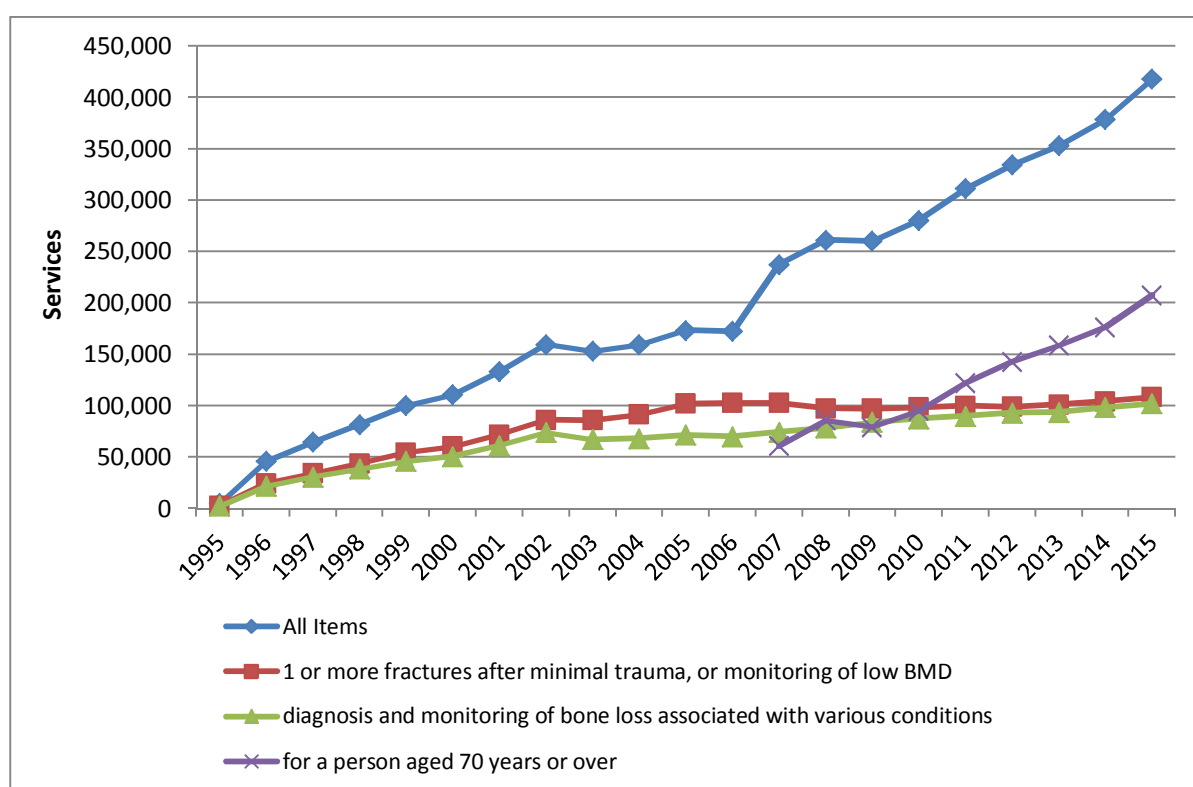


Figure 17: MBS services for bone densitometry items by indication Source: Medicare Item Reports (http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp). Note that these reports are based on quarter of processing, not quarter of service

Figure 17 shows that there was a large increase in the number of services in 2007 when a new MBS item was listed (12323) specifically for people aged 70 years and over. This listing was in response the expanded PBS listing of alendronate in April 2007 to patients who are 70 years or more at risk of fracture based on BMD testing (T-score ≤ -3.0). Use of MBS bone densitometry services has continued with an annual growth of 5-11% per annum.

It is not possible to count patients from the publically available data used for Figure 17. The item restrictions specify a limit of “1 service only in a period of 24 months” for all items

except for items 12312 and 12321, which specify a limit of “1 service only in a period of 12 months” and item 12323 (for a person aged 70 years or over) which had no specific time based restriction. Thus the non-age based indication plots in Figure 17 are likely to have only one service per patient per year.

Safety of osteoporosis medicines

DUSC (June 2016) requested that updated advice be sought from the Therapeutic Goods Administration (TGA) on the safety of denosumab particularly given the large number of people, many who are older, using this monoclonal antibody. DUSC has previously raised concern about the possible increased risks of infection with denosumab and noted that there have been case reports of peripheral neuropathy.

When recommending listing of denosumab on the PBS in July 2010 the PBAC was concerned about the long-term toxicity of denosumab. In addition to concerns about risks of cancer and serious infection, the PBAC noted that denosumab markedly suppressed osteoclast and osteoblast counts compared to placebo and alendronate. Dynamic bone formation parameters were also suppressed. Further, the FDA review suggests that long-term denosumab treatment may lead to delayed fracture healing, osteonecrosis of the jaw (ONJ) or atypical fracture. The PBAC also noted that the Advisory Committee on Prescription Medicines had recommended a risk management plan as a pre-requisite for registration, including the establishment of a patient registry. The PBAC requested that it be kept informed about any toxicity signals that may arise from this post-marketing surveillance.¹⁹

In the pre-DUSC response to the October 2013 meeting, the Sponsor of denosumab noted publication of six year follow-up data in women with post-menopausal osteoporosis from the FREEDOM trial.²⁰ A subsequent publication has reported 8 year follow-up data.²¹

The Product Information (PI) for denosumab for the treatment of osteoporosis (Prolia®) was revised in June 2016 to include the potential risk of QT prolongation associated with hypocalcaemia²². This issue was also reported in a TGA Medicines Safety Update in August 2016.²³ There was also an update regarding denosumab in the TGA Medicines Safety Update in April 2016.²⁴ However this was in regard to the higher dose product, Xgeva® which is for the prevention of skeletal-related events in adults with bone metastases from solid tumours. Xgeva is now contraindicated in patients with unhealed lesions from dental or oral surgery due to increased risk of osteonecrosis of the jaw. The PI was updated in March 2016.

¹⁹ PBAC Public Summary Document, Denosumab, July 2010, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-07/pbac-psd-Denosumab-july10>

²⁰ Bone et al. The effect of 3 or 6 years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. *J Clin. Endocrinol Metab* 2013 Nov; 98(11): 4483–4492

²¹ Papalopolous et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. *Osteoporosis Int* 2015 Dec;26(12):2773-83

²² TGA Product Information (PI) <https://www.tga.gov.au/product-information-pi>

²³ <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-7-number-4-august-2016>

²⁴ <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-7-number-2-april-2016>

The Secretariat requested that TGA provide an update to DUSC on the safety of denosumab.

Discussion and Secretariat comments

Osteoporosis is a very common preventable condition that is under-diagnosed and under-treated.^{25,26} Osteoporosis medicines are used to reduce the risk of subsequent fractures in people who have already experienced a minimal trauma fracture and to reduce the risk of a first fracture in patients with low bone mineral density meeting certain criteria.

The number of patients treated with PBS medicines for osteoporosis was steady between 2007 and 2014, but age-standardised rates indicate a 15% decline in treatment rates over this time. There is likely to be under-treatment both in patients who have already experienced a minimal trauma fracture^{25,26} and in patients with low BMD who have not yet experienced a fracture.²⁷ Further data will be needed to confirm if a small increase in treatment rate in 2015 (0.5%) is sustained.

One contributing factor to the decline in treatment rates may be concerns about the safety of osteoporosis medicines. In the mid-2000s there were several warnings in the medical literature and from the TGA regarding bisphosphonates²⁸. In February 2005 and August 2006 TGA published items in the Australian Adverse Drug Reactions Bulletin drawing attention to the association of bisphosphonates and ONJ. In December 2007 the TGA published a whole report on this subject. Also in December 2007 there was a report on ABC Television's "The 7.30 Report" on ONJ being related to alendronate²⁸.

Patients having treatment "holidays" may also influence treatment rates. Analysis of PBS prescription data shows an increasing number of patients who have had a break in treatment for at least 2 years returning to treatment (Figure 1). The optimal duration of treatment of osteoporosis medicines is uncertain. Drug holidays from bisphosphonates or switching to another medicine may be considered for some patients but there is limited evidence to guide this decision.^{26,29,30,31}

²⁵ Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: The Australian Bone Care Study. *Journal of Bone and Mineral Research* 2004;19(12):1969–75.

²⁶ The Royal Australia College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in post-menopausal women and older men. February 2010. Available at http://www.racgp.org.au/download/documents/Guidelines/Musculoskeletal/racgp_osteo_guideline.pdf

²⁷ <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-07/pbac-psd-alendronate-july11>

²⁸ Peeters, Geeske, Tett, Susan E., Duncan, Emma L., Mishra, Gita D., & Dobson, Annette J. (2014) Osteoporosis medication dispensing for older Australian women from 2002 to 2010: Influences of publications, guidelines, marketing activities and policy. *Pharmacoepidemiology and Drug Safety*, 23(12), pp. 1303-1311. <http://onlinelibrary.wiley.com/doi/10.1002/pds.3703/epdf>

²⁹ Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; 296(24): 2927–2938. doi:10.1001/jama.296.24.2927.

³⁰ Adler RA et al. Managing osteoporosis in patients on long term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral research. *J Bone Miner res* 2016; 31:16-35

³¹ Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2016

Older people living in residential aged care facilities are at considerably higher risk of suffering fractures than older people living in the community.³² Rates of treatment in this setting are unknown. DUSC suggested that an analysis of uptake of osteoporosis medicines in residential aged care facilities be undertaken. Use of medicines in residential aged care facilities (RACF) cannot be readily distinguished in the PBS prescription data and additional data sources and/or data linkage would be required. This has been flagged as a potential future area of research. The roll-out of the standardised PBS medication chart in residential aged care facilities may provide improved data to understand extent of use of osteoporosis medicines in this setting.

Despite the valid concern of under-diagnosis and under-treatment of osteoporosis, there has been a continual increase in the utilisation of MBS services for BMD testing (Figure 17). There is a potential for patients with low fracture risk to be inappropriately treated.³³ Fracture risk calculators are considered useful for identifying patients with low fracture risk who do not require treatment.³⁴

Denosumab is replacing the other agents in the osteoporosis market (see Figures 2 and 4). The extent of this replacement is greater than expected, as evidenced by the number of prescriptions and government expenditure for denosumab being approximately [REDACTED] that predicted for 2015 (see Table 8). The convenience of a 6 monthly subcutaneous injection may be one reason for the high uptake of denosumab. Preference and satisfaction questionnaires completed in clinical trials (noting limitations including that none of the studies were undertaken in Australia), indicate that patients prefer the less frequent denosumab regimen over weekly oral alendronate.³⁵

It is important that up to date, balanced information on the benefits and risks of osteoporosis medicines is available to clinicians and consumers particularly given past experience that safety concerns have impacted use of these medicines. The benefit to risk profile of bisphosphonates is now well understood, the risk profile of strontium has been recently been revised, and the Product Information for denosumab has recently been updated to include the potential risk of QT prolongation associated with hypocalcaemia. A range of awareness and education activities are underway that may increase treatment rates and optimise management of osteoporosis.^{36,37}

This report adds significantly to previous reviews of the utilisation of osteoporosis medicines that have relied on prescription counts and/or costs to monitor use. Prescription volumes have declined substantially because of the less frequent dosing regimens and prescription refills for zoledronic acid and denosumab (Figure 11). This information, in the absence of treatment rates, may be misleading. Assessing utilisation by counting the

³² Dugue et al Treatment for osteoporosis in Australian residential aged care facilities: consensus recommendations for fracture prevention. *MJA* 2010 Aug 2;193(3):173-9

³³ Fenton JJ et al. Osteoporosis overtreatment in a regional health care system. *JAMA Intern Med* 2016; 176: 391-393.

³⁴ Osteoporosis treatment: a missed opportunity. Frances Milat and Peter R Ebeling. *Med J Aust* 2016; 205 (4): 185-190. doi: 10.5694/mja16.00568

³⁵ Freemantle M et al. Final results of the DAPS (Denosumab Adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporosis Int* 2012 Jan;23(1):317-26

³⁶ <http://www.nps.org.au/publications/health-professional/nps-news/2015/osteoporosis>

³⁷ <http://www.knowyourbones.org.au/>

number of patients treated and adjusting for changes in the age distribution over time allows a more robust assessment of treatment rates in Australia.

Actions undertaken by the Secretariat

- A copy of the report has been provided to the TGA and an update was requested on the safety of denosumab particularly given the large number of people, many who are older, using this monoclonal antibody.
- A copy of the report has been provided to Osteoporosis Australia and the Royal Australia College of General Practitioners (RACGP) for comment.

DUSC consideration

DUSC noted that:

- Rates of treatment with osteoporosis medicines declined by 15% between 2007 and 2014 despite reports of increasing prevalence of osteoporosis. In 2015 the treatment rate increased. Further data will be needed to confirm if this increase is sustained.
- In 2015, 471,497 patients were treated with osteoporosis medicines through the PBS, and 15% of these people (72,132) commenced osteoporosis treatment for the first time.
- The average age when starting osteoporosis medicines is 71 years. This was similar between men and women.
- Osteoporosis is 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 has been much higher than expected. Approximately half of all 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.

The number of patients treated with PBS medicines for osteoporosis was steady between 2007 and 2014, but age-standardised rates indicated a 15% decline in treatment rates over this time. DUSC noted that there was a 3.4% increase in the number of prevalent patients in 2015 compared to 2014 but this only translated to a 0.5% increase in the treatment rate. DUSC considered that the lowering of the treatment rate may have occurred from safety concerns with the use of these medicines, such as the association of bisphosphonate drugs with osteonecrosis of the jaw and cardiovascular and venous thromboembolic risks with strontium. DUSC also considered that the clinical practice of taking drug 'holidays' from the bisphosphonates may also be a factor in the lower treatment rates. The analysis of PBS prescription data showed an increasing number of patients had a break in treatment for at least 2 years before returning to treatment. Patients continue to be monitored during these drug holidays and may continue to derive benefit given the mechanism of action and evidence of sustained effect beyond cessation of bisphosphonates. However, as patients are not supplied medicines during this time, they are not captured in the treatment rate analysis.

Denosumab is replacing the other agents in the osteoporosis market. The extent of this replacement was greater than expected, as evidenced by the number of prescriptions and government expenditure for denosumab being approximately [REDACTED] that predicted for 2015. DUSC noted that since August 2016, nurse practitioners have been permitted to initiate denosumab, which may lead to a further increase in its use. DUSC considered that the higher than expected use of denosumab may relate to patient and clinician preference and easier administration. Denosumab is a six monthly subcutaneous injection compared with oral bisphosphonates that require administration daily, weekly or monthly on an empty stomach with the patient needing to remain upright for at least 30 minutes. The different adverse event profiles may also be a factor contributing to the high uptake rate of denosumab. While the more common adverse events for oral bisphosphonates such as gastrointestinal disturbances are well understood, DUSC considered that adverse events for denosumab such as eczema may not be recognised or may be misattributed. DUSC considered that the six monthly frequency of denosumab administration may mean that it may not always be recorded on medication charts (for example in aged care settings) or be visible to all health practitioners involved in the care of the patient. There is also a risk of inadvertent co-administration of osteoporosis medicines. There were 9,537 patients (4.6%) supplied at least one prescription for a bisphosphonate, strontium, raloxifene or teriparatide within 5 months of initiating denosumab. DUSC considered that further education of general practitioners and pharmacists may be required to minimise the risk of co-administration of oral osteoporosis medicines with the injectable medicines, given 6 or 12 monthly. The sponsor of denosumab noted the finding that a small percentage of patients received a supply of a different osteoporosis medication within 5 months of initiation of denosumab and considered this finding to warrant further understanding and should also be explored for the other parenteral osteoporosis agent, IV zoledronic acid. If a quality use of medicine issue is confirmed, the sponsor indicated a willingness to work with relevant stakeholders to address this through appropriate educational activities.

DUSC noted that the sponsor of denosumab and clinicians consider that denosumab appears safe for use over extended periods time. DUSC considered that ongoing vigilance with the use of denosumab is required given the possibility of misattribution of adverse effects, the risk of hypocalcaemia particularly in patients with renal impairment, and that longer term data on efficacy and safety remain limited. DUSC noted that some patients commencing on denosumab are relatively young and may use denosumab for many years.

DUSC commented that the impact of denosumab on the immune system is not well understood particularly in the context of treatment in a large number of patients, many with multiple co-morbidities and who may be treated with multiple monoclonal antibodies. DUSC noted that while patients in residential care settings may be considered at higher risk of fractures than people living in the community, there may be a greater risk of adverse events and quality use of medicines concerns in this setting because of age and co-morbidities. DUSC noted the findings of a review of Ontario pharmacy claims data showing a greater use of denosumab over zoledronic acid in long-term care facilities,³⁸ but noted

³⁸ Burden et al. (2015) *Osteoporosis Int* 26:1525-1533.

that the use of osteoporosis medicines in residential aged care settings cannot not be identified in the PBS data alone.

DUSC noted that for bisphosphonates, a consensus statement had been developed to assess optimal durations of therapy that weighs up the benefits and risks and takes account of effects on bone that may continue after stopping these medicines (Adler et al 2015). Optimal use of denosumab, including duration and discontinuation, was yet to be established. The product information stated that in clinical studies examining the effects of discontinuation of denosumab (Prolia[®]), bone mass density returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with Prolia[®] is required to maintain the effect of the drug. DUSC noted that the time to resupply analysis (Figure 13) showed that although the majority of resupplies of denosumab occur at around six months, there is a long tail indicating that some patients may not be treated at the required interval for treatment effect. DUSC was concerned by reports in the published literature of vertebral fractures occurring after denosumab discontinuation and reiterated that ongoing vigilance and education on use of denosumab is required.

In the pre-DUSC response, the sponsor of denosumab claimed that in practice better health outcomes are being achieved for Australian osteoporosis patients with the introduction of denosumab. The sponsor presented a commissioned analysis of the 10% PBS sample and claimed that this showed that denosumab had a significant positive impact on long-term osteoporosis medication adherence in Australia. DUSC noted that the limited methods describing the analysis did not allow assessment of this claim. Further, no evidence was presented to establish that any improvement in adherence results in improved health outcomes compared with alternative therapies. DUSC considered that any claim of improved compliance and associated outcomes would need to be presented in the form of a major submission to the PBAC.

DUSC noted that denosumab was recommended on a cost-minimisation basis compared with zoledronic acid with an adjustment to the price to account for the different requirements for doctors' visits and administration. DUSC considered that monitoring requirements in clinical practice may not have been adequately accounted for in the cost-minimisation analysis and this may result in increased total costs to the health system. The product information for bisphosphonate therapy (including alendronate, risedronate, and zoledronic acid) and denosumab recommends monitoring for hypocalcaemia, vitamin D deficiency and renal impairment. While the PBAC had previously considered (July 2013) that the inclusion of calcium monitoring was not required for the cost-minimisation analysis, DUSC considered that monitoring in practice may differ, noting concerns with hypocalcaemia for denosumab. DUSC also considered that the requirement for continued use of denosumab compared with established practice for treatment holidays with bisphosphonates may impact on the comparative costs of the treatment options. DUSC also noted that the PBS expenditure per patient for osteoporosis had increased since 2012 as a result of pricing policy. Prices for zoledronic acid and other osteoporosis medicines had decreased while uptake of denosumab, which was in the F1 formulary and had not been subject to significant price reductions, had increased. Denosumab was subject to a 5% statutory price reduction on 1 April 2016.

DUSC noted that the report had been provided to Osteoporosis Australia, the Royal Australia College of General Practitioners (RACGP) and the sponsors of osteoporosis medicines listed on the PBS, for comment. Comments were received from Amgen Australia and the RACGP. DUSC noted that the RACGP considered that denosumab was a well-tolerated and effective treatment which appeared safe for use over the longer-term. DUSC noted Amgen Australia's response on the higher than expected use of denosumab, which the sponsor suggested could relate to the following factors: demonstrated efficacy across clinically important fracture sites; good tolerability; following the delisting of strontium ranelate, denosumab is the only subsidised non-bisphosphonate therapy for male and female patients; and its administration as a six monthly subcutaneous injection may promote adherence to therapy. DUSC noted the sponsor's suggestion to also seek comment on the report from the Australian and New Zealand Bone and Mineral Society (ANZBMS).

DUSC Actions

The DUSC requested that the report be provided to the PBAC.

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

The following sponsors have no comment; Actavis Pty Ltd, Amgen Australia Pty Ltd, Alphapharm Pty Ltd, Amneal Pharmaceuticals Pty Ltd, Apotex Pty Ltd, Arrow Pharma Pty Ltd, Aurobindo Pharma Pty Ltd, Bayer Australia Ltd, Dr Reddy's Laboratories Pty Ltd, Eli Lilly Australia Pty Ltd, Eris Pharmaceuticals Pty Ltd, Generic Health Pty Ltd, Hospira Pty Ltd, Merck Sharp & Dohme Pty Ltd, Novartis Pharmaceuticals Pty Ltd, Roche Products Pty Ltd, Sandoz Pty Ltd.

Disclaimer

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

The Department of Health (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^{39,40}

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.⁴¹

³⁹ TGA Product Information (PI) <https://www.tga.gov.au/product-information-pi>

⁴⁰ Australian Medicines Handbook 2013

⁴¹ Wiznenberg et al. Vitamin D and the musculoskeletal health of older adults. *Australian Family Physician* Vol. 41, no. 3, March 2012

Appendix B

Table B.1: 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 |
| 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 |
| 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. |

| | | |
|-----------|---|---|
| 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 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 | <p>Changed from Authority Required (STREAMLINED) to Restricted Benefit. Combination items including these drugs remained Authority Required (STREAMLINED)</p> |
| 1/08/2016 | STRONTIUM | <p>Delisted because the medicine was not cost-effective at the price proposed by the sponsor.</p> |

Appendix C

Table C.1: Osteoporosis drugs (packs) supplied via Remote Area Aboriginal Health Services

| Drug | Year of processing | STATE | | | | | | Total |
|---|--------------------|-----------|--------------|--------------|------------|-----------|--------------|---------------|
| | | NSW | NT | QLD | SA | TAS | WA | |
| CALCITRIOL* | 2010 | 24 | 609 | 288 | 11 | 7 | 821 | 1,760 |
| | 2011 | 6 | 610 | 293 | 4 | 7 | 870 | 1,790 |
| | 2012 | 5 | 669 | 303 | 14 | 8 | 1,038 | 2,037 |
| | 2013 | | 780 | 325 | 17 | 5 | 1,148 | 2,275 |
| | 2014 | | 762 | 321 | 30 | 7 | 1,234 | 2,354 |
| | 2015 | | 571 | 125 | 30 | 3 | 885 | 1,614 |
| CALCITRIOL Total | | 35 | 4,001 | 1,655 | 106 | 37 | 5,996 | 11,830 |
| ALENDRONATE | 2010 | 21 | 447 | 155 | 30 | | 310 | 963 |
| | 2011 | | 482 | 102 | 32 | | 307 | 923 |
| | 2012 | | 505 | 132 | 32 | | 369 | 1,038 |
| | 2013 | | 491 | 157 | 26 | | 267 | 941 |
| | 2014 | | 358 | 239 | 19 | | 298 | 914 |
| | 2015 | | 266 | 124 | 18 | | 237 | 645 |
| ALENDRONATE Total | | 21 | 2,549 | 909 | 157 | | 1,788 | 5,424 |
| RISEDRONATE | 2010 | | 38 | 10 | | | 95 | 143 |
| | 2011 | | 54 | 3 | 3 | | 146 | 206 |
| | 2012 | | 91 | 3 | 5 | | 110 | 209 |
| | 2013 | | 53 | | 1 | | 92 | 146 |
| | 2014 | | 59 | 12 | 7 | | 169 | 247 |
| | 2015 | | 92 | | 2 | | 124 | 218 |
| RISEDRONATE Total | | | 387 | 28 | 18 | | 736 | 1,169 |
| ALENDRONATE+COLECALCIFEROL | 2010 | | 39 | 36 | 3 | | 14 | 92 |
| | 2011 | | 48 | 18 | | | 44 | 110 |
| | 2012 | 5 | 53 | 28 | | | 41 | 127 |
| | 2013 | | 31 | 23 | 20 | | 70 | 144 |
| | 2014 | | 75 | 20 | 21 | | 41 | 157 |
| | 2015 | | 40 | 45 | 7 | | 74 | 166 |
| ALENDRONATE+COLECALCIFEROL Total | | 5 | 286 | 170 | 51 | | 284 | 796 |
| ALENDRONATE+COLECALCIFEROL(&)CALCIUM CARBONATE | 2010 | | | | 3 | | | 3 |
| | 2011 | | 12 | 4 | 7 | | 6 | 29 |
| | 2012 | | 34 | 10 | | | 22 | 66 |
| | 2013 | | 29 | 14 | 14 | 10 | 14 | 81 |
| | 2014 | | 63 | | 19 | 15 | 18 | 115 |
| | 2015 | | 30 | | 3 | 4 | 16 | 53 |
| ALENDRONATE+COLECALCIFEROL(&)CALCIUM CARBONATE Total | | | 168 | 28 | 46 | 29 | 76 | 347 |
| RALOXIFENE | 2010 | | 16 | 12 | | | 31 | 59 |
| | 2011 | | 23 | 20 | | | 34 | 77 |
| | 2012 | | 21 | 18 | | | 6 | 45 |
| | 2013 | | 20 | 21 | | | 4 | 45 |
| | 2014 | | 23 | 5 | | | 24 | 52 |
| | 2015 | | 18 | 6 | | | 10 | 34 |
| RALOXIFENE Total | | | 121 | 82 | | | 109 | 312 |
| RISEDRONATE(&)CALCIUMCARBONATE+COLE CALCIFEROL | 2010 | | 14 | | | | | 14 |
| | 2011 | | 42 | | | 2 | 2 | 46 |
| | 2012 | | 25 | | | | 8 | 33 |
| | 2013 | | 22 | | | | 7 | 29 |
| | 2014 | | 18 | | | | 11 | 29 |
| | 2015 | | 10 | | | | 8 | 18 |
| RISEDRONATE(&)CALCIUMCARBONATE+COLE | | | 131 | | | 2 | 36 | 169 |

| CALCIFEROL Total | | | | | | |
|---|------|-----------|--------------|--------------|------------|------------------------|
| STRONTIUM | 2010 | | | | | 4 4 |
| | 2011 | | | | | 11 11 |
| | 2012 | | 1 | | | 15 16 |
| | 2013 | | 23 | | | 25 48 |
| | 2014 | 7 | 3 | | | 25 35 |
| | 2015 | | | | | 14 14 |
| STRONTIUM Total | | 7 | 27 | | | 94 128 |
| RISEDRONATE(&)CALCIUMCARBONATE | 2010 | 13 | | | | 1 14 |
| | 2011 | 9 | | | | 3 12 |
| | 2012 | 1 | | | | 5 6 |
| | 2013 | 5 | | | | 35 40 |
| | 2014 | 1 | | | | 36 37 |
| | 2015 | | | | | 12 12 |
| RISEDRONATE(&)CALCIUMCARBONATE Total | | 29 | | | | 92 121 |
| DENOSUMAB | 2012 | 2 | 1 | | | 3 6 |
| | 2013 | 3 | | 1 | | 6 10 |
| | 2014 | 4 | | 2 | | 3 9 |
| | 2015 | 6 | 4 | 1 | | 15 26 |
| DENOSUMAB Total | | 15 | 5 | 4 | | 27 51 |
| ZOLEDRONICACID | 2010 | | | | | 1 1 |
| | 2011 | | | | | 1 1 |
| | 2012 | 1 | | | | 3 4 |
| | 2013 | | | | | 6 6 |
| | 2014 | | 1 | | | 1 1 |
| | 2015 | | 2 | | | 1 3 |
| ZOLEDRONICACID Total | | 1 | 3 | | | 12 16 |
| Total | | 61 | 7,695 | 2,907 | 378 | 72 9,250 20,363 |

* calcitriol can also be used for hypocalcaemia due to renal disease, hypoparathyroidism, hypophosphataemic rickets and vitamin D-resistant rickets.