Alendronate (Alendro Once Weekly, Fosamax Once Weekly, Fosamax Plus) for osteoporosis in people at high risk of fracture

(a-LEN-drun-AYT)

Summary

- **The PBS listing for alendronate has been extended to include the treatment of osteoporosis without fracture in people aged 70 years or older who have bone mineral density (BMD) T-scores of −3.0 or less.**
- **Only test BMD for people willing to accept treatment.**
- **Alendronate reduces the risk of fracture in people at high risk because of a previous fragility fracture, or because of old age and low BMD. The greater the absolute risk, the greater the benefit.**
- **Fractures may still occur with use of alendronate. In people with osteoporosis without a vertebral fracture, the risk of non-vertebral, hip and radiographically detected vertebral fractures is reduced, but there is no reduction in the number of clinically diagnosed vertebral or wrist fractures.**
- **Consider other risk factors for fracture, as some are at least partly independent of BMD and may not be modified by use of alendronate. Use other interventions such as calcium, vitamin D and falls prevention to help reduce overall risk.**
- **Limited data suggest that alendronate can be stopped after 5 years, but the optimal duration of treatment is not established. Longer treatment remains controversial but may be needed for people at highest risk (e.g. those with vertebral fractures).**
- **Osteonecrosis of the jaw is a rare but serious adverse effect that may occur months to years after starting bisphosphonates, including alendronate. Consider dental referral before starting treatment, especially for people at increased risk, such as the elderly and those receiving immunosuppressive therapy (e.g. corticosteroids). Reinforce the importance of good oral hygiene and of notifying their dentist that they take alendronate.**
- **Instruct patients or carers on the correct use of alendronate to reduce the risk of serious oesophageal adverse effects.**

PBS listing

Authority required

Alendronate was previously listed on the Pharmaceutical Benefits Scheme for the treatment of established osteoporosis in people with fracture due to minimal trauma.

The listing has now been extended to the treatment of osteoporosis without fracture, in people aged 70 years or older who have a bone mineral density (BMD) T-score of −3.0 or less. The initial authority application must state the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee agreed that the evidence suggests that alendronate reduces the risk of fracture in people at high risk (T-score of −2.5 or less) compared with placebo.[1] When the economic analysis used Australian fracture rates from the Dubbo Osteoporosis Epidemiology Study and the Geelong Osteoporosis Study, treatment at the proposed price became cost effective for women and men aged 70 years or older at lower threshold T-scores (−3.0 or less).[1]

Place in therapy

Alendronate is a bisphosphonate that reduces bone resorption by inhibiting osteoclasts.[2] Bisphosphonates are first line for treating osteoporosis.[2–4]

Alendronate reduces the risk of fracture in people at high risk because of a previous fragility fracture, and in those without fracture but at high risk because of old age and low BMD. Not all fractures are prevented, but the greater the risk the more likely the benefit from alendronate.

For those without fracture, discuss the implications of testing and only measure BMD in people willing to accept treatment if their T-score is −3.0 or less.

The greater the risk of fracture, the greater the benefit from alendronate

Before starting alendronate, assess the absolute risk of fracture against the likelihood of adverse effects (see Safety issues). Consider other risk factors that may contribute to fracture risk, especially those that are at least partly independent of BMD (Box 1).[5]

Advanced age, low BMD and previous fragility fracture independently increase fracture risk.[5–7] For example, people aged 80 years who have a T-score of −3.0 have a greater risk than people aged 70 years with the same T-score.[8]

Box 1: Risk factors for osteoporotic fracture[5–7]

Independent of BMD*	Dependent on BMD
Advanced age	Female gender
Previous fragility fracture	Asian or Caucasian race
Glucocorticoid use	Menopause
Family history of fragility fracture	Prolonged amenorrhoea
Falls†	Hypogonadism in men
High bone turnover	Prolonged immobilisation
Low body weight	Low dietary calcium
Cigarette smoking	Vitamin D deficiency
Excessive alcohol intake	

* Independent factors contribute to fracture risk over and above that of low BMD

† The risk of falls increases with age, previous falls, poor visual acuity, cognitive impairment, problems with gait and balance, reduced mobility and sedative use.

The relative risk of a fragility fracture:

- increases by 1.4–2.6 per standard deviation (−1) decrease in BMD[9]
- doubles after any fragility fracture[10,11]
- for vertebral fractures, increases fourfold after a previous vertebral fracture.[10]

The evidence for alendronate in people at high risk of fracture comes from the Fracture Intervention Trial, involving 6459 postmenopausal women (mean age 70 years) with BMD T-scores of −1.6 or less.[12–14]

In women with previous vertebral fractures, alendronate reduced the risk of both radiographically detected vertebral fractures* and any clinically diagnosed fracture* compared with placebo after 3 years of treatment (Table 1).[12,13] In women without vertebral fractures, the absolute risk of radiographically detected vertebral fractures was reduced by alendronate compared with placebo after 4 years (2.1% vs 3.8%); however, the primary outcome of any clinically diagnosed fracture was only significantly reduced in women with the lowest BMD (T-score of −2.5 or less).[14]

Women with T-scores of −2.5 or less had a similar baseline risk of clinically diagnosed fractures to that of women with previous vertebral fractures (Table 1). Consequently, alendronate reduced the risk similarly in both these groups. About one-third of women without vertebral fractures had a history of other fractures from the age of 45 years.[14] This is likely to have contributed to the effect of alendronate in the high-risk group.

Fractures still occurred despite treatment. In women with T-scores of −2.5 or less, the rate of clinically diagnosed non-vertebral fractures (12.3% vs 18.5%) including hip fractures (1.0% vs 2.2%) was significantly reduced with alendronate compared with placebo, but not for clinically diagnosed vertebral (1.5% vs 1.7%) or wrist fractures (4.2% vs 4.7%).[1,13,14]

* Radiographically detected (morphometric) vertebral fractures were defined as a decrease of 20% and at least 4 mm in any vertebral height from the baseline radiograph to that taken at the end of the study. Clinically diagnosed fractures were those at any site that were symptomatic and came to medical attention. Both radiographically detected and clinically diagnosed fractures may cause symptoms and increase the risk of another fracture.

Table 1: Fracture Intervention Trial: effect of alendronate in women with previous vertebral fractures and without vertebral fractures but low BMD (T-score of −2.5 or less)[1,12,14]

Patient group Type of fracture	Absolute risk (placebo)	Absolute risk (alendronate)	Absolute risk reduction	Relative risk reduction	NNT*
With fracture					
Any clinically diagnosed	18.2%	13.6%	4.6%	26%	22
Vertebral, on radiography†	15.0%	8.0%	7.0%	47%	14
Without fracture (T-score ≤ −2.5)					
Any clinically diagnosed‡	19.6%	13.1%	6.5%	33%	15
Vertebral, on radiography	5.8%	2.9%	2.9%	50%	34

Note: results presented are statistically significant
* NNT = number who need to be treated with alendronate for 3 years (with previous fracture) or 4 years (without fracture) instead of placebo to prevent one fracture
† Primary outcome for women with vertebral fractures at baseline
‡ Primary outcome for women without vertebral fractures at baseline

Other interventions remain important for modifying fracture risk

Many risk factors are at least partly independent of BMD and may not be modified by alendronate (Box 1). Some women in the Fracture Intervention Trial had other risk factors; for example, in the group with low BMD, about 25% had previous falls and 41% a maternal history of fracture.[13]

Use other interventions to maintain BMD or help reduce fracture risk, including smoking cessation, reduced alcohol intake, weight-bearing and resistance exercise (depending on age), balance training, hip protectors and occupational therapy.[3,4] Falls prevention is important for older people taking alendronate, because many fractures (especially hip) occur after a fall, and risk factors for falls increase with age.[3,5,6,15]

The effect of alendronate has mostly been studied in people with adequate calcium and vitamin D intake.[12,14] Ensure an adequate daily intake, which for people aged over 70 years is 1300 mg calcium and 600 units vitamin D.[16,17] A supplement may be needed if this cannot be met through diet and sunlight exposure. However, a higher dose is needed for people who are already vitamin D deficient, such as institutionalised or housebound elderly people, who are at greatest risk of deficiency.

Note: the combination product Fosamax Plus does not contain sufficient vitamin D to treat deficiency; for more information refer to the *NPS RADAR* review: Alendronate with cholecalciferol (vitamin D3) (Fosamax Plus) for osteoporosis.)

The optimal duration of treatment has not been established

Consider stopping alendronate after 5 years in people who improve their BMD and have not had a fracture during treatment. Monitor BMD every 2 years using the same dual-energy X-ray absorptiometry (DEXA) machine — an increase of 5% or more is a significant response to treatment.[4] Longer treatment may be needed for people at highest risk, such as those with multiple vertebral fractures.

While there are limited data on the optimal duration, prolonged treatment is controversial. Changes in BMD appear more favourable after 10 years of treatment, but 5 years has been shown to maintain levels at or above baseline.[18,19] Overall, no significant differences in fracture outcomes have been shown between 10-year and 5-year treatment, but this is not conclusive, as studies were only powered to detect differences in BMD.[18,19]

In an extension of the Fracture Intervention Trial[18], there was no significant difference in the risk of radiographically detected vertebral or any clinically

diagnosed fractures with 10 years of alendronate compared with 5 years' treatment. There were significantly fewer clinically diagnosed vertebral fractures with longer treatment (2.4% vs 5.3%). Although this risk difference is small, fewer than 40% of women were at the highest risk of fracture — i.e. those who may have benefited most from longer treatment.[18]

Safety issues

Alendronate can cause gastrointestinal adverse effects such as nausea, vomiting and diarrhoea.[2,20] Oesophagitis, oesophageal erosions and ulcers occur infrequently and are more likely in people who are elderly, have upper gastrointestinal disorders, take alendronate incorrectly or use NSAIDs.[2,20]

Osteonecrosis of the jaw has been reported rarely with alendronate, but is serious.[21–23] The incidence appears to increase with duration of use and with age and may become greater with the ageing population.[21,22]

See the Fosamax product information or the *Australian Medicines Handbook* for more information on adverse effects and drug interactions.

Report suspected adverse drug reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Be alert for signs and symptoms of oesophageal adverse effects

In the Fracture Intervention Trial, alendronate and placebo caused a similar incidence of upper gastrointestinal adverse effects (48% vs 46%), but more people discontinued alendronate because of oesophageal adverse effects (0.8% vs 0.3%; relative risk 2.9; 95% CI 1.4% to 6.5%).[24] These rates could be higher, as the study excluded those with major upper gastrointestinal mucosal erosive disease, recurrent or recent ulcer disease, oesophageal or gastric varices and daily use of medication for dyspepsia.[24] Additionally, women were counselled regularly on the use of alendronate and thus were more likely to take it safely.[24]

Do not use alendronate in people who cannot stand or sit upright for at least 30 minutes after the dose.[2,20] Use with caution in active upper gastrointestinal disorders.[2,20] In the Fracture Intervention Trial oesophageal adverse effects and gastroduodenal perforations, ulcers or bleeding were more frequent in women who had certain upper gastrointestinal disorders (e.g. reflux oesophagitis) than in those without such histories.[24]

Osteonecrosis of the jaw is rare but difficult to treat

Preventing osteonecrosis of the jaw is most important. It can develop months to years after starting bisphosphonates, and some cases do not resolve.[21–23] Signs and symptoms can vary and include painless exposed bone, severe jaw pain, numbness, recurrent or persistent soft tissue infection, oral odour, denture sore spots, loose teeth and impaired healing.[23,25]

Some risk factors for osteonecrosis of the jaw have been identified (Box 2). A review[22] of 368 reported cases found that most occurred after dental extraction (60%), with intravenous bisphosphonates (94%) and in patients with multiple myeloma or metastatic breast cancer (85%). However, about 4% of cases were related to oral bisphosphonates, including alendronate.[22] Of 106 reports received by ADRAC up to June 2006, 19 cases involved alendronate, compared with 69 and 33 cases with zolendronate and pamidronate, respectively.[23]

Check dental health before starting alendronate, including in people with dentures, as treatment may be

Box 2: Risk factors for bisphosphonate-induced osteonecrosis of the jaw[21,22,26,27]

- Intravenous > oral bisphosphonates
- History of dental surgery, local trauma or infection
- Higher cumulative doses
- Prolonged use (> 1 year)
- Older age (> 65 years)
- Diagnosis of cancer (e.g. multiple myeloma)
- Immunosuppressive therapy (e.g. chemotherapy, corticosteroids)
- Comorbidities (e.g. pre-existing oral disease)

needed to minimise future extractions.[21,25] It is not known if stopping alendronate before extractions reduces the risk.[22,25] Reinforce the need for good oral hygiene (especially with long-term use), perform an oral exam when possible and refer to a dentist if signs develop in the maxillofacial region after dental surgery, infection or local trauma.[21,25]

Dosing issues

The dose of Fosamax Once Weekly and Fosamax Plus is one 70 mg tablet once a week in the morning, swallowed whole (not chewed or sucked) with a full glass of water, at least 30 minutes before the first food, drink and medication of the day (including antacids, calcium, iron or mineral supplements).[2,20] Patients must not lie down for at least 30 minutes after the dose, and not until after the first food for the day.[2,20]

Information for patients

Inform patients or carers that alendronate reduces the risk of fractures but that these may still occur. Other interventions such as calcium, vitamin D and balance training remain important for managing osteoporosis.

Advise patients or carers:

- about gastrointestinal side effects such as nausea, vomiting and diarrhoea, and how to avoid oesophageal adverse effects (see Dosing issues)
- to stop alendronate and seek medical help if there is pain or difficulty with swallowing, retrosternal pain or new or worsening heartburn
- if a dental check-up is needed before starting alendronate because of the rare but serious adverse effect of osteonecrosis of the jaw
- to report signs and symptoms of osteonecrosis in the jaw, gums or tooth sockets such as exposed bone, soreness, pain, loose teeth or infection
- to maintain good oral hygiene (such as cleaning and flossing) and to tell their dentists before a check-up that they use alendronate.[2,20,23,27]

Suggest or provide the Fosamax Once Weekly consumer medicine information (CMI) leaflet.

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