



VERDICT & SUMMARY

Alendronate

(Fosamax[®])

For the treatment of osteoporosis

Committee's Verdict: **CATEGORY A (Q1)**

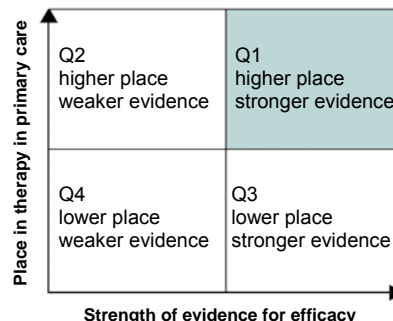
BNF: 6.6.2

Alendronate is suitable for prescribing in primary care for the management of osteoporosis. Alendronate can cause severe irritation of the gastrointestinal tract, and GPs should stress the need for patients to adhere to the strict administration requirements.

Category A: suitable for prescribing in primary care

Q1 rating: The evidence for the comparative efficacy and safety of alendronate was considered to be relatively strong. Four randomised controlled trials showed that alendronate treatment significantly reduced the incidence of vertebral fracture in men and women with osteoporosis compared with alfacalcidol or placebo. In patients with glucocorticoid-induced osteoporosis, alendronate significantly increased bone mineral density. Its well-established use gave it a high place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid.
The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.



MTRAC updated its review of this drug because of new NICE guidance.

Licensed indication

Alendronate is indicated for:¹

- the treatment of osteoporosis in men and postmenopausal women to prevent fractures
- the prevention of fractures in postmenopausal women considered at risk of developing osteoporosis
- the prevention and treatment of glucocorticoid-induced osteoporosis

Background information

Osteoporosis is a disease characterised by low bone mass with increased fragility and susceptibility to fracture. It results from an imbalance between resorption and regeneration of bone. Its prevalence increases with age, especially in women after the menopause because of loss of the protective effect of oestrogen. Other risk factors include smoking, low body-mass index, physical inactivity and long-term corticosteroid use. The National Institute for Health and Clinical Excellence (NICE) estimated that there were about 180,000 symptomatic osteoporotic fractures per year in England and Wales in 2005.²

Management of osteoporosis includes addressing lifestyle factors, such as stopping smoking, encouraging weight-bearing exercise, and ensuring an adequate intake of calcium and vitamin D. Pharmacological intervention includes bisphosphonates (alendronate, etidronate, risedronate, and ibandronate), raloxifene, hormone

replacement therapy, teriparatide and strontium ranelate. The bisphosphonates inhibit bone resorption.

Clinical efficacy

In postmenopausal women, two double-blind randomised controlled trials (RCTs) evaluated the efficacy of alendronate compared with placebo or alfacalcidol using fracture incidence as the primary endpoint.

In the Fracture Intervention Trial (n = 6,459; duration 3 to 4 years depending on baseline fracture status),^{3,4} alendronate 10 mg/day was compared with placebo in postmenopausal women with osteoporosis, with or without a vertebral fracture at baseline. Alendronate treatment significantly reduced the incidence of vertebral fractures compared with placebo (NNT 14, 59 respectively).^{3,4}

In a smaller RCT (n = 365; 24 months)⁵ in Japanese women and men (4% of total) with osteoporosis, alendronate 5 mg/day treatment was compared with alfacalcidol 1 µg/day treatment. The number of patients with vertebral fractures during months 6 to 24 of treatment was significantly lower in the alendronate-treated group compared with the alfacalcidol-treated group (4.3% vs. 12.7%, NNT 12).⁵

One randomised study (n = 1,258; 12 months)⁶ evaluated the efficacy of a daily dose of alendronate (10 mg) compared with a twice-weekly (35 mg) and once-weekly dose (70 mg) in postmenopausal women

with osteoporosis; there was no control group. The study found no significant differences in the primary endpoint: the change in spine bone mineral density (BMD) or fracture incidence between the three treatment groups from baseline to study end.⁶

In the Fosamax Actonel Comparison Trial (n = 1,053; 12 months) the increase in hip trochanter BMD (primary outcome) was 3.4% with alendronate 70 mg weekly vs. 2.1% with risedronate 35 mg weekly (p < 0.001).⁷

In men with osteoporosis, two randomised studies, one open label,⁸ and one double-blind⁹ (n = 375, two years extended to three in open-label study¹⁰), evaluated alendronate 10 mg/day compared with alfacalcidol 1 microgram/day⁸ or placebo.⁹

The increase in BMD from baseline of the spine^{8,9} and femoral neck⁹ (primary endpoint) was significantly greater in alendronate patients compared with alfacalcidol- (p ≤ 0.009)⁸ or placebo-treated patients (p < 0.001).⁹

The incidence of new vertebral fractures (secondary endpoint) was also significantly lower in alendronate-treated men compared with alfacalcidol (p = 0.04)⁸ after three years, or compared with placebo-treated men (p = 0.02) after two years' treatment.⁹ There were no significant differences in the incidence of non-vertebral fractures.

For patients with **glucocorticoid-induced osteoporosis**, combined results were reported for two double-blind RCTs (n = 477; 48 weeks)¹¹ that evaluated alendronate at doses of 5 or 10 mg/day compared with placebo, in addition to corticosteroids. The primary endpoint was the change in BMD of the spine; vertebral fracture incidence was a secondary outcome. After 48 weeks' treatment, the mean BMD in patients treated with 5 or 10 mg/day alendronate was significantly increased at the spine compared with baseline and placebo (p ≤ 0.01). There were no significant differences between the treatment groups in the incidence of vertebral fractures.¹¹

NICE guidance

A Technology Appraisal on the bisphosphonates, raloxifene and teriparatide recommended that the bisphosphonates be used as a treatment option for the secondary prevention of osteoporotic fractures in postmenopausal women.²

Adverse effects

Alendronate can cause local irritation of the gastrointestinal mucosa, which can be severe, and lead to oesophagitis or oesophageal ulceration. Other common clinical adverse events included

musculoskeletal events (bone, muscle, or joint pain) and headache.

Additional information

The recommended daily dose of alendronate is 5 or 10 mg daily, or 70 mg weekly depending on the indication. See the Summary of Product Characteristics for details and administration requirements.¹

At current prices, one year's treatment with alendronate 5 or 10 mg daily costs £301 to £331. The once-weekly formulation (70 mg) costs £270 per year.

References

1. Merck Sharp & Dohme Ltd. Fosamax. *Summary of Product Characteristics* 2004.
2. National Institute for Clinical Excellence. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. *Technology Appraisal Guidance* 2005;**87**.
3. Black DM, Cummings SR, Karpf DB *et al*. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet* 1996;**348**:1535-41.
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6. Schnitzer TJ, Bone HG, Crepaldi G *et al*. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging Clin Exp Res* 2000;**12**:1-12.
7. Rosen CJ, Hochberg MC, Bonnick SL *et al*. Treatment with once-weekly alendronate 70mg compared with once-weekly risedronate 35mg in women with postmenopausal osteoporosis: A randomized double-blind study. *J Bone Miner Res* 2005;**26**:141-51.
8. Ringe JD, Faber H, Dorst A. Alendronate treatment of established primary osteoporosis in men: results of a 2-year prospective study. *J Clin Endocrinol Metab* 2001;**86**:5252-5.
9. Orwoll E, Ettinger M, Weiss S *et al*. Alendronate for the treatment of osteoporosis in men. *N Engl J Med* 2000;**343**:604-10.
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Launch date: September 1995

Manufacturer: Merck Sharpe & Dohme

PL 0025/0360, 0326, 0399

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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