

Alendronate with cholecalciferol (vitamin D₃) (Fosamax Plus) for osteoporosis

(a-LEN-drun-AYT with KOLL-ee-kal-SIFF-er-ol)

Summary

- A new formulation of alendronate with cholecalciferol (vitamin D₃) (Fosamax Plus) contains twice the cholecalciferol dose of the previous formulation — 5600 units in a once-weekly dose, equivalent to 800 units/day.
- The cholecalciferol 2800 unit formulation is gradually being phased out by the manufacturer.
- Vitamin D and calcium are essential for people with osteoporosis; 5600 units cholecalciferol weekly is an adequate dose for patients taking alendronate who cannot obtain enough vitamin D from sunlight and diet — who do **not** already have moderate to severe vitamin D deficiency. Some may need a higher dose.
- The cholecalciferol dose in either formulation of Fosamax Plus is not sufficient for sole treatment of moderate to severe vitamin D deficiency.
- Vitamin D supplementation does not clearly benefit people who have normal vitamin D status — there is no reason to switch such patients from alendronate to the combination product.

PBS listing

Authority required (streamlined)

Treatment of established osteoporosis in patients with fracture due to minimal trauma.

OR

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.

Patients can only receive one PBS-subsidised anti-resorptive agent at a time.¹

Reason for PBS listing

Alendronate 70 mg with cholecalciferol 2800 units (Fosamax Plus) was first PBS listed in August 2006, on the basis of similar efficacy to that of alendronate (Fosamax) for the same cost — that is, cost-minimisation. The submission to the Pharmaceutical Benefits Advisory Committee (PBAC) did not claim any greater effectiveness in fracture prevention with the vitamin D component in the combined product.²

Although there was no issue of cost, the PBAC was concerned that the original product containing cholecalciferol 2800 units might be inappropriately used to treat vitamin D deficiency. While recognising that patients prescribed bisphosphonates require adequate vitamin D and calcium, the PBAC noted that the target group for the cholecalciferol 2800 units weekly dosage was not clearly defined.

A new formulation containing cholecalciferol 5600 units was PBS listed on 1 August 2008.


Vitamin D₃ supplements are not listed on the PBS except in combination with bisphosphonates. Calcitriol is listed but is not recommended for routine treatment of vitamin D deficiency.³ [www](#)

[www](#) Refer to this review at www.nps.org.au for additional information about vitamin D deficiency and supplementation.

Place in therapy

Bisphosphonates (such as alendronate or risedronate) are considered appropriate initial choices for osteoporosis.^{3,4} For more information about treatments for osteoporosis, go to www.nps.org.au and search for 'osteoporosis drugs'. This *NPS RADAR* review focuses on the role of the combination preparation.

Adequate calcium and vitamin D are important for maintaining bone health and for the effectiveness of anti-resorptive therapy.³ Inadequate vitamin D can result in decreased calcium absorption⁵, increased parathyroid hormone concentrations and increased bone turnover.⁶ Low calcium intake may increase vitamin D metabolism and deplete vitamin D.

Whether a vitamin D supplement is needed in addition to alendronate depends on vitamin D status and the risk of deficiency. [www](#) 


People without vitamin D deficiency or obvious risk factors for deficiency are unlikely to benefit from a supplement and there is no reason to switch such patients from alendronate to the combined formulation.

Cholecalciferol 5600 units weekly is adequate for people who need a supplement, but not those with moderate to severe vitamin D deficiency

The dose of vitamin D in Fosamax Plus may not be suitable for all people being treated with alendronate.

Cholecalciferol 5600 units weekly (800 units/day) is an adequate dose for vitamin D supplementation

if sunlight and dietary sources are inadequate.^{4,7,8*} Higher dose supplements may be indicated in some cases (up to 2000 units per day).^{3,7} People with inadequate sun exposure usually require a supplement, as it is difficult to gain this amount through diet.^{6,9}

Be aware that people with low dietary vitamin D intake and inadequate sunlight exposure (e.g. people who are housebound) may already be vitamin D deficient. [www](#) 

If deficiency is suspected, testing serum 25-hydroxyvitamin D (25-OHD) may be needed to determine the extent of the deficiency and the appropriate treatment dose. (See Box 1).

Treat moderate to severe deficiency (25-OHD \leq 25 nmol/L) with high-dose supplements of 3000–5000 units/day for 6–12 weeks, until normal levels are achieved.^{6,10} The maintenance dose to prevent further deficiency is 1000 units/day.^{3,6} Current recommendations are to maintain serum 25-OHD concentration at 50 nmol/L or more.^{3,6}

Changes in serum 25-OHD concentrations may not be detectable until treatment has continued for 3–4 months.⁶

* US dietary guidelines recommend intakes of 1000 units of vitamin D for older Americans and those in high-risk groups, to maintain 25-OHD at the higher target of 80 nmol/L.⁸ 2008 UK consensus guidelines for osteoporosis suggest 800 units as an appropriate intake of vitamin D for people with osteoporosis.⁴ Note that individual vitamin D status can be influenced by latitude, season, skin colour, and age.

Box 1: Serum vitamin D deficiency and insufficiency^{3,6,10}

Severity of deficiency	Serum 25-OHD range (nmol/L)*	Consequences	Treatment
Mild (or insufficiency)	25–50	Mildly elevated serum parathyroid hormone concentrations, increased bone turnover and likely long-term bone loss	Cholecalciferol — treatment dose is not stated in guidelines, but improvements in 25-OHD levels have been seen with doses > 400 units/day ¹¹
Moderate	12.5–25	Secondary hyperparathyroidism, reduced bone density, high bone turnover	Cholecalciferol 3000–5000 units/day for 6–12 weeks. [†] Continue with 1000 units/day after concentration reaches the normal range
Severe	<12.5	Osteomalacia	

* Note that reference ranges given by laboratories may differ from those shown.

† There is little risk of vitamin D₃ toxicity in doses of up to 4000 units/day⁶, except in rare cases such as with sarcoidosis.¹⁰

Are there any benefits of supplementing alendronate with vitamin D?

The benefits of vitamin D supplementation in people with adequate serum vitamin D concentrations are unproven.^{6,9} (See Does vitamin D reduce fracture risk?)

In a clinical trial of the combination, people who avoided sunlight for the trial maintained adequate vitamin D levels better by taking alendronate with cholecalciferol than alendronate alone.¹² This appears to have been the case for both cholecalciferol doses¹³ (full trial details have not been published). None of the participants had vitamin D deficiency, and only 21% had mild vitamin D deficiency or 'insufficiency' at baseline.[†] Although the higher dose seemed to result in slightly higher vitamin D concentrations, differences were not significant after 39 weeks of treatment, when 97% and 95% of all participants had 25-OHD concentrations above the insufficiency cut-off used in the trial (for the 5600 unit and 2800 unit doses respectively).^{12,13}

Does vitamin D reduce fracture risk?

The role of vitamin D in reducing fracture risk remains uncertain. In people with an existing fracture (secondary prevention), vitamin D₂ or D₃ alone or in combination with calcium supplementation does not reduce the risk of a further fracture.^{14,15}

In primary prevention (mostly postmenopausal women with no previous fracture):

- vitamin D₃ alone does not reduce fracture risk when trials are pooled (n = 16,115, relative risk 1.02, 95% confidence interval [CI] 0.92 to 1.13).¹⁴
- vitamin D₃ (700–800 units/day) with calcium supplementation (around 1000 mg) might have some effect in reducing hip fracture risk (n = 4242, relative risk 0.75, 95% CI 0.62 to 0.91).¹⁴ One trial (the Women's Health Initiative study¹⁶), published after this meta-analysis, found a small effect on hip fracture in people who adhered to treatment with calcium 1000 mg and vitamin D₃ 400 units/day (hazard ratio 0.71, 95% CI 0.52 to 0.97), but no effect on vertebral

or total fractures, or in the primary outcome analysis. About 50% of the women were also taking oestrogen, which is known to decrease fracture risk, making the effect of vitamin D difficult to distinguish.¹⁶

Safety issues

The most common adverse effects of alendronate are gastrointestinal; see the Fosamax Plus product information or the Australian Medicines Handbook¹⁰ for more information on adverse effects and interactions.

Since marketing, new adverse events identified for alendronate include ocular inflammations (uveitis, iritis, scleritis), myalgia and arthralgia, as well as rare instances of jaw osteonecrosis (the latter mostly with high-dose bisphosphonate treatment in patients with cancer, and generally associated with dental work).^{13,17,18}

Contraindications and precautions

- Alendronate is contraindicated in people with oesophageal disorders that delay emptying and in those not able to stand or sit upright for 30 minutes after administration.¹⁰
- Vitamin D is contraindicated in hypercalcaemia.¹⁰
- Alendronate is contraindicated in hypocalcaemia.¹³
- Vitamin D₃ is converted to the active form of vitamin D (1,25-OH₂D, or calcitriol) in the kidneys; do not use in severe renal impairment.¹⁰
- Be aware that vitamin D is available in some over-the-counter and complementary medicines.


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

[†] People with vitamin D deficiency (defined as 25-OHD < 22.5 nmol/L) were excluded. Insufficiency was defined as 25-OHD < 37.5 nmol/L. See Box 1 to compare with vitamin D deficiency ranges defined by Australian experts.

Dosing issues

As both dosage forms of alendronate with cholecalciferol (2800 units and 5600 units) may still be available, specify when prescribing if a particular formulation is required.

Check for use of other vitamin D supplements (including cod liver oil).

Changes in serum 25-OHD levels may not be detectable until treatment has continued for 3–4 months. [www](#) 

Information for patients

Advise patients to take alendronate with cholecalciferol in the morning, with a full glass of water, at least 30 minutes before food or drink; they should remain upright for 30 minutes (sitting, standing or walking around). Antacids, calcium, iron or mineral supplements taken within 30 minutes of alendronate may interfere with absorption.

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

Advise patients of the need for adequate sunlight exposure and how to obtain this in a sun-safe manner.

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The information contained in *NPS RADAR* is derived from a critical analysis of a wide range of authoritative evidence and is current at the time of publication. Any treatment decisions based on the information provided in *NPS RADAR* should be made in the context of the clinical circumstances of each patient.

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