

The background features a complex, repeating pattern of circular shapes. The circles are arranged in a grid-like fashion, with some overlapping. The colors range from light beige to deep teal and blue. Several of the circles contain highly reflective, metallic-looking spheres that mirror the surrounding patterns and colors, creating a sense of depth and complexity.

Risedronate now fully subsidised:

What is its place in practice?

Risedronate has been fully subsidised in New Zealand without restriction since 1 September, 2013. It is indicated for the treatment of osteoporosis and for the prevention of glucocorticoid-induced osteoporosis. Oral risedronate, taken once weekly, is likely to become the treatment of choice for patients with osteoporosis or at risk of osteoporotic fractures, due to its unrestricted subsidy access compared to alendronate or zoledronic acid and its superior efficacy and simpler dosing regimen compared to etidronate.

Bisphosphonates and bone metabolism

Throughout a person's lifetime, bone is constantly remodelled. However, in later life resorption exceeds formation of new bone, which leads to bone loss. Over time this process can result in bone weakness and an increased risk of fragility fractures, especially in people with risk factors such as frailty or immobilisation, low body weight, a calcium-deficient diet or a history of smoking or alcohol misuse. Osteoporosis is not simply a "disease of ageing". Many medical conditions (e.g. diabetes, inflammatory bowel disease, rheumatoid arthritis, anorexia nervosa) and medicines (e.g. corticosteroids, proton pump inhibitors, excessive thyroid hormones, depo-medroxyprogesterone, methotrexate, anticonvulsants) can increase the risk of osteoporosis.

Bisphosphonates are the recommended treatment for osteoporosis because they bind to bone and reduce the resorptive function of osteoclasts (cells in bone which resorb tissue) and accelerate osteoclast apoptosis (programmed cell death). Bisphosphonates are specific to bone; 40 – 60% of the administered dose binds to bone and the remainder is excreted unmetabolised in the urine.¹ Etidronate was the first bisphosphonate introduced into clinical practice in the 1970s. This was followed by the more potent bisphosphonates, alendronate and zoledronic acid. Oral risedronate sodium is now the latest potent bisphosphonate to become available in New Zealand.

It has been demonstrated that bisphosphonate treatment can reduce the incidence of osteoporotic fractures.¹ Relative vertebral fracture risk reduction in post-menopausal females with osteoporosis ranges from 40 – 70% after treatment with bisphosphonates, and relative hip fracture risk reduction

ranges from 40 – 50%.¹ Bisphosphonates lower fracture risk by increasing bone mass and reducing the rate of bone resorption.¹ Bone mineral density (BMD), usually measured by dual-energy x-ray absorptiometry (DEXA) at the hip and spine, is increased by approximately 5% following two years of treatment with a potent bisphosphonate.² Markers of bone resorption decrease quickly with bisphosphonate treatment, usually reaching their lowest point within 90 days of treatment initiation.³

Risedronate is now a first-line treatment option for osteoporosis

The availability of fully-subsidised risedronate on the community Pharmaceutical Schedule, and its comparable efficacy and safety profile to alendronate, means that it is likely to become the first-line oral treatment option for osteoporosis and the prevention of glucocorticoid-induced osteoporosis. Risedronate is simpler to access than alendronate as it does not require Special Authority approval for subsidy (see: "Alendronate and zoledronic acid subsidy requires Special Authority", Page 21). Risedronate is considered to be more effective than etidronate (Page 21), and in addition, risedronate dosing is simpler than the cyclical dosing regimen that is required for etidronate. Zoledronic acid remains an effective once-yearly intravenous (IV) treatment option for osteoporosis in patients who qualify for subsidy where treatment adherence, patient preference or intolerance to oral treatment is likely to be an issue (Special Authority approval is required).



For further information about IV administration of zoledronic acid, see: "Community-based IV administration: primary care reducing hospital admissions", BPJ 38 (Sep, 2011).

Which patients are most likely to benefit from risedronate?

Risedronate is indicated for the treatment of osteoporosis and postmenopausal osteoporosis, and the prevention of glucocorticoid-induced osteoporosis.

Osteoporosis can be diagnosed following assessment of BMD by DEXA. Osteoporosis in post-menopausal females and males aged 50 years and older is defined as a BMD standard deviation of 2.5 or more below the young female adult mean at the femoral neck (T-score ≤ -2.5).⁴ A presumptive diagnosis may be reached in elderly patients with multiple hip or vertebral fractures in the absence of major trauma.⁵ In younger populations osteoporosis can be diagnosed following comparison of BMD with a young-adult reference population of the same sex.⁵

N.B. Be aware that not all patients that are prescribed risedronate will qualify for subsidised treatment with alendronate or zoledronic acid, if risedronate is not tolerated and an alternative bisphosphonate is required. For example, risedronate may be prescribed to a patient with a T-score of -2.5 , but subsidy for alendronate or zoledronic acid is only for patients with a T-score ≤ -3.0 (without previous fractures).

Prevention of glucocorticoid-induced fractures

Patients taking long-term glucocorticoids, i.e. ≥ 7.5 mg* prednisone (or equivalent), daily, for more than three months, with the following risk factors are likely to benefit from risedronate treatment:^{6,7}

- Aged 65 years or over
- Aged under 65 years with a previous fragility fracture
- Aged under 65 years without a previous fragility fracture but a T-score ≤ -1.5

Ideally, a DEXA scan should be requested, but if there will be delay in performing the scan then risedronate may be considered in advance for people at risk.⁷ If bisphosphonate treatment is not indicated, due to a T-score of between zero and -1.5 , then the DEXA scan should be repeated in one to three years time, if glucocorticoid treatment is continued.⁷

* European League Against Rheumatism (EULAR) guidelines consider patients taking ≥ 7.5 mg prednisone to be at risk of glucocorticoid-induced fractures, however, Special Authority approval criteria for alendronate and zoledronic acid allow for patients taking ≥ 5 mg prednisone to qualify for subsidised treatment. Risedronate may be considered at lower long-term doses of prednisone (i.e. ≥ 5 mg) in selected patients, depending on clinical judgement

How effective is risedronate compared to other bisphosphonates?

The clinical effectiveness of bisphosphonates depends on two main factors: bone-binding affinity and the level of inhibition of a key enzyme.³ Bisphosphonates with a higher affinity will bind more strongly, but will be less widely distributed through bone. In contrast, bisphosphonates with a lower affinity will be more widely distributed, but will be lost at a greater rate if treatment is stopped. Zoledronic acid binds more strongly to bone than alendronate, which in turn binds more strongly than risedronate.³ Bisphosphonates are taken up into osteoclasts as they begin to resorb bone, where they inhibit an enzyme in the mevalonate pathway (farnesyl pyrophosphate synthase), resulting in decreased bone resorption. Zoledronic acid is a more potent inhibitor of this enzyme than risedronate, which in turn is more potent than alendronate.³

The ability of a bone-sparing medicine to reduce fracture risk is the most important indicator of treatment efficacy. However, BMD and serum levels of bone resorption markers are often used as surrogate indicators in research to compare the efficacy of bisphosphonates. This is because there is a lack of head-to-head trials comparing the effectiveness of bisphosphonates in reducing osteoporotic fracture risk.

It is not possible to state conclusively that one bisphosphonate is clearly better than another, but risedronate, alendronate and zoledronic acid are reported to have significantly higher anti-resorptive potencies than etidronate,² and are considered to be more effective at reducing osteoporotic fracture risk.

Risedronate compared to placebo

Risedronate is significantly more effective than placebo treatment in the secondary prevention of osteoporotic fractures. A Cochrane systematic review concluded that risedronate reduced the number of vertebral, non-vertebral and hip fractures, but not wrist fractures, in females who had experienced a previous vertebral compression fracture or had a BMD T-score ≤ -2.0 .⁸ Only a small number of patients were included in the primary prevention trials, so the meta-analysis was unable to detect if risedronate produced a statistically significant risk reduction for the primary prevention of osteoporotic fracture.⁸

Overall, risedronate has been shown to reduce the incidence of vertebral fractures by approximately 41 – 49% and non-vertebral fractures by 36% over three years, with a significant reduction in risk being apparent in patients with a prior vertebral fracture after one year of treatment.⁵ Risedronate is generally well tolerated with adverse events reported at

similar rates between placebo and treatment groups.⁸ Upper gastrointestinal symptoms are the main adverse events that influence long-term adherence (as with alendronate).

Risedronate compared to alendronate

Risedronate and alendronate appear to be equally effective at reducing fracture risk.² Risedronate and alendronate also have similar risk profiles.⁹

A large study has shown that use of alendronate or risedronate reduces the rate of vertebral and non-vertebral fractures in females aged over 65 years at risk of osteoporotic fractures.¹⁰ Both treatment options reduced the relative risk of vertebral fracture by more than 50% after one year.¹⁰ Non-vertebral and hip fractures were also reduced by approximately 20 – 30% by both risedronate and alendronate.¹⁰

Alendronate is the only bisphosphonate available in New Zealand co-formulated with colecalciferol (cholecalciferol).⁹ This is a treatment option for patients who qualify for subsidised alendronate treatment, and also require vitamin D supplementation and do not wish to take a monthly colecalciferol tablet.

Risedronate compared to etidronate

There are very few head-to-head trials comparing risedronate with etidronate. Etidronate has not been shown to reduce the incidence of any non-vertebral fracture, including hip fracture. The small amount of data comparing the two medicines suggests that risedronate is more effective than etidronate at reducing osteoporotic vertebral fracture risk.

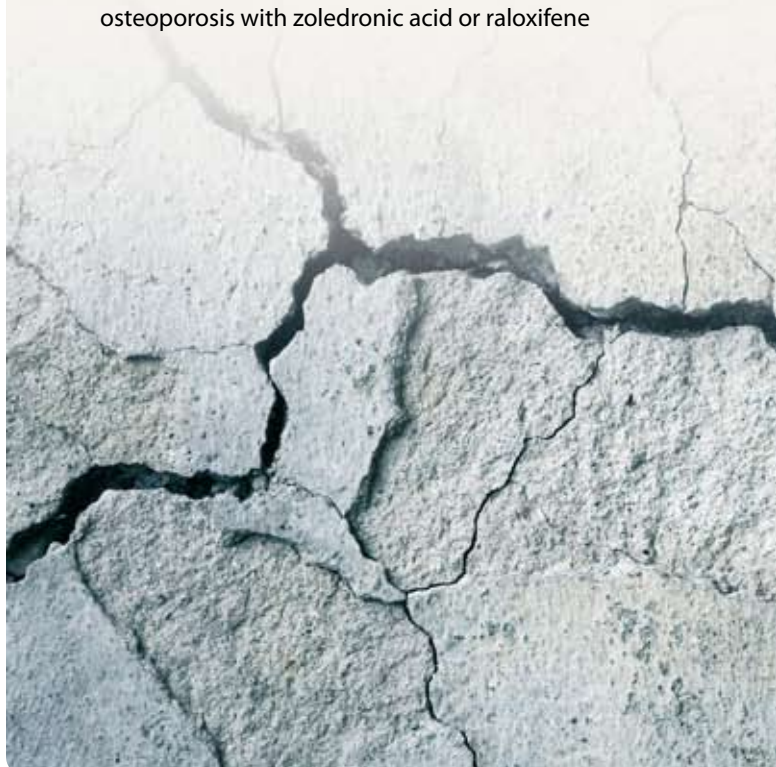
In a study of 235 patients in Japan with age-related osteoporosis, risedronate was found to significantly increase the BMD of the spine, compared to etidronate.¹¹ Risedronate use was not associated with new vertebral fractures, while a small, non-significant number of fractures occurred in the etidronate group.¹¹ Another Japanese study compared risedronate treatment with etidronate over 96 weeks.¹² The cumulative incidence of fractures was 12.3% in the group taking risedronate and 14.2% in the group taking etidronate.¹² It was concluded that the effect of risedronate on the incidence of vertebral fracture was not inferior to etidronate.¹² Height loss was also significantly less in the risedronate treatment group.¹² In both studies there was no difference in adverse effects between risedronate and etidronate.^{11, 12}

Risedronate, once weekly, is a more convenient dosing regimen than etidronate 400 mg, taken daily, for 14 days, followed by elemental calcium for 76 days; repeated as 90-day cycles.⁹

Alendronate and zoledronic acid subsidy requires Special Authority


Access to a subsidy for alendronate, with or without colecalciferol, or zoledronic acid requires Special Authority approval and patients must have at least one of the following:


- One significant previous osteoporotic fracture (demonstrated radiologically) and a T-score ≤ -2.5 , as measured by DEXA
- One significant osteoporotic fracture (demonstrated radiologically) in an older patient, or in a patient where DEXA cannot be reasonably performed
- A history of two significant osteoporotic fractures demonstrated radiologically
- A T-score ≤ -3.0
- A ten-year hip fracture risk $\geq 3\%$ calculated using a risk assessment algorithm incorporating BMD, e.g. FRAX or Garvan (Page 22)
- A previous Special Authority for the treatment of osteoporosis with alendronate, zoledronic acid or raloxifene
- Has received or will be receiving systemic corticosteroid treatment ≥ 5 mg prednisone per day (or equivalent), for at least three months and has one of: a BMD T-score ≤ -1.5 , one significant osteoporotic fracture demonstrated radiologically, a previous Special Authority for the treatment of osteoporosis with zoledronic acid or raloxifene




Osteoporosis risk assessment tools

FRAX is a fracture risk assessment algorithm that calculates the ten-year probability of a patient experiencing a major fracture. It includes the risk factors of age, sex, ethnicity, height, body mass index (BMI), personal history of fragility fracture, family history (in parents) of hip fracture, glucocorticoid use, rheumatoid arthritis and other secondary causes of osteoporosis. The FRAX assessment tool can also incorporate the patient's BMD into the fracture risk calculation. A BMD value is not necessary to calculate the patient's fracture risk, but is required if this calculation is being used to meet Special Authority requirements for subsidy of alendronate or zoledronic acid.

 A version of the FRAX tool that is calibrated for New Zealand practice is available from: www.shef.ac.uk/FRAX/tool.aspx?country=23

 For further information on FRAX, see: "Osteoporotic fracture prevention: a new approach", Best Tests (Nov, 2008).

Garvan fracture calculator is a fracture risk assessment tool that calculates the ten-year probability of a patient experiencing a fragility fracture. The Garvan calculator has been shown to be as, or more, effective than FRAX calculators in predicting subsequent fractures in healthy older women with normal bone mineral density.¹³ It uses five risk factors to calculate risk: age, sex, falls over the previous twelve months, weight and where available, BMD measurements. As with the FRAX tool, the Garvan calculator can be used without BMD data, although it is more accurate if it is incorporated. It was developed in Australia based on the Dubbo Osteoporosis Epidemiology Study, the longest running study of its kind worldwide.

 The Garvan calculator is available from: <http://garvan.org.au/promotions/bone-fracture-risk/calculator/>

Prescribing risedronate

Before beginning risedronate treatment review the patient's diet to ensure adequate calcium intake and discuss ways to maximise vitamin D synthesis or intake (see: "Calcium and vitamin D supplementation", Page 25).¹⁴ N.B. Laboratory testing of calcium or vitamin D is neither required, nor recommended, before prescribing supplementation.

Contraindications

Risedronate, along with any bisphosphonate treatment, is contraindicated in people with hypocalcaemia.⁹ Bisphosphonates should also not be prescribed to patients with impaired kidney function, i.e. eGFR < 30 – 35 mL/min/1.73 m².⁹ Bisphosphonates should be avoided during pregnancy and oral formulations used with caution in any patient with oesophageal abnormalities or any condition that delays movement through, or emptying of, the oesophagus.⁹

Prescribing regimen for risedronate

The recommended dose of risedronate is 35 mg, once weekly.⁹ Risedronate tablets should be taken with a full glass of water in the morning, after getting out of bed, 30 minutes before any food or other liquids are taken.⁹ Although less preferable, tablets can be taken later in the day if food and drink is avoided for two hours before or after the dose to optimise absorption/bioavailability.⁹ Patients should sit upright or stand for at least 30 minutes after taking a tablet, to reduce the risk of oesophageal complications.⁹

Adverse effects

The main adverse effect associated with risedronate, and other bisphosphonates, are gastrointestinal disturbances including: oesophagitis, abdominal pain, dyspepsia, diarrhoea and constipation.⁹ Headache and musculoskeletal pain may also occur.⁹ Patients should be advised to discontinue treatment and seek medical attention if they develop difficulty or pain while swallowing, chest pain or heart burn.⁹ Patients with gastrointestinal symptoms associated with oral bisphosphonates may tolerate an annual infusion of zoledronic acid as an alternative.


Osteonecrosis of the jaw is rare and is estimated to occur in 1 in 100 000 – 250 000 people taking bisphosphonates.¹ There is no evidence that it is any more common in people taking bisphosphonates for osteoporosis than it is in people with osteoporosis not using these medicines. Most instances of osteonecrosis of the jaw that have been associated with



bisphosphonates have occurred in patients taking high doses of IV bisphosphonates for cancer treatment.¹ The majority of cases are precipitated by dental extraction or oral surgery.¹ Additional factors which increase risk include: poor oral hygiene, poorly fitting dental appliances, intra-oral trauma, use of corticosteroids, diabetes and alcohol misuse.¹

Atypical femur fractures have been reported following an average of five to seven years of bisphosphonate treatment.¹ Atypical femur fractures are fractures located in the subtrochanteric and shaft regions of the femur, with radiological characteristics of stress or fatigue fractures. They are rare and account for less than 1% of all hip and femur fractures.¹ These reports of atypical fractures are often associated with co-morbidities or the use of other medicines, e.g. glucocorticoids or proton pump inhibitors.¹ In trials of over 17 000 patients using oral bisphosphonates there were no recorded instances of atypical femur fractures.¹ Atypical fractures can also occur in the humerus.

Ocular inflammation, including uveitis and scleritis, is a very rare adverse effect of bisphosphonate treatment.¹⁵ Symptoms are most likely to occur within the first month of treatment, and can include conjunctival injection (red eye), reduced vision, photophobia and moderate to severe pain. Symptoms usually resolve with treatment, after withdrawal of the medicine.

 For further information, see: "Causes, complications and treatment of a red eye", BPJ 54 (Aug, 2013).

Monitoring patients at risk of hypocalcemia

Serum calcium levels should be monitored during treatment with risedronate in patients with an intercurrent illness (e.g. an illness causing hypovolaemia), renal impairment, hypoparathyroidism or with signs and symptoms that may be suggestive of hypocalcaemia.⁹ Hypocalcaemia is associated with non-specific symptoms such as muscle cramps, numbness or tingling in fingers and toes, fatigue and irritability.

How long should risedronate be prescribed for?

Risedronate should be prescribed for an initial period of three to five years. A re-assessment of bone density and of interval fracture history after this time allows a determination of whether continued treatment is appropriate.

There is increasing evidence that the majority of the benefit of bisphosphonate treatment in patients who have an increased fracture risk occurs within the first five years of treatment.³ This is because a reservoir of bone-bound bisphosphonate accumulates that can then be released into circulation


Falls prevention

Advice about falls prevention should occur alongside bisphosphonate treatment. Exercise can reduce falls in people who have an increased fracture risk by improving strength, agility and posture.⁵ Weight-bearing exercises involving movement while standing and muscle strengthening exercises, using weights or resistance training, are recommended as lifelong activities in all adults.⁵

Older people should be encouraged to participate in daytime activities and to avoid taking daytime naps, to improve sleep quality, and therefore reduce the risk of night-time falls.²² Where necessary, the patient's home/room should be assessed for fall safety and the use of hip protectors considered for patients at risk of falling who are able to use them appropriately.²²

Older people should have regular medicine reviews, involving a pharmacist if possible, and medicines which increase falls risk, e.g. benzodiazepines, should be avoided.²²

Fracture risk can be assessed using a tool such as FRAX or Garvan.

 Find out what activities are available locally for older adults, e.g. gyms, Tai Chi classes, services for older people such as Enliven.



years after treatment has ceased.³ This has led to the idea of “drug holidays” to allow bone resorption to recover and to reduce the risk of rare adverse effects associated with bisphosphonates.^{1,3}

Patients with bone density T-scores above -2.0 at the femoral neck, after three to five years of bisphosphonate treatment are most likely to benefit from a period of discontinued treatment.¹⁶ It has also been suggested that reduced doses of bisphosphonates, rather than a drug holiday, may be appropriate for some patients who have received treatment for five years or more, e.g. risedronate 35 mg, fortnightly.¹⁶

The fracture risk of patients taking drug holidays, or reduced doses, should be reassessed periodically. When this should occur depends on the bone binding affinity of the medicine that has been discontinued, e.g. after one year for risedronate, one to two years for alendronate and two to three years for zoledronic acid.³ Bisphosphonate treatment can be resumed in patients with low bone mass and a ten-year hip fracture risk greater than 3%.⁵

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Calcium and vitamin D supplementation

Dietary intake of calcium needs to be adequate throughout a person's life to maintain bone health. There is a lack of rigorous data from which to determine optimal calcium intake, but expert opinion is that 700 – 1000 mg per day is likely to be adequate for most people.

People at risk of osteoporosis can be advised to eat calcium rich foods, e.g. dairy products and some seafoods. Table 1 contains the approximate calcium content of examples of calcium rich foods readily available in New Zealand.

Table 1: Examples of foods rich in calcium

Food type	Approximate calcium content (mg)
250 mL of milk	300
40 g cheese – two to three slices of cheddar. Softer cheeses have less calcium.	300
Half a cup of tofu	300
One cup of mussels	300
100 g canned salmon with bones	280
125 g pottle of yoghurt	200
Half a cup of raw almonds	200

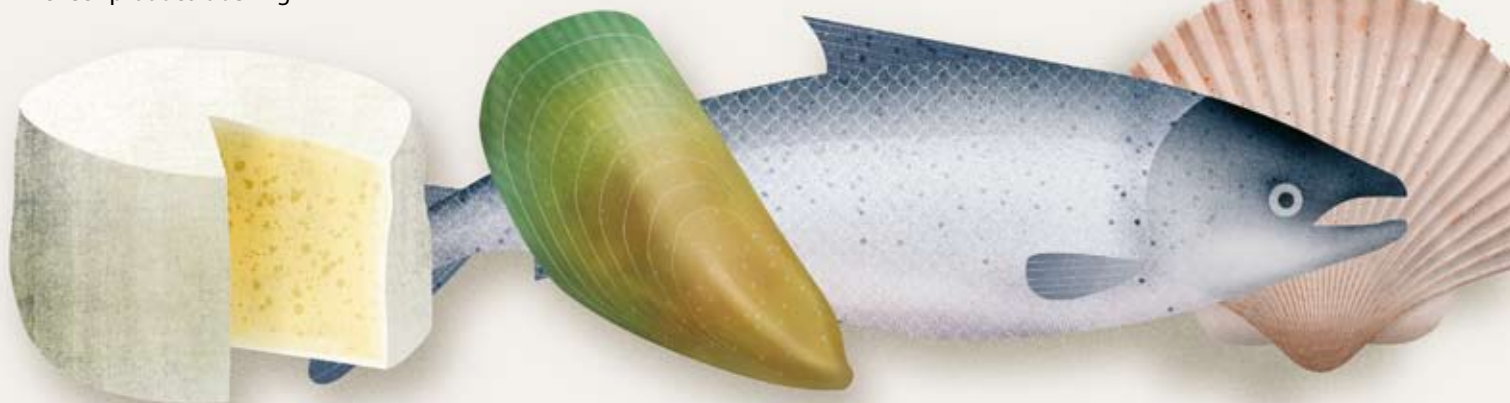
N.B. Calcium-fortified products such as cereals and juices are also a good dietary source of calcium; calcium content varies, check product labelling

Calcium supplementation should not be routinely prescribed to patients at increased risk of fractures, but may be required if dietary intake is insufficient. Excessive calcium supplementation (i.e. > 1000 mg/day, including dietary intake) should be avoided as it is reported to increase the risk of kidney stones and soft-tissue calcification. There is some evidence that calcium supplementation is associated with adverse cardiovascular effects,^{17, 18, 19} however, this is subject to current debate.²⁰ There are currently no restrictions or warnings associated with the prescription of calcium in terms of cardiovascular risk, but clinicians may wish to convey the possibility of this risk to patients if they are prescribed calcium supplements. N.B. Calcium interferes with the absorption of bisphosphonates and should be taken at a different time of the day.

Vitamin D is synthesised in the skin and sufficient exposure to the UVB in sunlight will allow a healthy person to meet all their daily vitamin D requirements. However, the amount of sunlight a person is exposed to can vary greatly and dark skin pigmentation reduces the amount of vitamin D that a person can produce.

Many older people routinely receive vitamin D supplementation for osteoporosis prevention. However, a recent systematic review and meta-analysis of the effects of vitamin D supplements on bone mineral density has concluded that it seems to be inappropriate for older people to receive supplementation for this reason alone, unless they have specific risk factors for vitamin D deficiency.²¹

If patients are suspected of having a vitamin D deficiency, e.g. frail elderly who are house-bound, the recommended treatment is colecalciferol, 1.25 mg, monthly.⁹ **Laboratory testing of vitamin D levels is not necessary.**



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