

## Zoledronic acid (Aclasta) for osteoporosis

(ZOL-eh-DRON-ick acid)

### Summary

- Zoledronic acid is an intravenous bisphosphonate. It is given as a **once-yearly infusion** for osteoporosis in women with a minimal-trauma fracture or at high risk of fracture (age  $\geq 70$  years and a bone mineral density [BMD] T-score of  $-3.0$  or less), and in men with a minimal-trauma hip fracture.
- Some patients may prefer zoledronic acid to oral therapy for dosing convenience. However, calcium and vitamin D supplements will still need to be taken daily.
- Oral bisphosphonates should be stopped in patients starting zoledronic acid.
- Before prescribing zoledronic acid, check if patients have already had an infusion (e.g. in hospital).
- Acute-phase reactions, such as fever, myalgia, flu-like illness and headache, frequently occur within 3 days of infusion.
- Like other bisphosphonates, zoledronic acid may cause hypocalcaemia, and has been associated with serious, often delayed, adverse effects, including renal dysfunction, inflammatory ocular disorders, osteonecrosis of the jaw and possibly atrial fibrillation.

### PBS listing

#### Authority required

Treatment as the sole anti-resorptive agent for established osteoporosis in:

- women with any fracture due to minimal trauma
- men with a hip fracture due to minimal trauma.

A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

In all cases, the fracture must have been demonstrated radiologically, with the year of plain X-ray, CT or MRI scan documented in the patient's medical records when treatment is initiated.

Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in women aged 70 years or older with a bone mineral density (BMD) T-score of  $\leq -3.0$ . The date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated.

Only **three treatments per patient** (i.e. one treatment each year for 3 years) will be subsidised on the PBS for any indication.

### Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of zoledronic acid for osteoporosis with or without fracture on a cost-minimisation basis — that is, similar efficacy and cost — compared with alendronate.<sup>1,2</sup> The equi-effective doses for this comparison were zoledronic acid 5 mg once yearly and alendronate 70 mg once weekly.

The PBAC accepted that zoledronic acid is no worse than alendronate in preventing new vertebral, non-vertebral or hip fractures in established osteoporosis.<sup>1</sup> This was based on an indirect comparison of zoledronic acid, in both women and men who had a recent hip fracture, with alendronate in postmenopausal women who had a vertebral fracture.<sup>1</sup>

The PBAC was uncertain that the efficacy and safety profile of zoledronic acid was no worse than that of alendronate in the primary prevention population.<sup>2</sup> The indirect comparisons found no significant differences in fracture outcomes between women receiving zoledronic acid and those receiving alendronate, but this may have

reflected a lack of statistical power and differences between trial populations.<sup>2</sup>

The PBAC also considered that the balance of benefits and harms with zoledronic acid may not be as favourable in primary prevention.<sup>2</sup> However, on the basis of cost-minimisation, the PBAC recommended that the listing for zoledronic acid be extended to women aged 70 years or older with a BMD T-score of  $\leq -3.0$ .<sup>2</sup>

### Place in therapy

Zoledronic acid is a potent intravenous bisphosphonate.<sup>3</sup> Once-yearly infusion of zoledronic acid 5 mg is a new treatment option for osteoporosis. Zoledronic acid 4 mg (usually infused every 3–4 weeks) is used to treat hypercalcaemia and to prevent skeletal-related events in people with malignancies.<sup>4</sup>

Zoledronic acid 5 mg infusion is TGA approved for treating osteoporosis in postmenopausal women, and in women and men aged over 50 years with a minimal-trauma hip fracture.<sup>3</sup>

The anti-fracture efficacy of zoledronic acid has not been directly compared with that of other bisphosphonates but appears to be similar to that of alendronate and risedronate. Its adverse-effect profile is mostly similar to that of oral bisphosphonates, with some notable differences (see Safety issues).

Zoledronic acid can be considered as an alternative to oral bisphosphonates. However, experience of its use in osteoporosis is more limited than for other bisphosphonates, and for people with malignancies. Zoledronic acid may have a particular role for people in whom an oral bisphosphonate is unsuitable or not tolerated, such as those who:

- are unable to stay upright for at least 30 minutes after a dose
- have an oesophageal disorder that precludes use of an oral bisphosphonate
- are experiencing intolerable gastrointestinal upset or other oesophageal adverse effects.

Some people may prefer annual intravenous doses to the daily or weekly oral doses for other bisphosphonates. It is important to note that they will need to continue with daily calcium and vitamin D supplements.

There is evidence for using zoledronic acid in people with osteoporosis who have previously taken an oral bisphosphonate, raloxifene, hormone replacement therapy or calcitonin.<sup>5</sup> For people switching from other treatments, note that<sup>5,6</sup>:

- oral bisphosphonates should be stopped
- specialist advice should be sought if zoledronic acid is to be used after strontium, because this has not been studied.

### Zoledronic acid reduces fracture risk after hip fracture and in postmenopausal women with osteoporosis

In postmenopausal women with osteoporosis (63% of whom had a vertebral fracture), an annual infusion of zoledronic acid for three years reduced the risk of vertebral and hip fractures compared with placebo (Table 1). The effects on fracture risk were seen whether or not women were using a concomitant non-bisphosphonate treatment (mainly raloxifene, oestrogen therapy or calcitonin), or had previously used a bisphosphonate.<sup>5,7</sup>

An analysis of the primary prevention subgroup of postmenopausal women from this trial was used in the PBAC submission (see Reason for PBS listing).<sup>2</sup> In this analysis, zoledronic acid had a significant effect compared with placebo only for the outcome of morphometric vertebral fracture.<sup>2</sup> However, the trial was not designed to assess fracture outcomes in the primary prevention subgroup, but in a mixed population of women with or without vertebral fracture (Table 1).

Annual infusion of zoledronic acid also significantly reduced the risk of a new clinical fracture (vertebral or non-vertebral) in women and men aged 50 years and over with a recent minimal-trauma hip fracture, compared with placebo (Table 1).<sup>6</sup> There was no significant difference in the incidence of hip fracture (2.0% vs 3.5%), but the trial was not designed to assess this outcome.<sup>6</sup>

The efficacy of zoledronic acid has not been compared with that of other drugs for osteoporosis in a head-to-head trial. Indirect comparisons of fracture outcomes should be interpreted cautiously because trial populations differ.

**Table 1: HORIZON trials: effect of annual zoledronic acid infusions on fracture rates in postmenopausal osteoporosis and after hip fracture<sup>5,6</sup>**

Primary outcome	Placebo	Zoledronic	Relative risk or hazard* (95% CI)	NNT <sup>†</sup>
<b>Postmenopausal women with or without vertebral fracture</b>				
New morphometric vertebral fracture <sup>‡</sup>	10.9%	3.3%	0.30 (0.24 to 0.38)	14
Hip fracture	2.5%	1.4%	0.59 (0.42 to 0.83)	91
<b>Women and men aged 50 years and over with hip fracture</b>				
Any new clinical fracture	13.9%	8.6%	0.65 (0.50 to 0.84)	19

\* New clinical and hip fractures reported as hazard ratios.

† Number who need to be treated with zoledronic acid 5 mg once a year instead of placebo to prevent one fracture (over 2 years of treatment for people with hip fracture, 3 years for postmenopausal women).

‡ Defined as a reduction in vertebral height of at least 20% and 4 mm by quantitative morphometry, and confirmed by an increase of one severity grade or more on semi-quantitative analysis.

## Stop oral bisphosphonates before starting zoledronic acid

Zoledronic acid may be used once people have stopped their previous bisphosphonate. Before starting zoledronic acid, consider that its effect on fracture risk soon after extensive pre-treatment with other bisphosphonates is not known. Patients in trials had not taken a bisphosphonate for some time (e.g. previous use for  $\geq 48$  weeks required a 2-year washout period).<sup>5</sup>

## Ensure adequate calcium and vitamin D intake

People need a daily intake of at least 1000 mg of calcium (1300 mg for women aged over 50 years and men over 70 years) and 400–800 units (10–20 micrograms) of vitamin D (800–2000 units [20–50 micrograms] if they have limited sun exposure).<sup>8</sup> Supplements are needed if these daily requirements cannot be met through diet and sunlight exposure.

The effect of zoledronic acid on fracture risk was only studied in conjunction with adequate calcium and vitamin D. Patients in trials received a daily supplement of calcium 1000–1500 mg and vitamin D 400–1200 units (800–1200 units for patients with recent hip fracture).<sup>5,6</sup>

## Safety issues

The adverse-effect profile of zoledronic acid is similar to that of oral bisphosphonates. However, it is important to note that for zoledronic acid:

- infusion-related acute-phase reactions are common

- serious oesophageal adverse effects are not expected
- it is not known if the risk of osteonecrosis of the jaw differs from that with oral bisphosphonates in people treated for osteoporosis.

Like other bisphosphonates, zoledronic acid may cause hypocalcaemia, and has been associated with serious, and often delayed, adverse effects, including renal dysfunction, inflammatory ocular disorders, osteonecrosis of the jaw and possibly atrial fibrillation.<sup>3–7</sup>

Hypersensitivity reactions have been reported post marketing, including bronchoconstriction, urticaria, angioedema and anaphylaxis.<sup>3</sup>

There is currently limited experience with zoledronic acid in people with osteoporosis. Most safety data are from use at higher doses for malignancy.

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

## Acute-phase reactions are common

Post-dose symptoms, including fever, myalgia, flu-like illness, headache, nausea, extremity pain and arthralgia, were commonly reported in trials within 3 days of infusion of zoledronic acid.<sup>5–7,9</sup> These were usually mild to moderate in severity and became less frequent with subsequent doses<sup>5–7</sup>: in a trial of postmenopausal women, the incidence after the first infusion of

zoledronic acid (32%) and placebo (6%) decreased with the second (7% vs 2%) and third infusions (3% vs 1%).<sup>5</sup>

Paracetamol may be given shortly after infusion to reduce post-dose symptoms (nonsteroidal anti-inflammatory drugs are not recommended).<sup>3</sup>

### Severe musculoskeletal pain may develop

Bisphosphonates, including zoledronic acid, have been associated with severe, sometimes incapacitating, bone, joint or muscle pain within days, months or years after starting treatment.<sup>3,10</sup> Symptoms may resolve rapidly, slowly, or not at all after stopping the bisphosphonate, and are unrelated to acute-phase reactions that resolve in a few days.<sup>10</sup>

Advise against further doses of zoledronic acid if severe musculoskeletal symptoms develop and persist for longer than expected after infusion.<sup>10</sup>

### Transient hypocalcaemia is possible

Like all bisphosphonates, zoledronic acid may lower serum calcium concentrations after administration.<sup>4,5</sup> The risk is increased in people with pre-existing hypocalcaemia, vitamin D deficiency or other disturbances of mineral metabolism.<sup>3</sup> Appropriate tests should be performed if these conditions are suspected, and any abnormalities corrected, before starting zoledronic acid.<sup>3</sup>

### Be alert for renal dysfunction

Zoledronic acid may increase serum creatinine concentrations after infusion<sup>5</sup> and, rarely, has caused acute renal failure.<sup>3,4</sup> While this is more likely to occur in people with malignancies receiving frequent and high doses, it has been reported after a single infusion and in people with osteoporosis.<sup>3,7,11</sup>

Be alert for changes in renal function, especially in the elderly.<sup>3</sup> The effect of zoledronic acid on renal function may be delayed by weeks<sup>11</sup>, and does not appear to reduce in frequency, as for other post-dose symptoms.<sup>7</sup>

The Adverse Drug Reactions Advisory Committee (ADRAC) reported on cases of renal impairment or renal failure with zoledronic acid.<sup>11</sup> Two-thirds of the reports had a delayed time to onset (1–3 months).<sup>11</sup> Many cases involved patients with pre-existing renal impairment, and most were being treated for malignancies.<sup>11</sup> The risk of renal damage with zoledronic acid may also be increased by rapid infusion rates, severe dehydration,

multiple treatment cycles and concomitant nephrotoxic drugs.<sup>3,11</sup>

Zoledronic acid is contraindicated in people with significant renal impairment (creatinine clearance < 35 mL/min).<sup>3</sup> Infuse zoledronic acid over at least 15 minutes to minimise the risk of renal toxicity (see Dosing issues).

### The incidence of osteonecrosis of the jaw is not established

As with other bisphosphonates, zoledronic acid has been associated with osteonecrosis of the jaw, although this is rare. Discuss with the patient that necessary dental work should be completed before starting treatment.<sup>3</sup> People who are receiving zoledronic acid, or any other bisphosphonate, should avoid dental extraction or surgery if possible, and not proceed until their risk of this adverse effect has been assessed (Box 1).<sup>3,12</sup>

There are limited data on the risk of osteonecrosis of the jaw in people receiving zoledronic acid for osteoporosis. A systematic review of published cases involving use of bisphosphonates for osteoporosis (3 with zoledronic acid) identified similar risk factors for people who are treated for malignancies.<sup>13</sup> One patient with osteoporosis who was given zoledronic acid in a trial, and one patient given placebo, developed symptoms consistent with osteonecrosis of the jaw; the patient receiving zoledronic acid had multiple comorbidities and previous tooth extractions.<sup>14</sup>

#### Box 1: Risk factors for osteonecrosis of the jaw in people receiving bisphosphonates<sup>13,15,16</sup>

- Intravenous bisphosphonates
- Diagnosis of cancer and related therapy
- Dental surgery, local trauma or infection
- Age > 60 years
- Poor oral hygiene
- Longer duration of therapy or higher cumulative dose
- Use of corticosteroids or other immunosuppressants
- Pre-existing dental or periodontal disease
- Alcohol and/or tobacco abuse
- Comorbidities (e.g. diabetes)

There is more information on the risk of osteonecrosis of the jaw with use of zoledronic acid for malignancies. People with multiple myeloma or bony metastases who use bisphosphonates are at increased risk (see Box 1).<sup>12,15</sup> In one study, the incidence after dental extraction was 6.7% to 9.1% in people with malignancies, compared with 0.1% to 0.3% in people with osteoporosis (who mainly used oral bisphosphonates).<sup>17</sup>

Although the doses of zoledronic acid used for osteoporosis are lower than those used for malignancies, it is not known to what degree this will lower the risk of osteonecrosis of the jaw. Furthermore, there is a lack of data comparing the risk between intravenous and oral bisphosphonates in people with osteoporosis.<sup>15</sup>

For more information, refer to the NPS fact sheet *Incidence and avoidance of osteonecrosis of the jaw associated with use of bisphosphonates*, available at [www.nps.org.au](http://www.nps.org.au) (go to 'Health professionals', then 'Publications' and click on 'Factsheets').

### Inflammatory eye disorders can be serious

Inflammatory eye disorders have been reported with both oral and intravenous bisphosphonates.<sup>18</sup> Do not start zoledronic acid in people with a history of bisphosphonate-induced uveitis, or in those with current or recent uveitis.<sup>3</sup> People who develop ocular symptoms after infusion (e.g. eye pain, redness and abnormal vision) should be referred for urgent (within 1–2 days) ophthalmological review.

Zoledronic acid was associated with a higher risk of inflammatory ocular adverse events in osteoporosis trials, compared with placebo.<sup>5–7,9</sup> The most frequent ocular event was conjunctivitis. Cases of uveitis, iritis and episcleritis were also reported, but the incidence was low (0.2% over 3 years).<sup>3,5,6</sup> Most events in one trial occurred within 15 days of infusion and resolved with outpatient treatment.<sup>5</sup>

### The risk of atrial fibrillation is low but uncertain

In a trial studying women with postmenopausal osteoporosis, more women receiving zoledronic acid than placebo experienced an arrhythmia.<sup>5</sup> This was mainly due to a significant increase in the incidence of serious atrial fibrillation events (1.3% vs 0.5%)<sup>5</sup> that were life-threatening or caused hospitalisation or disability.

The clinical significance of this adverse effect is unclear and remains to be confirmed. The risk of atrial fibrillation with zoledronic acid has not been found in patients with recent hip fracture<sup>6</sup> or malignancies.<sup>7</sup> A trend to an increased risk has been observed with alendronate, but studies are conflicting.<sup>19–21</sup>

### Effects of treatment beyond 3 years are unknown

Zoledronic acid should not be used for more than 3 years because its efficacy and safety beyond this time are not known.<sup>3,7</sup> Evidence for use over 5 years is limited to a small unblinded extension study (n = 119)<sup>22</sup>, and is not sufficient to support longer treatment.

The long-term effect of zoledronic acid on bone, and the effect of stopping the drug if adverse effects in bone occur, is unknown. Bisphosphonates remain in bone for many years.<sup>7</sup> In trials of zoledronic acid the rate of impaired or delayed fracture healing did not differ significantly compared with placebo; however, the trials were not powered to assess this outcome.<sup>5,6</sup>

People who develop atypical fractures, such as subtrochanteric or atypical stress fractures, may need to stop further doses of zoledronic acid.<sup>3</sup> It is not known if the risk of these fractures with zoledronic acid is increased in people previously treated with a bisphosphonate.

### Dosing issues

The recommended dose of zoledronic acid for treating osteoporosis is 5 mg (in 100 mL of solution) given intravenously once a year via a vented infusion line **over at least 15 minutes**.<sup>3</sup> The duration of therapy is restricted to no more than 3 years.<sup>3</sup>

Patients must be adequately hydrated when receiving zoledronic acid; advise them to drink two glasses of fluid (such as water) before and after the infusion.<sup>3</sup>

No dosage adjustment is necessary for patients with a creatinine clearance of  $\geq 35$  mL/min, including the elderly.<sup>3</sup>

The sponsor has established a patient registry and national infusion service for zoledronic acid. The patient registry provides an annual reminder to prescribers and patients about the next infusion, and monitors for inadvertent duplicate dosing. Patients are prescribed zoledronic acid by their usual doctor, and the dispensed product may be administered by a trained roving

registered nurse. More information is available from Novartis on 1800 671 203. General practitioners may also administer zoledronic acid, and set up annual reminders (e.g. recall systems).

### Avoid confusion between zoledronic acid preparations

Zoledronic acid is also available as a 4 mg/5 mL concentrated injection for infusion (brand name Zometa).<sup>3</sup> This preparation is for use in patients with malignancies only. The dose contained in a single Zometa preparation is less than the recommended once-yearly dose for patients with osteoporosis (i.e. 5 mg/100 mL).

### Patients may have already received an infusion in hospital

Treatment with zoledronic acid could be started in a hospital setting. Consequently, the first infusion may not have been PBS subsidised. Three further doses prescribed on the PBS leads to a total of 4 years of treatment, which is currently not approved. Unless this is documented on hospital discharge, or otherwise, ask patients if they have ever had an infusion for their osteoporosis before prescribing zoledronic acid.

## Information for patients

Instruct patients:

- to stop taking oral treatments for osteoporosis that have been stopped by their doctor
- to continue with their daily calcium and vitamin D supplements

Discuss with the patient that necessary dental work should be completed **before** starting zoledronic acid (prescribers should provide a referral letter explaining that bisphosphonate therapy is indicated).

Advise patients that symptoms such as fever, sore muscles or joints, flu-like illness, headache, pain in the limbs, and sometimes nausea, may occur within 3 days of an infusion. These symptoms are usually not severe and become less common with subsequent infusions.

To minimise or help prevent adverse effects with zoledronic acid, the patient should<sup>3</sup>:

- drink plenty of fluids on the day of the infusion
- take paracetamol after an infusion for post-dose symptoms
- maintain good oral hygiene
- promptly report signs and symptoms of serious adverse effects such as exposed bone or pain in the jaw, severe musculoskeletal pain, redness or pain in the eye and abnormal vision.

Discuss the Aclasta consumer medicine information (CMI) leaflet with the patient (available at [www.nps.org.au](http://www.nps.org.au)).

### Medicine Update

An NPS *Medicine Update* leaflet on zoledronic acid is available for consumers from [www.nps.org.au](http://www.nps.org.au). *Medicine Update* helps consumers to ask the right questions about new medicines and helps them compare the potential benefits and harms of a new medicine with those of other medicines.

