

# NEW DRUG EVALUATION

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## ZOLEDRONIC ACID FOR POST-MENOPAUSAL OSTEOPOROSIS

Zoledronic acid is a bisphosphonate licensed for the treatment of osteoporosis in post-menopausal women. The recommended dose is 5 mg administered by intravenous infusion annually. It may be a treatment option for patients in whom oral bisphosphonates are contraindicated, not tolerated, or when concordance is a particular issue. It should not normally be used prior to adequate therapeutic trials of these established oral treatments. There is a lack of long-term safety and efficacy data with zoledronic acid compared with other established oral treatments, and its use will have significant financial and service delivery implications.

### What is it?

Zoledronic acid (Aclasta<sup>®</sup>, Novartis) is the first annual bisphosphonate licensed for the treatment of osteoporosis in post-menopausal women at increased risk of fractures.<sup>1</sup> The recommended dose is 5 mg given as an intravenous (IV) infusion over at least 15 minutes.<sup>1</sup> It is also licensed at this dose for the treatment of Paget's disease of the bone.<sup>1</sup>

### How effective is it?

The efficacy of zoledronic acid (5 mg) has been assessed in two large, randomised, placebo-controlled trials.<sup>2,3</sup> The HORIZON pivotal fracture trial (HORIZON-PFT), conducted over three years, assessed the incidence of new vertebral fractures and hip fractures in post-menopausal women (n = 7,736).<sup>2</sup> The patient population included women with a confirmed diagnosis of osteoporosis and those with evidence of clinical fracture.<sup>2</sup> Prior to randomisation patients were stratified according to their use of concomitant osteoporosis medications (including hormone replacement therapy, raloxifene and calcitonin but not other bisphosphonates).

Only patients with a baseline radiograph and  $\geq$  one follow-up radiograph were used to assess the rate of new vertebral fractures (2,822 (73%) and 2,853 (74%) in the zoledronic acid and placebo groups, respectively). In women not receiving concomitant medication, new vertebral fractures occurred at a rate of 3.3% in those treated with zoledronic acid compared with 10.9% given placebo (absolute risk reduction (ARR) = 7.6%,  $p < 0.001$ ).<sup>2</sup> The remaining fracture data were calculated using women from both treatment arms, where hip fractures also occurred less frequently in the zoledronic acid treatment group (1.4%) than the placebo group (2.5%; ARR = 1.1%,  $p = 0.002$ ).<sup>2</sup> Secondary outcomes included any clinical fractures (8.4% vs. 12.8%), clinical vertebral fractures (0.5% vs. 2.6%), multiple vertebral fractures (0.2% vs. 2.3%) and non-vertebral fractures (8.0% vs. 10.7%,  $p < 0.001$  for each comparison).<sup>2</sup>

The HORIZON recurrent fracture trial (n = 2,127) assessed the impact of zoledronic acid given within 90 days after surgical repair of a hip fracture, on the incidence of further fractures and mortality.<sup>3</sup> Men and women aged 50 years and over who were unable or unwilling to take an oral bisphosphonate were included in the trial population (76% female). Patients were randomised to zoledronic acid (5 mg) or placebo infusion every 12 months with 11% taking concomitant osteoporosis medications. Originally the primary endpoint was defined as the time to first fracture. This was revised due to a low

fracture rate and redefined as incidence of fracture in each of the groups at 24 months (zoledronic acid 8.6%, placebo 13.9%,  $p = 0.001$ ). When assessed individually, the rates of non-vertebral and vertebral fractures at this time point were significantly lower in the zoledronic acid group ( $p < 0.05$ ), whereas the incidence of hip fracture was not significantly different (2.0% vs. 3.5%,  $p = 0.18$ ). Improvement in bone mineral density (BMD) at 12, 24 and 36 months ( $p < 0.001$ ) and mortality rate were pre-defined secondary endpoints. In general, estimates of relative mortality risk in the 12 months after hip fracture vary from two to greater than 10, depending on age. However, it is unclear to what extent this can be independently attributed to the fracture itself.<sup>4</sup> The mortality rates in the first 12 months of this study were similar in both treatment arms. However, at 24 months a significant difference was demonstrated for zoledronic acid compared with placebo (9.6% vs. 13.3% respectively,  $p = 0.01$ ).<sup>3</sup>

In both of the HORIZON trials participants received daily doses of calcium (1 - 1.5 g) and vitamin D (400 - 1,200 IU).<sup>2,3</sup> Previous use of oral bisphosphonates did not result in exclusion from these studies, but an appropriate 'wash out' time was required (e.g.  $\geq 48$  weeks use required two years 'wash out').<sup>2,3</sup>

One small (n = 225), double-blind, randomised trial compared annual zoledronic acid 5 mg with once-weekly oral alendronic acid 70 mg.<sup>5</sup> This trial was designed as a non-inferiority study and demonstrated that zoledronic acid and alendronic acid have similar effects on lumbar spine BMD at 12 months (0.17% and 0.81% improvement from baseline, respectively).<sup>5</sup>

### How safe is it?

The most commonly reported adverse events were pyrexia (16%), myalgia (9.5%), 'flu-like symptoms' (7.8%), headache (7.1%), and arthralgia (6.3%), the majority of which occurred after the first infusion of zoledronic acid.<sup>2</sup> A sub-analysis of HORIZON-PFT demonstrated an increased incidence of serious adverse events associated with atrial fibrillation (1.3% with zoledronic acid compared with 0.5% in the placebo group,  $p < 0.001$ ).<sup>2</sup> The hazard ratio associated with active treatment was calculated as 2.4 (95%CI 1.4 to 3.9,  $p = 0.001$ ).<sup>6</sup> To date no increased risk of osteonecrosis of the jaw (ONJ) has been reported with zoledronic acid for post-menopausal osteoporosis.<sup>2,3,5</sup> However these trials are of relatively short duration, and further information is required to establish the degree of risk in these patients compared with oncology patients in whom cases of ONJ have been reported.

A full review of the safety data for bisphosphonates has been conducted as part of the Safer Medication Use series of bulletins.<sup>7</sup> Dose adjustment is not necessary in patients with creatinine clearance as low as 40 ml/min.<sup>1</sup> All suspected adverse reactions to black triangle drugs such as zoledronic acid should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

Four oral bisphosphonates are licensed for the treatment of post-menopausal osteoporosis; alendronic acid, cyclical disodium etidronate plus calcium, risedronate and ibandronic acid.<sup>8</sup> For an updated review of bisphosphonate treatment in osteoporosis see Drug Update No 58.<sup>9</sup>

Other treatment options include IV ibandronic acid (given three-monthly), strontium ranelate, raloxifene and teriparatide. The National Institute for Health and Clinical Excellence is currently

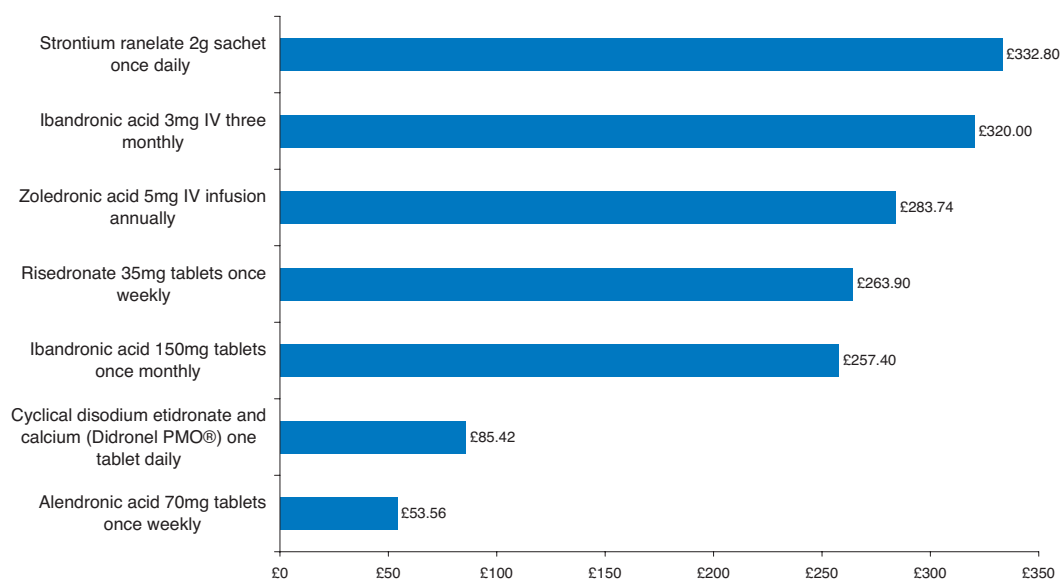
reviewing its guidance on primary and secondary prevention of osteoporotic fractures in post-menopausal women.<sup>4,10</sup>

### When should it be used?

There is no evidence that annual zoledronic acid is more effective than other bisphosphonates. As it is administered as an infusion and is considerably more expensive than alendronic acid 70 mg once-weekly, its use will have significant financial and service delivery implications. It should not normally be used prior to adequate therapeutic trials of established oral treatments.<sup>9</sup> It may be an option in patients unable to tolerate oral bisphosphonates, or who have specific contraindications to their use, or when concordance is a particular issue. Longer-term safety data are required, as are data on which specific patient groups (e.g. age, T-score, primary or secondary prevention of fractures) will derive most benefit from this treatment option.

### How much does it cost?

Cost of one year's treatment (Drug Tariff/ eMIMS January 2008)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. These figures relate to drug costs only and do not include the cost of IV administration (where this is conducted in secondary care as a follow-up out-patient appointment this will incur an additional cost of £94).

## REFERENCES

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KEY Abs – abstract, G - guideline, R - review, RCT - randomised controlled trial.

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