

Zoledronic acid infusion for prevention and treatment of osteoporosis

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Abstract: Osteoporotic fractures are associated with significant morbidity, reduced quality of life, increased mortality, and high health care costs. Bisphosphonates are standard therapy for treatment of osteoporosis. However, patient compliance and persistence with oral weekly or monthly bisphosphonate therapy are suboptimal and may lead to reduced effectiveness. Zoledronic acid (ZOL) is an intravenous bisphosphonate that is given once yearly for the treatment of osteoporosis via a medically supervised 15-minute infusion. This ensures compliance for a full 12 months. In clinical trials, an annual infusion of ZOL 5 mg has shown sustained efficacy in reducing hip and spine fractures in postmenopausal women with osteoporosis. It has also been shown to increase bone density in postmenopausal women with osteopenia (low bone mass) and in men with osteoporosis. Transient flu-like symptoms are the most common adverse effects following ZOL infusion, and these can generally be managed with acetaminophen. The availability of an intravenous bisphosphonate that ensures compliance over a long dosing interval may help to overcome barriers to efficacy resulting from poor long-term compliance with oral agents.

Keywords: fractures, intravenous bisphosphonate, osteoporosis, zoledronic acid

Introduction

Osteoporosis affects an estimated 75 million persons in Europe, the United States, and Japan¹ and is associated with an estimated 9 million new fractures every year worldwide,¹ including more than 2 million fractures per year in the United States.² Osteoporosis-related fractures are associated with significant morbidity, increased mortality, and enormous financial costs.³

Oral nitrogen-containing bisphosphonates (eg, alendronate, risedronate, and ibandronate) are the standard of care in osteoporosis.⁴ These bone-specific agents inhibit farnesyl diphosphate synthase, a key branch point of the mevalonate pathway, and thus, inhibit protein prenylation in osteoclasts.⁵ This activity makes bisphosphonates potent inhibitors of bone resorption and remodeling activity.⁶ Oral bisphosphonates have been shown to increase bone mineral density (BMD) and reduce fracture risk. However, the “real world” effectiveness of oral treatment is compromised by suboptimal patient compliance and persistence with prescribed regimens.^{7–11}

Zoledronic acid (ZOL) is an intravenous, nitrogen-containing bisphosphonate with a prolonged dosing interval, a characteristic that has the potential to increase patient compliance with bisphosphonate therapy and thereby to improve patient outcomes. ZOL 5 mg currently is approved by the Food and Drug Administration for the treatment of postmenopausal osteoporosis, treatment of male osteoporosis, and treatment

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and prevention of glucocorticoid-induced osteoporosis as a once-yearly infusion. It is also approved for prevention of osteoporosis in postmenopausal women as an infusion given once every 2 years.¹²

Osteoporosis: a pervasive problem

Although the population of individuals with identified osteoporosis is quite large, it is also clear that these conditions are underdiagnosed and undertreated.^{13–15} For example, the IMPACT study reported in 2005 that re-evaluation of routine spine X-rays of postmenopausal women aged 65–80 years resulted in lack of reporting of vertebral fracture findings for 45.2% of X-rays in North America, 46.5% in South America, and 29.5% in Europe/South Africa/Australia.¹³

The prevalence of osteoporosis increases with age; overall, it is estimated that 1 in 2 women and 1 in 4 men aged more than 50 years will have an osteoporosis-related fracture in their remaining lifetime.¹⁶ The aging of the world's population is accompanied by a resultant marked increase in the projected overall prevalence and cost of osteoporosis-related fractures.^{2,17} Thus, in the United States, eg, it is estimated that the number of women and men with osteopenia/osteoporosis will increase from 44 million to more than 61 million by 2020^{16,18} and that by 2025, annual fractures and associated costs in the United States will increase by nearly 50%.² Likewise, worldwide projections of the incidence of hip fracture indicate that it will increase by 240% in women and 310% in men between 1990 and 2050.¹⁹

The primary health burden imposed by osteoporosis is increased risk for bone fractures and their sequelae.²⁰ Fractures are associated with disability, reduced quality of life, increased risk of subsequent fracture, increased mortality, and high health care costs.^{1–3,21–23} In the United States, costs of osteoporosis-related fractures were estimated at \$19 billion for 2005 and are expected to increase to 25.3 billion by 2025.¹⁶ In the European Union, osteoporosis-related fractures now costs more than €48 billion per year for hospital health care alone,³ and disability associated with osteoporosis is greater than that associated with cancers, excluding lung cancer, and comparable with that associated with rheumatoid arthritis, asthma, and hypertension-related heart disease.¹ In European women aged 45 years and above, osteoporosis accounts for more days spent in the hospital than diseases such as diabetes, myocardial infarction, or breast cancer.¹ It has been reported that 26% of patients suffer another fracture in the year following a vertebral fracture,²³ and it is estimated that 24% of patients aged more than 50 years with a hip fracture die from fracture-related complications during the following year.¹⁶

Diagnosis

BMD correlates with bone strength and predicts fracture risk. BMD measurements by means of dual-energy X-ray absorptiometry scans of the hip and spine are used as the primary basis for the diagnosis of osteoporosis. The World Health Organization (WHO) defines osteoporosis in men and women as a BMD of 2.5 or more standard deviations (SD) below that of a young normal adult (T-score of -2.5 or lower); osteopenia, or low bone mass, as a BMD between 1.0 and 2.5 SD below that of a young normal adult (T-score between -1.0 and -2.5); and normal BMD as within 1 SD of the reference value for a young normal adult (T-score of -1.0 or higher). The presence of a low-trauma fracture is also sufficient for the diagnosis of osteoporosis in patients with T-scores between -1.0 and -2.5 .

Treatment decisions for patients with osteopenia should be made based on overall fracture risk. The WHO has developed an Internet-based fracture risk assessment tool (FRAX).²⁴ FRAX allows the user to predict the 10-year probability of a hip or other major osteoporotic fracture (clinical spine, wrist, and proximal humerus) on the basis of femoral neck BMD and other risk factors (age, gender, weight and height, personal history of fracture, parental history of hip fracture, smoking, glucocorticoid use, presence of rheumatoid arthritis, presence of secondary osteoporosis, and alcohol consumption). Figure 1 shows a sample FRAX calculation. The FRAX tool is free and can be accessed at <http://www.shef.ac.uk/FRAX>.

Treatment recommendations

Osteoporosis is undertreated, even in patients with the most advanced disease – ie, those who have the highest risk of fracture and are the most important target population for pharmacologic intervention. For example, a recent National Health and Nutrition Examination Survey (NHANES) study indicated that antiresorptive medication was being taken by only 17% of women aged more than 65 years who had sustained a prior fracture after 50 years of age.¹⁴ An earlier study based on Medicare claims between 1995 and 2004 and involving more than 15,000 patients with hip fracture aged 65 years or more showed that the percentage of patients receiving osteoporosis treatment within 6 months after fracture reached a high of only 31% in 2002 and remained stable thereafter.²⁵

According to the 2008 National Osteoporosis Foundation guidelines,²⁶ treatment should be considered in postmenopausal women and men aged more than 50 years, who present with any one of the following:

Country: **US (Caucasian)** Name/ID: About the risk factors

Questionnaire:

1. Age (between 40–90 years) or Date of birth
 Age: Y: M: D:

2. Sex ☐ Male ☒ Female

3. Weight (kg)

4. Height (cm)

5. Previous fracture ☒ No ☐ Yes

6. Parent fractured hip ☒ No ☐ Yes

7. Current smoking ☐ No ☒ Yes

8. Glucocorticoids ☒ No ☐ Yes

9. Rheumatoid arthritis ☒ No ☐ Yes

10. Secondary osteoporosis ☒ No ☐ Yes

11. Alcohol 3 more units per day ☐ No ☒ Yes

12. Femoral neck BMD (g/cm²)
 T-score: **-2.4**

BMI **23.2**

The ten year probability of fracture (%)

with BMD

Major osteoporotic	21
Hip fracture	10

Figure 1 Example of a fracture risk calculation using FRAX, a Web-based fracture risk assessment tool (available at: <http://www.shef.ac.uk/FRAX>).

Abbreviations: BMD, bone mineral density; BMI, body mass index.

1. Hip or vertebral (clinical or morphometric) fracture
2. T-score of ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
3. Low bone mass and a 10-year probability of hip fracture of $\geq 3\%$ or a 10-year probability of any major osteoporosis-related fracture of $\geq 20\%$ based on the FRAX calculation

Poor compliance with oral therapies

Poor compliance and persistence limit the effectiveness of current osteoporosis therapies. It has been found that approximately 50% of patients fail to comply or persist with osteoporosis therapy within the first year of treatment, and that poor compliance is associated with higher fracture rates and increased morbidity, mortality, and health care costs.^{7–11,27,28} Compliance is particularly problematic for patients aged 65 years and above, who are more likely to have cognitive impairment and polypharmacy issues. Weekly and monthly regimens introduced for the past several years may have produced modest improvements compared with daily regimens in compliance and persistence, but rates nevertheless remain suboptimal.^{29–31}

The most commonly prescribed oral bisphosphonates must be taken in the morning on an empty stomach with 6–8 ounces of plain water, and the patient must not ingest food or beverages other than water for 30–60 minutes after administration, since these can significantly reduce absorption. The patient must also remain sitting or standing upright for

30–60 minutes after ingestion in order to avoid upper gastrointestinal irritation. It has been shown in one study that 25% of patients disregarded at least one dosing requirement despite detailed instructions from health care providers.³²

In addition to the well-established absorption issues associated with beverages such as juice or coffee, it has become apparent that plain drinking water can also be problematic under some circumstances. Calcium ingestion at the time of bisphosphonate administration can inhibit absorption,³³ and it has been found that the calcium concentration of waters (tap and bottled) across the United States and Canada range from 1 to 135 mg/L,³⁴ with some water having enough calcium to potentially interfere with bisphosphonate absorption.

ZOL 5 mg: an intravenous bisphosphonate for the prevention and treatment of osteoporosis

Increased compliance and persistence with bisphosphonate treatment could improve patient outcomes and reduce the social and economic burdens of osteoporosis. The ability to provide a medically supervised dose of a bisphosphonate ensures compliance and persistence for the duration of the dosing interval. Intravenously administered ZOL circulates for approximately 24 hours and rapidly binds to bone. Any drug that is not bound to bone is excreted through the kidneys. The prolonged duration of action of ZOL is due to its high binding affinity to bone mineral.¹²

The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly (HORIZON) clinical trial program has included studies of ZOL in postmenopausal women with osteoporosis, men and women with hip fracture, men with osteoporosis, and postmenopausal women with osteopenia.

Efficacy in treating osteoporosis in the HORIZON trials

Postmenopausal women with osteoporosis

In the HORIZON-Pivotal Fracture Trial (HORIZON-PFT), postmenopausal women with osteoporosis were randomized to receive a 15-minute infusion of ZOL 5 mg ($n = 3,889$) or placebo ($n = 3,876$) at baseline, 12 months, and 24 months and were followed for 3 years.³⁵ At 3 years, compared with placebo, ZOL 5 mg reduced risk of morphometric vertebral fracture by 70% (3.3% vs 10.9%, $P < 0.0001$), risk of hip fracture by 41% (1.4% vs 2.5%, $P = 0.002$), risk of nonvertebral fractures by 25% (8.0% vs 10.7%, $P < 0.001$), and risk of clinical vertebral fractures by 77% (0.5% vs 2.6%, $P < 0.001$) (Figure 2). ZOL significantly increased BMD at the total hip (6.0%), lumbar spine (6.7%), and femoral neck (5.1%) compared with placebo ($P < 0.001$ for all comparisons). Thus, ZOL was shown to be effective over a 3-year period in preventing fractures and increasing bone mass at key skeletal sites in postmenopausal women.

Women and men with hip fracture

In the HORIZON-Recurrent Fracture Trial (HORIZON-RFT), women and men more than 50 years of age who had suffered a recent hip fracture were randomized to receive annual

infusions of ZOL 5 mg ($n = 1,065$) or placebo ($n = 1,062$) within 90 days after hip fracture repair.³⁶ The trial was event-driven, with the stopping point determined by occurrence of a prespecified number of fracture events. The median follow-up duration was 1.9 years. Compared with placebo, ZOL 5 mg reduced the rate of new clinical fractures and clinical vertebral fractures by 35% (8.6% vs 13.9%, $P = 0.001$) and 46% (1.7% vs 3.8%, $P = 0.02$), respectively (Figure 3). Total hip BMD increased in the ZOL group by 2.6%, 4.7%, and 5.5% at 12, 24, and 36 months and decreased in the placebo group by 1.0%, 0.7%, and 0.9%, respectively ($P < 0.001$ for all comparisons). HORIZON-RFT demonstrated that ZOL was effective in preventing secondary fractures and increasing bone mass in this high-risk patient population.

Men with osteoporosis

In the HORIZON Male trial, 302 men with osteoporosis aged 25–85 years were randomized to receive an annual infusion of ZOL 5 mg or oral alendronate 70 mg weekly.³⁷ The primary efficacy end point was change in BMD from baseline over 2 years. The results showed an increase in lumbar spine BMD of 6.1% in the ZOL treatment group and 6.2% in the alendronate group (nonsignificant difference). This led to the approval of ZOL for men with osteoporosis.

Efficacy in prevention of osteoporosis

Although patients diagnosed with osteoporosis have the highest fracture risk, patients with osteopenia also sustain fractures.^{20,38} In the National Osteoporosis Risk Assessment (NORA) study, which measured peripheral bone density in

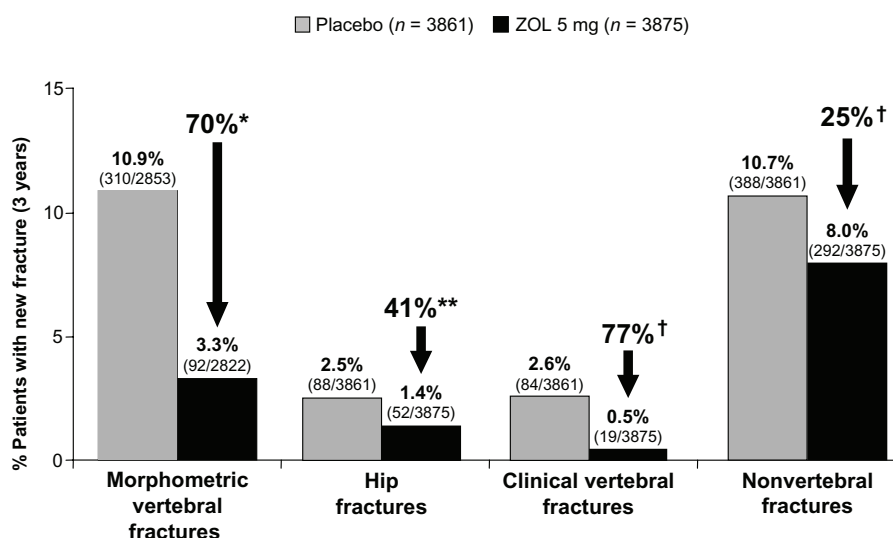


Figure 2 Cumulative 3-year fracture incidence in postmenopausal women with osteoporosis receiving once-yearly ZOL 5 mg or placebo in HORIZON-PFT.

Notes: * $P < 0.0001$; ** $P = 0.002$; † $P < 0.001$, relative risk reduction vs placebo. Created from data of Black et al.³⁵

Abbreviations: ZOL, zoledronic acid; HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial.

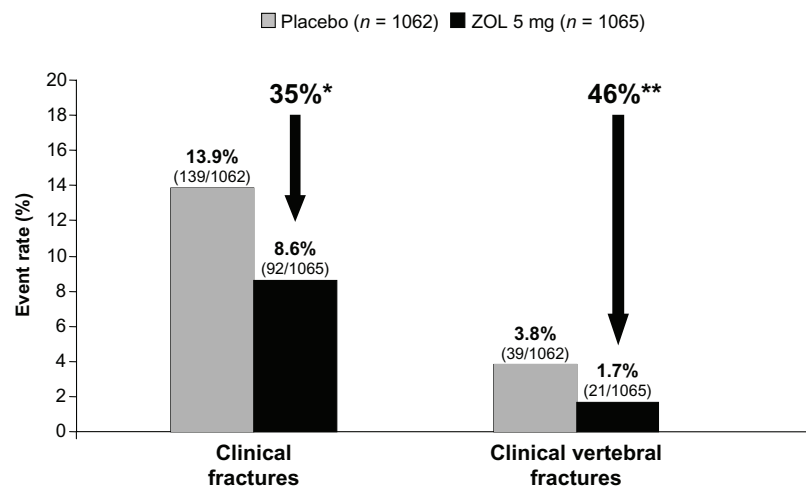


Figure 3 Cumulative fracture incidence in the HORIZON-RFT.³⁶

Notes: * $P = 0.001$ and ** $P = 0.02$, risk reduction vs placebo.

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Abbreviations: ZOL, zoledronic acid; HORIZON-RFT, Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Recurrent Fracture Trial.

more than 200,000 postmenopausal women aged 50 years or above with no prior osteoporosis diagnosis, 39.6% had osteopenia and 7.2% had osteoporosis on the basis of T-scores.³⁸ For women with T-scores diagnostic of osteopenia, the relative risk of developing clinical fractures within the first 12 months of follow-up was 1.73 (95% confidence interval, 1.57–1.91).³⁸ These findings indicate that although low BMD is a clear risk factor for future fracture, other risk factors play a role, and BMD should not be the sole determinant in risk assessment.^{20,39,40} As noted earlier, the National Osteoporosis Foundation recommends treatment for patients with low bone mass (BMD T-score between -1.0 and -2.5) and a 10-year probability of hip fracture of $\geq 3\%$, or of any major osteoporosis-related fracture of $\geq 20\%$, based on the FRAX calculation.²⁶

ZOL has also been shown to increase bone mass in postmenopausal women with osteopenia. In the HORIZON Prevention trial, 581 postmenopausal women with osteopenia (BMD T-scores between -1.0 and -2.5 at the lumbar spine and greater than -2.5 at the femoral neck) were randomized to receive an infusion of ZOL 5 mg at baseline and at 1 year (once-yearly administration), an infusion of ZOL at baseline and a placebo infusion at 1 year (administration once every 2 years), or a placebo infusion at baseline and at 1 year.⁴¹ The change in lumbar spine BMD at 2 years, the primary endpoint of the trial, was $+5.18\%$ with yearly ZOL and $+4.42\%$ with ZOL once every 2 years, compared with a loss of 1.32% in the placebo group ($P < 0.001$ for both comparisons) (Figure 4). Significantly greater increases for both ZOL regimens vs placebo were also observed in lumbar spine BMD at 12 months and at proximal femur sites (total hip,

femoral neck, and trochanter) at both 12 and 24 months ($P < 0.001$ for all comparisons). Thus, ZOL given once every 2 years was effective in preventing bone loss in postmenopausal women with low bone mass.

ZOL administered every 2 years is currently approved for prevention of osteoporosis. However, once-yearly administration of ZOL could also be considered for patients with BMD T-scores approaching -2.5 (the diagnostic cutoff point for osteoporosis) and a FRAX score indicating a 10-year risk of $>20\%$ for major osteoporotic fracture and/or $\geq 3\%$ for hip fracture. This decision, however, must be made by the physician on a case-by-case basis.

Safety and tolerability of ZOL and potential bisphosphonate safety issues

ZOL 5 mg infusions have been well tolerated in clinical trials. Postdose symptoms (eg, pyrexia, myalgia, headache, flu-like symptoms, and arthralgia) were the most commonly reported adverse events but were generally mild and transient. These symptoms tended to occur within 3 days of infusion and resolve within 3 days of onset (although resolution could take up to 14 days), and they were effectively managed with over-the-counter anti-inflammatory analgesics such as acetaminophen.^{12,35–37}

Renal effects

HORIZON-PFT included monitoring of renal effects in more than 5,000 patients after each study infusion.³⁵ Transient serum creatinine increases were reported in 1.8% of ZOL patients and 0.8% of placebo patients within 10 days of dosing, and in all cases resolved without specific therapy.¹²

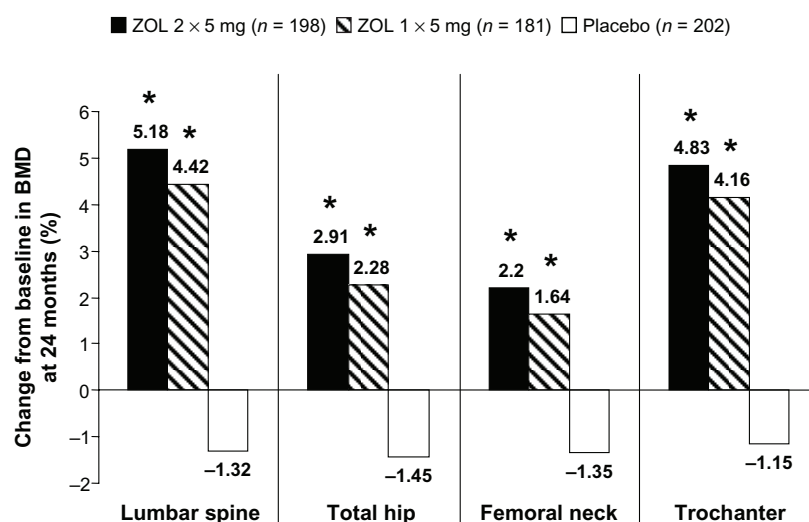


Figure 4 Percent change in BMD from baseline to 24 months in postmenopausal women with osteopenia in the HORIZON prevention of osteoporosis trial.

Notes: ZOL 2 × 5 mg, ZOL 5 mg given at baseline and at 1 year; ZOL 1 × 5 mg, ZOL 5 mg given at baseline and placebo given at 1 year; placebo, placebo given at baseline and at 1 year. * $P < 0.001$ vs placebo. Created from data of McClung et al.⁴¹

Abbreviation: ZOL, zoledronic acid.

No differences in long-term renal effects were observed more than 3 years between ZOL and placebo. ZOL should not be used in patients with impaired renal function (creatinine clearance <35 mL/min). ZOL should be administered over at least 15 minutes, and patients should be appropriately hydrated prior to administration.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been observed primarily in patients with multiple myeloma or metastatic cancer of the bone receiving IV bisphosphonates, with the majority of cases preceded by dental surgical procedures.⁴² A review published in 2007 indicates that there is a very low risk of ONJ in patients receiving oral bisphosphonates for osteoporosis (between 1 in 10,000 and <1 in 100,000 patient-treatment years).⁴³ There were no spontaneous reports of ONJ in ZOL clinical trials. A search of the HORIZON-PFT adverse event database identified potential cases of ONJ in 1 ZOL patient and 1 placebo patient. Both patients experienced delayed healing, and both cases resolved with antibiotics and/or debridement.³⁵

Hypocalcemia

A low incidence of hypocalcemia (<7.5 mg/dL; $\sim 0.2\%$) was observed in HORIZON-PFT, and no treatment-emergent cases were reported in HORIZON-RFT.¹²

Atrial fibrillation

In HORIZON-PFT, the overall incidence of all atrial fibrillation events was similar to ZOL and placebo, but more of

these events resulted in hospitalization in the ZOL group (1.3%) than in the placebo group (0.5%) and were classified as serious adverse events.³⁵ The majority of these events occurred more than 30 days after infusion, when active drug would be absent from the systemic circulation. Moreover, an electrocardiography substudy in 559 patients evaluated prior to and 9 to 11 days after the third infusion showed no significant difference in prevalence of atrial fibrillation in the ZOL group (2.1%) vs the placebo group (2.8%). In HORIZON-RFT, serious atrial fibrillation events occurred in 1.1% of ZOL patients and 1.3% of placebo patients (no significant difference). Preclinical and other clinical trials of ZOL have suggested no association between this agent and atrial fibrillation.³⁶

Oversuppression of bone remodeling and atypical fractures

As clinical experience with patients on bisphosphonate therapy has accumulated, case reports have emerged of subtrochanteric or femoral shaft fractures in patients on long-term treatment (usually >4 years). Some of these fractures have exhibited characteristics that are atypical of osteoporotic fracture (eg, transverse rather than spiral; preceded by thigh pain for weeks or months; bilateral; and associated with thick rather than thin bone cortices).⁴⁴⁻⁴⁸ Concerns have been raised that these fractures may be associated with long-term suppression of bone remodeling, resulting in stress fractures that do not heal. However, more information needs to be collected and evaluated in order to understand the cause of these fractures.

Appropriate prescribing and administration of ZOL 5 mg

The following are key aspects of appropriate prescribing and administration of ZOL 5 mg for prevention and treatment of osteoporosis:

1. Patients who are taking oral bisphosphonates can be safely switched to ZOL 5 mg. In a study in 225 postmenopausal women who had been on oral alendronate therapy for at least 1 year, a single infusion of ZOL 5 mg maintained lumbar spine BMD at 1 year and had a safety profile similar to that of weekly oral alendronate 70 mg.⁴⁹
2. Patients should have an adequate daily intake of calcium and vitamin D: 1,200 mg elemental calcium and 800–1,000 IU vitamin D.^{12,26}
3. Preexisting hypocalcemia and disturbances of mineral metabolism (eg, those associated with hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, or excision of small intestine) must be effectively treated before initiating therapy with ZOL.
4. Patients should drink at least 2 glasses of fluid within a few hours before receiving a ZOL 5 mg infusion.
5. ZOL should not be used in patients with impaired renal function (creatinine clearance <35 mL/min).
6. ZOL 5 mg infusion should be given over at least 15 minutes at a constant infusion rate.
7. Administration of acetaminophen following ZOL 5 mg administration may help reduce the incidence of postdose reaction symptoms.
8. For patients diagnosed with osteoporosis, once-yearly ZOL infusion may be prescribed.
9. For patients diagnosed with osteopenia and with low fracture risk according to FRAX, ZOL infusion every 2 years may be prescribed; for patients diagnosed with osteopenia and high fracture risk according to FRAX, once-yearly ZOL infusion may be considered.

A new approach to the prevention and treatment of osteoporosis

The availability of ZOL 5 mg as a once-yearly or once-every-2-years infusion offers a new approach to treatment and prevention of osteoporosis. ZOL has proven antifracture efficacy at key skeletal sites in placebo-controlled trials. Although there have not been any head-to-head trials comparing oral bisphosphonates with ZOL that provided fracture outcome data, ZOL has been shown to provide comparable efficacy to alendronate with respect to BMD gains.³⁷ Use of ZOL typically requires a separate appointment for administration of the infusion; however, by guaranteeing compliance for the duration of its

prolonged dosing interval, ZOL potentially removes barriers to optimal therapeutic outcomes.

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Disclosure

The author reports no conflicts of interest in this work.

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