

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
Prevention of aromatase inhibitor-associated bone loss (AIBL) in postmenopausal women	Zoledronic acid 4 mg IV every 6 months	Moderate quality; Fracture incidence	Reasonable choice for postmenopausal women with declines of a T-score* to ≤ -2.5 SD; women with decline of a T-score to ≤ -2 SD who have either a history of a previous fracture or have clinically important risk factors may be considered for treatment on an individualized basis, based on evaluation of fracture risk. (Accepted)	No conflicts of interest were identified for this application.	May 2008
Prevention of aromatase inhibitor-associated bone loss (AIBL) in premenopausal women	Zoledronic acid 4 mg IV every 6 months	Moderate quality; Changes in T-scores and BMD	Not fully established		

* T-score: A value derived from a bone mineral density (BMD) measurement that is reported as the number of standard deviations (SD) above or below the mean BMD values for a young healthy adult

Clinical Trial Summary:

Zoledronic acid to prevent bone loss in postmenopausal women receiving aromatase inhibitor therapy

Z-FAST/ZO-FAST Study

- Z-FAST (Zometa-Femara Adjuvant Synergy Trial) [ZO-FAST in non-US sites]^{1,2} is a study evaluating the effects of zoledronic acid on bone mineral density (BMD) of both the lumbar spine and total hip, changes in bone-turnover markers (at 12, 24, 36, and 60 months), the incidence of fractures (at 3 years), and time to disease progression. Inclusion criteria included postmenopausal women receiving letrozole (an aromatase inhibitor) without evidence of a lumbar spine or hip fracture, no history of a low-intensity fracture, no chronic corticosteroid use, and a baseline T-score of ≥ -2 at both sites.
- When compared with women in the delayed group (i.e., those who received treatment only after a diagnosis of osteopenia with T-score of < -2 or the development of a non-traumatic fracture), women receiving zoledronic acid in the upfront group had mean percent differences in BMD that were statistically significant at both the lumbar spine (LS) and total hip (TH) sites at 1 and 2 years (LS 4.4 and 5.9%; TH 3.3 and 4.7%, respectively).
- At 12 months, 8.3% of patients in the delayed group met criteria to receive zoledronic acid; by 24 months, 12.7% of the women received zoledronic acid.
- Bone turnover marker analysis at 1 year revealed a significant decrease in both serum N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) concentrations in the upfront group (-15.1 and -8.8% , respectively); whereas, concentrations were increased for both markers in the delayed group (19.9 and 24.3%, respectively).
- At 24 months, less than 3% of the women in the upfront group experienced a BMD decline of $\geq 8\%$ from baseline compared with a progressive increase in the delayed group of 3 to 15% at 6 and 24 months, respectively [$p < 0.001$].
- At 1 year, the incidence of mild to moderate osteopenia ($-1 \geq$ T-score ≥ -2) was 3.4% in the upfront group versus 12.6% in the delayed group in women with a normal BMD at baseline; in women with pre-existing osteopenia, progression to severe osteopenia (T-score < -2), occurred more frequently in those receiving delayed treatment compared with upfront treatment arm (14.8 versus 1.4%).
- The incidence of fractures at 2 years was similar between groups: 4.3 (upfront) versus 4% (delayed).

NCCTG-N03CC Study

- Data from a phase III randomized study, the North Central Cancer Treatment Group (NCCTG) – N03CC trial, has shown an improvement in BMD at the LS, TH and femoral neck using zoledronic acid (i.e., 4 mg every 6 months) in an upfront versus a delayed schedule – in women receiving letrozole (an aromatase inhibitor) following prior tamoxifen therapy. A 1.7% increase compared with a 3.7% decrease in LS BMD was reported in the upfront versus delayed group at one year. ($p = < 0.001$).³
- A statistically significant difference in the rate of decline of a clinically meaningful BMD at the LS, defined as a BMD decrease of $> 5\%$, was reported at one year following treatment as 3% (upfront) and 20.7% (delayed) [$p = < 0.0001$].
- The incidence of hip fractures at one year was reported as similar for both groups.

Zoledronic acid to prevent bone loss in premenopausal women receiving aromatase inhibitor therapy

- The Austrian Breast and Colorectal Cancer Study Group-12 (ABCSG-012) is a study evaluating the long-term effects (i.e., 5 years) of zoledronic acid on BMD for premenopausal women receiving the combination of either tamoxifen + goserelin or anastrozole (an aromatase inhibitor) + goserelin (AG).⁴
- BMD results reported at 3 years, based on the remaining patients (approximately 1/3 of those originally enrolled), showed a mean LS T-score change of -2.6 in the AG group compared with an improvement of $+0.88$ in the AG + zoledronic acid group; changes in the trochanter T-score were -0.85 and $+0.029$ in the AG and AG + zoledronic acid groups, respectively. Bone loss at the LS was reported as 17% in the AG group compared with 3% with the addition of zoledronic acid; 12 and 1% losses were reported for the same groups, respectively, at the trochanter site.
- 44% of the women receiving AG + zoledronic acid developed osteopenia at the LS after 36 months compared with 54% of those receiving AG alone; the incidence of osteoporosis was reported as 0% in the zoledronic acid arm compared with 25% in the AG only arm.
- No fracture data has been reported for this study.

Discussion:

Background

The ASCO 2003 guidelines recommend a baseline and an annual dual-energy x-ray absorptiometry (DEXA) scan for postmenopausal women receiving aromatase inhibitors and for premenopausal women with therapy-induced menopause — both populations of women considered at high-risk for fractures. These guidelines recommend bisphosphonate therapy for high-risk women with osteoporosis, defined as a T-score of ≤ -2.5 of the LS or TH; however, no recommendations are made for the use of bisphosphonates in women with osteopenia.⁵

Prevention in Postmenopausal Women

Zoledronic acid, given in the upfront setting for postmenopausal women with a normal BMD (T-score of > -1), results in an improvement of BMD of both the LS and TH compared with women who received zoledronic acid only after osteopenia was diagnosed or in women not receiving zoledronic acid. Experts have suggested that a $>5\%$ decline in BMD over 2 years may be a clinically significant measurement to evaluate bone loss and a threshold to consider bisphosphonate therapy in high-risk women.⁶ Additionally, a reduction in 1 standard deviation (SD) of a T-score exponentially increases the 5-year fracture risk in women 65 years of age and older.⁷ Patients receiving upfront zoledronic acid in the Z-FAST/ZO-FAST trials experienced less decline in BMD compared with patients in the delayed group; however, only 15% of the women in the delayed group experienced a clinically significant bone loss after 2 years.⁴ Absolute reductions in T-scores were not reported for the Z-FAST study. The clinical significance of the small changes in BMD observed in women receiving upfront zoledronic acid is not fully known. However, results from a meta-analysis have revealed that changes in BMD (or T-scores) correlate with vertebral fracture risk reduction in a non-linear fashion; thereby, suggesting that other changes to bone strength, independent of BMD, may be contributing to the reduction in fractures seen with antiosteoporotic therapy.⁸ A

decline in bone turnover markers may therefore, reflect an early process contributing to the reduction of both vertebral and nonvertebral fractures prior to, and independent of an improved BMD measurement.⁹

Data from the NCCTG study showed a significant decline in BMD of the LS in women receiving zoledronic acid on a delayed schedule versus on upfront schedule; however, the data is preliminary at one year and no published information on the fracture rate is available. The investigators indicated the incidence of hip fractures is similar between the two groups after one year of treatment. Women in this study are stratified by the duration of tamoxifen therapy, the interval between tamoxifen therapy and the initiation of letrozole, baseline T-score, and whether they have received adjuvant chemotherapy. Bone-turnover marker (e.g., NTx and BSAP) concentrations are to be analyzed at 3, 6 and 12 months; whereas, BMD measurements will be assessed annually until 5 years after the completion of therapy. The incidence of osteoporosis, fracture rate, and time to disease progression will also be reported for this study.¹⁰ Theoretically, prior exposure to tamoxifen could result in a bone-loss sparing effect for women receiving subsequent aromatase inhibitor therapy; therefore, results from this study will provide information on the long-term effects of bisphosphonate therapy in women treated with this adjuvant hormonal combination.

The primary end point FDA has used to approve bisphosphonate therapy for the prevention of osteoporosis in postmenopausal women without breast cancer is the combination of both BMD improvements and a reduction in fracture rate; however, BMD measurements alone may be considered when existing clinical trial results have demonstrated a reduced fracture rate and there are no clinically important safety issues.¹¹ The incidence of fractures at 2 years in the Z-FAST study was the same for women receiving zoledronic acid using an upfront or a delayed schedule. Within the delayed group, only 13% of the patients met the criteria to receive zoledronic acid based on their progression to osteopenia; 87% of the women did not require any intervention. The Z-FAST/ZO-FAST investigators plan to collect fracture and BMD data for a total of 3 and 5 years, respectively; therefore, the full benefit and impact of zoledronic acid on the reduction of fractures will be clearer at this time.

Prevention in Premenopausal Women

Premenopausal women receiving the combination of an aromatase inhibitor (AI) plus a gonadotropin-releasing hormone (GnRH) to induce ovarian suppression are at an increased risk for accelerated bone loss, defined by a 16% decrease in BMD at 2 years.¹² The addition of zoledronic acid to the AG combination in the ABCSC-012 study resulted in improved BMD and less decline in T-scores at 36 months, compared with women receiving AG alone. Additionally, the use of zoledronic acid with an AI + GnRH regimen reduced the progression to osteoporosis; however, no fracture-reduction data has been reported for this study. Therefore, the long-term clinical effects of zoledronic acid are not fully established for this patient population. The use of bisphosphonates has not been studied in premenopausal women receiving single-agent AI therapy, with or without prior tamoxifen therapy, for the prevention of AIBL.

Summary:

Until studies reach their predetermined end points, thereby providing a complete assessment of the impact on fracture incidence, the use of bisphosphonate therapy in postmenopausal women receiving AI therapy without additional risk factors, should be limited to those who have a T-score decline to ≤ -2.5 . The interim results of the Z-FAST study at 2 years show improvements in BMD and bone turnover markers, but no difference in fracture rates, in women whose fracture risk is defined by their menopausal status and treatment with an aromatase inhibitor. The use of zoledronic acid in women with low BMD measurements (or T-scores), with additional clinically important risk factors, has not been studied, and therefore, is not fully established. Low BMD measurements are predictive for the relative-risk of fracture in postmenopausal women;⁷

however, identification of other risk factors is important to determine the absolute fracture risk and to establish the need for preventive therapy. Women with a history of prior fracture, or with clinically important risk factors (e.g., age, maternal history of fracture, a low weight or BMI),¹³ or other lifestyle-related factors, as defined by the World Health Organization (WHO),¹⁴ with moderate osteopenia (a T-score < -2.0 as studied in the Z-FAST study), may be characterized as moderate to high risk, and therefore, may be considered for bisphosphonate therapy on an individualized basis. Results from the SABRE study, which stratifies patients by their fragility-fracture risk, may help to further define the role of bisphosphonate therapy in such patients.¹⁵

Dosage

The dose that has been studied for the prevention of AIBL in premenopausal and postmenopausal women is 4 mg IV every 6 months. The long-term safety and efficacy of semi-annual (or more frequent) bisphosphonate administration are not fully known in these patient populations. It should be noted that the dosage studied in these patients is higher than the approved dosage for the treatment of osteoporosis in postmenopausal women not receiving AIs (i.e., 5 mg IV once yearly).¹⁶

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