AHFS Final Determination of Medical Acceptance: Off-label Use of Zoledronic Acid for the Prevention of Aromatase Inhibitor-associated Bone Loss

Drug/Drug Combination: Zoledronic acid

Off-label Use: Prevention of aromatase inhibitor-associated bone loss

Criteria Used in Selection of Off-label Use for Review:

Postmenopausal women:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in January 2009. At the time of the original review, the use of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss was a reasonable choice (accepted) for postmenopausal women with declines of a T-score to ≤-2.5 standard deviations (SD) and could be considered on an individualized basis, based on evaluation of fracture risk, in women with declines of a T-score to ≤-2 SD who have either a history of a previous fracture or clinically important risk factors.

Premenopausal women:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in January 2009. At the time of the original review, the use of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in premenopausal women was not fully established.

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Bone mineral density

Grade of Recommendation:

Zoledronic acid 4 mg IV every 6 months for 5 years

Postmenopausal women: Reasonable choice (Accepted, with possible conditions)

Premenopausal women: Not fully established

Narrative Summary:

Prevention in Postmenopausal Women

Efficacy and safety of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in women receiving adjuvant hormonal therapy for early-stage breast cancer have been studied in several phase 3, open-label, randomized studies (Zometa-Femara Adjuvant Synergy Trial [Z-FAST], ZO-FAST, E-ZO-FAST,

and North Central Cancer Treatment Group [NCCTG]-N03CC study).[10017, 10019, 10021, 10022] The Z-FAST, ZO-FAST, and E-ZO-FAST studies included postmenopausal women with stage I–IIIa estrogen receptor-positive and/or progesterone receptor-positive breast cancer; patients had a baseline T-score of -2 standard deviations (SD) from normal or better and did not have a history of a low-intensity fracture or evidence of an existing fracture.[10001, 10019, 10022] Patients enrolled in these studies were randomized to receive upfront or delayed zoledronic acid.[10017, 10019, 10022] Women in the upfront group received zoledronic acid following randomization; women in the delayed group did not begin treatment with zoledronic acid until their T-score declined to less than -2 standard deviations or after occurrence of a nontraumatic fracture or evidence of an asymptomatic fracture.[10001, 10002, 10019, 10022] Patients received zoledronic acid 4 mg by IV infusion over 15 minutes every 6 months for 5 years in addition to oral calcium and vitamin D.[10001, 10019, 10022] All patients received letrozole 2.5 mg orally daily for 5 years.[10001, 10018, 10022] Patients enrolled in these studies were not permitted to receive other drugs known to affect the skeleton (e.g., IV bisphosphonates, chronic corticosteroids) during the study or for a specified period of time prior to study entry.[10001, 10019, 10022]

In the Z-FAST study, bone mineral density (BMD) in both the lumbar spine and total hip sites was improved at 61 months for the upfront group but declined in the delayed group in women still remaining in the study at that time (approximately 60% of those initially enrolled), regardless of baseline T-score, clinically important risk factors, or chemotherapy status.[10017] A decline in BMD of at least 8% in the lumbar spine in women with a normal BMD at baseline (defined as T-score better than -1 SD from normal) occurred more frequently in those receiving delayed treatment than in those receiving upfront treatment (20 versus 1.7%, respectively, based on intent-to-treat analysis).[10017] In women with preexisting mild to moderate osteopenia (i.e., a decline to a T-score between -1 and -2 SD), a BMD decrease of at least 8% in the lumbar spine occurred in 5.7 and 0.3% of patients in the delayed and upfront treatment groups, respectively, based on intent-to-treat analysis.[10017] At 61 months, upfront administration of zoledronic acid reduced progression to mild to moderate osteopenia in women with a normal BMD at baseline compared with delayed administration of the drug (2 versus 11%, respectively), and reduced progression to severe osteopenia (i.e., a decline to a T-score below -2 SD) in women with preexisting mild to moderate osteopenia (0 versus 4.9%, respectively).[10001, 10017] The 2-year fracture rate was similar (4.3 and 4%) for both treatment groups, with an increase at 5 years to 9.3 and 11% in the upfront and delayed groups, respectively.[26, 10002, 10017] The mean difference in percentage change from baseline BMD for the lumbar spine and total hip sites at 61 months was 8.9 and 6.7%, respectively, between the upfront treatment and delayed treatment groups.[10017] At the time of the final analysis at a follow-up of 61 months, 24.6% of the women in the delayed group had begun treatment with zoledronic acid; 66.2% of these women had met protocol-defined criteria to receive zoledronic acid.[10017] Bone turnover marker analysis at 61 months revealed lower serum N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) concentrations in the upfront group than in the delayed group.[10017] Renal impairment occurred at a similar rate in both treatment groups; however, potential osteonecrosis of the jaw occurred more frequently in women receiving upfront therapy than in those receiving delayed therapy (2 versus 0 cases).[10017]

Data from the ZO-FAST study also demonstrated improvement of BMD in both the lumbar spine and total hip sites at 60 months for the upfront group but BMD declined in the delayed group.[10019] Upfront administration of zoledronic acid increased BMD in the lumbar spine by 3.9% in women with a normal BMD at baseline, but a 7.1% decrease occurred in those receiving delayed administration of the drug.[10019] Upfront zoledronic acid substantially improved BMD in the lumbar spine by 5.3% compared with delayed administration, which resulted in a 4.2% decrease in women with established (natural) postmenopausal status.[10019] In women who were newly (induced) postmenopausal, a decrease of 0.3 or 9.3% in BMD in the lumbar spine was reported in the upfront or delayed treatment groups, respectively.[10019] At the time of the final

analysis, the mean difference in percentage change from baseline BMD in the lumbar spine and total hip sites was 9.7 and 5.8%, respectively, between the upfront treatment and delayed treatment groups.[10019] At the time of the final analysis at a follow-up of 60 months, 27% of the women in the delayed group had met criteria to receive zoledronic acid.[10019] Renal impairment occurred at a similar rate in both treatment groups, and 9 potential osteonecrosis of the jaw events were reported in the overall study population.[10019]

Data from the E-ZO-FAST study were consistent with the Z-FAST and ZO-FAST studies.[10022] Improvement of BMD at both the lumbar spine and total hip sites was observed at 12 months for the upfront group, but BMD declined in the delayed group regardless of baseline T-score, postmenopausal status, or chemotherapy status.[10022] At 12 months, 13% of the women in the delayed group had met criteria to receive zoledronic acid.[10022] In this study, upfront administration of zoledronic acid reduced progression to osteopenia in women with a normal BMD at baseline compared with delayed administration of the drug (2.1 versus 12.5%, respectively).[10022] In women with preexisting osteopenia, improvement to a normal BMD occurred more frequently in women receiving upfront administration of zoledronic acid compared with those receiving delayed administration of the drug (18.3 versus 8%, respectively), and maintenance of a normal BMD in women with a normal BMD at baseline occurred more frequently in those receiving upfront therapy than in those receiving delayed therapy (71.1 versus 57.2%, respectively).[10022] The 1-year fracture rate was 0.8 and 1.9% in the upfront and delayed groups, respectively.[10022] At 12 months, the mean difference in percentage change from baseline BMD in the lumbar spine and total hip sites was 5.4 and 3.3%, respectively, between the upfront and delayed treatment groups.[10022] Among women with established postmenopausal status and those who were recently (induced) menopausal, the percentage change from baseline BMD between the upfront and delayed treatment groups was 5.2 and 6.8%, respectively.[10022] Adverse effects generally were similar in both treatment groups, although bone pain (8.3 versus 4.1%), pyrexia (6.7 versus 0%), and influenza-like illness (6 versus 1.1%) occurred more frequently in women in the upfront group compared with those in the delayed group.[10022] Osteonecrosis of the jaw occurred in 0.4% of women receiving upfront therapy compared with none of those receiving delayed therapy.[10022]

Data from a similarly designed study (NCCTG-N03CC) also demonstrated an improvement in lumbar spine BMD in postmenopausal women treated with letrozole who had received prior tamoxifen therapy and were randomized to receive upfront zoledronic acid therapy.[10020, 10021] At the time of the final analysis at a follow-up of 60 months, 42% of women initially enrolled in the study were evaluable for the primary BMD end point and 14.7% of women in the delayed group crossed over to receive zoledronic acid.[10021] Clinically important lumbar spine bone loss (i.e., BMD decrease of 5% or greater from baseline) occurred more frequently in women receiving delayed therapy compared with those receiving upfront therapy (41.2 versus 10.2%), and clinically important total hip and femoral neck bone loss was reported in 45.8 or 7.6% of those receiving delayed or upfront therapy, respectively; a BMD decrease of 10% from baseline in the lumbar spine occurred in 16.8 and 5.1% of women in the delayed and upfront treatment groups, respectively.[10021] The mean difference in BMD for the lumbar spine was 9.4% between the upfront treatment and delayed treatment groups.[10021] However, there was no difference between the groups in the 5-year fracture rate.[10021] Adverse effects generally were similar between both treatment groups, although pyrexia (9 versus 3%) and elevated serum creatinine concentrations (9 versus 5%) occurred more frequently in women receiving upfront therapy compared with those receiving delayed therapy.[10021] Osteonecrosis of the jaw occurred in 2 or 1% of women receiving upfront or delayed therapy, respectively.[10021]

Although longer-term follow-up of the 3 companion Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, E-ZO-FAST) and NCCTG-N03CC study is needed to further clarify between-treatment differences

in fracture incidence,[10017, 10019, 10021, 10022] upfront administration of zoledronic acid in postmenopausal women receiving aromatase inhibitor therapy significantly prevented lumbar spine and total hip BMD losses compared with those whose therapy was delayed until a decline in T-score to less than -2 SD, nontraumatic fracture, or evidence of an asymptomatic fracture occurred.[10017, 10019, 10021, 10022] Based on current evidence, use of zoledronic acid in postmenopausal women receiving aromatase inhibitor therapy may be considered a reasonable choice (accepted, with possible conditions); factors that should be considered when determining the optimal time to initiate therapy are baseline BMD and history of prior fractures.

Prevention in Premenopausal Women

Efficacy and safety of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in premenopausal women receiving adjuvant hormonal therapy plus a gonadotropin-releasing hormone (GnRH, luteinizing hormone-releasing hormone) agonist (e.g., goserelin) for stage I or II estrogen receptor-positive or progesterone receptor-positive breast cancer were studied in a BMD substudy of a phase 3, open-label, randomized study (Austrian Breast and Colorectal Cancer Study Group-12 [ABCSG-12]).[10004] The ABCSG-12 study included premenopausal women with early-stage estrogen receptor-positive and/or progesterone receptor-positive breast cancer.[10004] In this substudy, 401 patients were randomized in a 1:1:1:1 ratio to receive hormonal therapy with tamoxifen (20 mg orally daily) or anastrozole (1 mg orally daily) plus a GnRH agonist (goserelin acetate 3.6 mg by subcutaneous injection every 28 days) to induce ovarian suppression with or without zoledronic acid.[10004] An initial zoledronic acid dosage of 8 mg IV every 6 months was used; the protocol was subsequently amended to reduce the dosage to 4 mg by IV infusion over 15 minutes every 6 months following reports of increased toxicity (e.g., nephrotoxicity) with the higher dose.[10004] Therapy was continued for a duration of 3 years in all treatment groups.[10004]

A lower rate of decline in bone loss after 3 years of treatment was reported in those premenopausal women still remaining in the study at that time (about one-third of those initially enrolled) who were receiving zoledronic acid with anastrozole-goserelin or tamoxifen-goserelin compared with those receiving anastrozole-goserelin or tamoxifen-goserelin alone.[10004] The incidence of osteopenia at 3 years in the lumbar spine was 44 or 54% in patients receiving zoledronic acid-anastrozole-goserelin or anastrozole-goserelin alone, respectively.[10004] Osteoporosis was not reported in patients receiving zoledronic acid-anastrozole-goserelin, but 25% of women receiving anastrozole-goserelin alone became osteoporotic.[10004] Two years after the completion of the study treatment, partial improvement in BMD at both the lumbar spine and trochanter sites was observed in those receiving anastrozole-goserelin or tamoxifen-goserelin alone, although BMD had not fully recovered to the baseline measurement; in contrast, an improvement in BMD was reported in those receiving zoledronic acid with anastrozole-goserelin or tamoxifen-goserelin.[10025] Although not specific for the anastrozole-goserelin regimen, no fractures were reported in patients receiving zoledronic acid at 5 years; 2 fractures occurred in women receiving anastrozole-goserelin or tamoxifen-goserelin alone.[10025]

Improvements in BMD were observed in premenopausal women with early-stage breast cancer when zoledronic acid was administered concurrently with an aromatase inhibitor and GnRH agonist.[10004] However, longer-term follow-up of this study is needed, especially as these women enter menopause, to further clarify lasting clinical efficacy (i.e., clinically important fracture reduction) and late adverse effects of zoledronic acid therapy.[10004] Based on current evidence, use of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in premenopausal women is not fully established because of unclear risk/benefit.

Dosage:

Prevention of Aromatase Inhibitor-associated Bone Loss in Postmenopausal Women

When zoledronic acid has been used for prevention of bone loss associated with use of aromatase inhibitor therapy in postmenopausal women, zoledronic acid 4 mg has been administered by IV infusion over 15 minutes every 6 months for 5 years.[10001, 10019, 10022] In clinical trials, patients were encouraged to take supplemental oral calcium (500 mg to 1.2 g daily) and vitamin D (400–800 units daily).[10001, 10019, 10022]

References:

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10024. Gnant M, Mlineritsch B, Stoeger H et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol*. 2015; 26:313-20.

10025. Gnant M, Mlineritsch B, Luschin-Ebengreuth G et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density study. *Lancet Oncol*. 2008; 9:840-9.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); bone mineral density

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Postmenopausal women:

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Premenopausal women:

Recommended use (Accepted): 0 votes

Reasonable choice (Accepted, treatment option): 0 votes

Not fully established (Unclear risk/benefit or equivocal): 5 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Prevention in Postmenopausal Women

Although longer-term follow-up of the 3 companion Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, E-ZO-FAST) and NCCTG-N03CC trial are needed to further clarify between-treatment differences in fracture incidence,[10017, 10019, 10021, 10022] upfront administration of zoledronic acid in postmenopausal women receiving aromatase inhibitor therapy significantly prevented lumbar spine and total hip BMD losses compared with those who delayed therapy until a decline in T-score to less than -2 SD or nontraumatic fracture or evidence of an asymptomatic fracture occurred.[10017, 10019, 10021, 10022] Based on current evidence, use of zoledronic acid in postmenopausal women receiving aromatase inhibitor therapy may be considered a reasonable choice (accepted, with possible conditions); factors that should be considered when determining the optimal time to initiate therapy are baseline BMD and history of prior fractures.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Prevention in Premenopausal Women

Improvements in BMD were observed in premenopausal women with early-stage breast cancer when zoledronic acid was administered concurrently with an aromatase inhibitor-gonadotropin-releasing hormone agonist regimen.[10004] However, longer-term follow-up of this study is needed, especially as these women enter menopause, to further clarify lasting clinical efficacy (i.e., clinically important fracture reduction) and late adverse effects of zoledronic acid therapy.[10004] Based on current evidence, use of zoledronic acid for the prevention of aromatase inhibitor-associated bone loss in premenopausal women is not fully established because of unclear risk/benefit.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Postmenopausal women:

Reviewer #1: Either upfront or delayed therapy (i.e., T-score declined to less than -2 standard deviations or prior symptomatic or asymptomatic fracture) are acceptable. Encouraged to be given with calcium and vitamin D. No data to support therapy beyond 5 years.

Reviewer #2: Based on data provided. Reasonable risk-benefit.

Reviewer #3: A number of high-quality clinical trials have demonstrated positive results in identical patients on AIs resulting in improvement in BMD and, in some, a reduction in fracture rates. The best results are obtained when started earlier in treatment versus a delay to a definitive diagnosis of osteoporosis or a bone fracture. I agree with an update from reasonable [choice] to recommended for those at risk, as defined.

Premenopausal women:

Reviewer #1: While there is a reduction in BMD and osteopenia/osteoporosis, the short follow-up precludes clear benefit especially since therapy would be initiated for osteoporosis when identified.

Reviewer #2: Data presented include one study. Looking at AI + Zometa. Subgroup used for 3-year follow-up (33% [135 patients])- showed 25% of control group- roughly 33 patients with osteoporosis - 2 fractures. Need more data given potential risks.

Reviewer #3: Biggest concern is that most of the data, while encouraging, comes from one group and has not been widely validated. I could go with the reasonable choice or not fully established as the group prefers. Data has matured since 2008 AHFS off-label determination- which is the strongest point.

Comments on Draft Narrative Summary:

Reviewer #2: [Premenopausal women] Risk vs benefit ratio - reversible versus sustained AEs?

Comments on Proposed Consensus Recommendation:
None.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP

AHFS Oncology Expert Committee Members (reviewing and voting): Raymond Hohl, M.D., Ph.D.; Ron Walters, M.D., MBA, MHA, MS; LeAnn Norris, Pharm.D., BCPS, BCOP; Mandy Gatesman, Pharm.D., BCOP; Sandra Kurtin, RN, MS, AOCN, ANP-C

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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