

Looking Beyond the “Obvious” to Promote Bone Health

ASHP Advantage E-Newsletter

Winter 2010

Current Controversies in Bone Health and Osteoporosis Prevention and Treatment: The Experts Answer Questions from Health-System Pharmacists

A Midday Symposium on promoting bone health was held at the 44th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, on December 8, 2009. Attendees at the symposium submitted questions about osteoporosis screening, prevention, and treatment that were later addressed by the faculty in a live webinar conducted on January 27, 2010. Highlights from this webinar, as well as other emerging information related to bone health, are summarized in this newsletter. An update on vitamin D requirements for bone health and emerging treatments for osteoporosis prevention and treatment will be provided in another newsletter to be released this Spring.

Question: Central dual-energy X-ray absorptiometry (DXA) and the World Health Organization automated fracture risk assessment tool known as FRAX are widely used to screen for low bone mineral density (BMD) and assess the risk for osteoporotic fractures. Are there other tools that can be used for screening and risk assessment?

Clinicians often have difficulty determining which patients are at risk for osteoporosis and therefore candidates for BMD testing. Clinical prediction rules have been developed to assist with decision making about BMD testing by identifying postmenopausal women at risk for osteoporosis.¹ Two such clinical prediction rules, the Simple Calculated Osteoporosis Risk Estimation (known as SCORE) and the Osteoporosis Risk Assessment Instrument (known as ORAI), involve the use of weighted point values for various osteoporosis risk factors. In a previously characterized population of postmenopausal women, these clinical prediction rules were found to perform poorly as general screening tools for osteoporosis, although these clinical prediction rules may be useful for identifying women who do not need BMD testing, especially younger postmenopausal women (e.g., 45-65 years of age).

Several alternatives to central DXA are available, including quantitative computed tomography (QCT), peripheral QCT (known as pQCT), peripheral DXA (referred to as pDXA), and quantitative ultrasound (QUS).² The heel QUS

Faculty

Eric J. MacLaughlin,
Pharm.D., FCCP, BCPS
Initiative Chair
Associate Professor and Head of
Adult Medicine Division
School of Pharmacy
Texas Tech University Health
Sciences Center
Amarillo, Texas

Laura Boehnke Michaud,
Pharm.D., FASHP, BCOP
Clinical Pharmacy Specialist
Manager, Clinical Pharmacy
Services
The University of Texas M. D.
Anderson Cancer Center
Houston, Texas

Sheryl F. Vondracek,
Pharm.D., FCCP, BCPS
Associate Professor
School of Pharmacy
University of Colorado Denver
Aurora, Colorado

test (Figure 1) is commonly used to predict the risk for fractures in postmenopausal women and men 65 years of age or older.^{3,4} The lack of exposure to radiation is an advantage of this test over central DXA. The T-scores from the two methods are not directly comparable.

“ The convenience, ease of use, low cost, and portability of QUS equipment and the lack of certification requirements for users of the equipment make QUS suitable for screening for low bone mineral density in the community, especially in rural settings where access to DXA equipment is limited. ”

— Eric J. MacLaughlin, Pharm.D., FCCP, BCPS



Figure 1. Heel Quantitative Ultrasound.

The online QFracture tool (<http://www.qfracture.org/>) is an alternative to FRAX (<http://www.shef.ac.uk/FRAX/>) for estimating the 10-year risk for hip or other major osteoporotic fractures.⁵ The QFracture tool was developed from a United Kingdom database of more than 2 million records. It is used primarily as a research tool. Customized versions of the FRAX tool are available for residents of a wide variety of countries and Asians, blacks, Caucasians, and Hispanics living in the United States.⁶

Question: For how long should bisphosphonate therapy be continued? What factors should be considered in making decisions about taking a “drug holiday”?

Taking a bisphosphonate “drug holiday” (i.e., discontinuation of therapy with follow-up monitoring of BMD using central DXA and markers of bone turnover to detect a need to restart therapy) has been suggested for patients who have taken the drugs for a long time for several reasons. Lack of persistence (i.e., a short duration of treatment) and nonadherence to prescribed bisphosphonate therapy may be a problem because of short-term gastrointestinal adverse effects and the lack of a readily apparent immediate benefit from the drugs.⁷ Concerns have been raised about rare long-term effects from bisphosphonate therapy, particularly atypical fractures from prolonged suppression of bone turnover and osteonecrosis of the jaw.^{8,9} Evidence of a fracture benefit from continuing bisphosphonate therapy beyond 5 years is lacking.⁸ The possible need for lifelong bisphosphonate therapy can be daunting, and the promise of a drug holiday may make lack of persistence and nonadherence less of a problem. Guidelines for which patients taking long-term bisphosphonate therapy are candidates for a drug holiday are not available.

A protective effect of bisphosphonates against fractures appears to persist for a substantial amount of time after discontinuing therapy despite decreases in BMD and increases in bone turnover after stopping the drug.^{10,11} The best evidence of these effects was found in the Fracture Intervention Trial Long-term Extension (FLEX) trial, a randomized, double-blind study of more than 1000 postmenopausal women who had received alendronate in the Fracture Intervention Trial (known as FIT) for a mean of 5 years and had a total hip T-score of -3.5 or better.¹⁰ Enrollees in the FLEX trial

were randomly assigned to receive alendronate or placebo for an additional 5 years. The placebo group represents women taking a drug holiday. At the end of the 5-year FLEX trial, there was a moderate decline in BMD and increase in bone turnover markers in the placebo group compared with the group continuing alendronate therapy. The BMD and bone turnover markers did not return to pretreatment values in all patients. There was no significant difference between the two groups in most fracture outcomes, although there was a 55% reduction in the risk of clinical vertebral fractures in the group continuing alendronate therapy (2.4%) compared with the placebo group (5.3%). These findings suggest that taking a bisphosphonate drug holiday after 5 years of treatment does not increase the risk for fractures in most postmenopausal women. The investigators suggested continuation of bisphosphonate therapy beyond 5 years only in women at very high risk for clinical vertebral fractures (e.g., with a history of low-trauma fractures) based on a subgroup analysis.

The risk for osteoporotic fracture during a drug holiday may depend on the rate of compliance with and duration of bisphosphonate therapy before discontinuation and the duration of the drug holiday. In an analysis of a large database of elderly women receiving bisphosphonates, the incidence of hip fractures was significantly higher in women taking a drug holiday than in women not taking a holiday.¹² However, the increased risk of hip fracture associated with the drug holiday was attenuated by a high rate of compliance or a long duration of therapy (e.g., 3 years) before taking the drug holiday. The risk for hip fracture appeared to increase when the drug holiday extended beyond 1 year compared with a shorter time frame.

Bisphosphonates are retained in bone for a long time because they bind rapidly to exposed hydroxyapatite and are incorporated into newly formed bone.¹³ The drug is later released into the circulation for recycling during bone remodeling. A period of bisphosphonate “bone loading” may occur during initial therapy. If a drug holiday is taken after this bone-loading period, the release of bisphosphonate from bone may suffice to maintain BMD and prevent increased bone turnover for a long time. A minimum period of bisphosphonate use may be required to achieve sufficient bone loading that will maintain BMD during a drug holiday.^{10,11} More data are needed to understand both the minimum time to be on bisphosphonates before considering a drug holiday and the maximum duration of the holiday. Very likely these durations will vary for the different bisphosphonates depending on their bone binding affinity and potency.

The four bisphosphonates used to prevent or treat osteoporosis (Figure 2) differ in their affinity for bone mineral and uptake into the skeleton, with progressive decreases among the agents in the following sequence: zoledronic acid > alendronate > ibandronate > risedronate.¹⁴ These agents also differ in their potency based on the extent to which they inhibit farnesyl pyrophosphate synthase, a key enzyme in osteoclast function. Enzyme inhibition decreases progressively in the following sequence: zoledronic acid > risedronate > ibandronate > alendronate. The clinical implications of these differences among bisphosphonates are unknown.

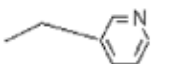
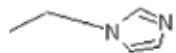
Agent	R ₁ side chain	R ₂ side chain
Alendronate	-OH	$-(\text{CH}_2)_3\text{-NH}_2$
Ibandronate	-OH	$-\text{CH}_2\text{-CH}_2\text{N} \begin{cases} \text{CH}_3 \\ (\text{CH}_2)_4\text{-CH}_3 \end{cases}$
Risedronate	-OH	
Zoledronate	-OH	

Figure 2. Differences in Bisphosphonate Chemical Structures.

Given the lack of guidelines regarding duration of bisphosphonate therapy, Dr. Vondracek recommends making the decision to stop therapy on a case-by-case basis considering individual patient preference and the risk-to-benefit ratio. The best evidence to date for a bisphosphonate drug holiday is in postmenopausal women, such as those enrolled in the FLEX trial, who have received alendronate for approximately 5 years. It seems reasonable to consider a drug holiday in postmenopausal women—and possibly men—at lower risk for fracture who have received bisphosphonate therapy for a shorter period (i.e., 3 years) or received therapy with a bisphosphonate that may have a shorter bone retention, such as risedronate or ibandronate. Monitoring of patients during drug holidays is extremely important to detect if substantial bone loss occurs, signaling the need to restart therapy.

“ Because no guidelines are available, decisions about bisphosphonate drug holidays should be made on a case-by-case basis, taking into consideration patient preferences and the risks and benefits of interrupting therapy. ”

— Sheryl F. Vondracek, Pharm.D., FCCP, BCPS

Question: How do the selective estrogen receptor modulators (SERMs) differ in their clinical effects on the bones?

Tamoxifen, the prototypical SERM, has been the gold standard for the treatment of breast cancer for more than four decades. The Food and Drug Administration (FDA)-approved indications for tamoxifen include palliative treatment of metastatic breast cancer in women and men, adjuvant treatment of noninvasive and invasive early stage breast cancer in women, and reduction of the incidence of breast cancer in women at high risk.¹⁵ The drug has a well-established safety profile based on experience in these patient populations.

A reduction in the risk of fractures was associated with tamoxifen therapy in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Study, a large, 5-year, placebo-controlled breast cancer prevention trial.¹⁶ Tamoxifen also increased the risk for endometrial cancer and vascular events (e.g., stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis). These adverse effects and bone benefits were observed primarily in women 50 years of age or older. This age group had a 21% reduction in the risk for fractures.

Raloxifene is the only SERM approved by FDA for use in women with or at risk for osteoporosis.¹⁷ The drug also is used to reduce the risk of invasive breast cancer in postmenopausal women at high risk for the malignancy or with osteoporosis.^{17,18} Raloxifene is not used to treat breast cancer.

A meta-analysis of studies of the effectiveness of various treatments in reducing the risk for fractures in patients with low BMD or osteoporosis demonstrated that raloxifene reduces the risk for vertebral fractures but not the risk for nonvertebral fractures.¹⁹ The drug also increases the risk for thromboembolism.

In the NSABP Study of Tamoxifen and Raloxifene P-2 Study (also known as STAR), another large breast cancer prevention study of nearly 20,000 postmenopausal women with a shorter duration of follow up (median of 3.9 years), the incidence of fractures was similar with the two drugs.²⁰ Lack of a treatment difference might reflect the low overall rate of fractures in this study, which was powered to detect differences in breast cancer, not fractures. Analysis of the drug effects on endometrial cancer rate was hindered by the fact that half of the participants had undergone

hysterectomy before enrollment, short study duration, and low overall rates of endometrial cancer. Nevertheless, compared with tamoxifen, raloxifene was associated with a 38% lower risk for endometrial cancer in women who had not undergone hysterectomy. Raloxifene also was associated with a 30% lower risk for thromboembolism compared with tamoxifen.

A third SERM, toremifene, is used for breast cancer treatment. However, few clinical data are available pertaining to its effects on bone.

In summary, tamoxifen and raloxifene have similar effects on fracture rates in healthy women, but raloxifene is associated with fewer serious adverse events, particularly endometrial cancer and thromboembolism. Raloxifene may be used to prevent or treat osteoporosis in postmenopausal women. Based on indirect comparisons, SERMs generally are considered less effective than bisphosphonates for increasing BMD and preventing or treating osteoporosis.²¹⁻³¹ The patient's age, ability to tolerate bisphosphonates, and the presence of risk factors for breast cancer, endometrial cancer (i.e., presence of a uterus), and thromboembolism (e.g., cigarette smoking) may enter into decisions about the approach to use to promote bone health in women with or at risk for osteoporosis.

Osteonecrosis of the jaw is a rare adverse effect of bisphosphonates seen primarily in patients with cancer undergoing dental procedures and receiving intravenous (i.v.) bisphosphonates.^{32,33} A dental examination with appropriate preventive dentistry should be considered before treatment with bisphosphonates in patients with a history of cancer, chemotherapy, radiotherapy, corticosteroids, or other risk factors. These patients should avoid invasive dental procedures if possible during bisphosphonate treatment.

Question: Do bisphosphonates have an effect on breast cancer incidence?

Emerging evidence suggests that the use of both oral and i.v. bisphosphonates to prevent cancer treatment-related bone loss also may prevent breast cancer recurrence in premenopausal and postmenopausal women.³⁴⁻³⁷ The mechanism for this beneficial effect on breast cancer is unclear.

In 2008, Chlebowski and colleagues³⁸ reported the results of a retrospective analysis of the association between bisphosphonate use and breast cancer incidence in 154,768 postmenopausal women participating in the Women's Health Initiative (WHI) clinical trials involving diet, hormone therapy, and calcium and vitamin D supplementation or an observational study. The investigators attempted to control for the influence of BMD, which is an indication for bisphosphonate therapy, because a low BMD is known to reduce the risk of breast cancer compared with higher BMD values.^{39,40} A multivariate analysis was used with many variables, including the estimated 5-year risk of hip fracture. This estimate was obtained using a fracture risk assessment tool developed from the WHI cohort of women, and it adjusts for BMD differences between bisphosphonate users and nonusers. The multivariate analysis also adjusted for age, ethnicity, smoking, alcohol use, physical activity, body mass index, mammogram in the last 2 years, prior hormone use, total calcium, total vitamin D, and Gail 5-year breast cancer risk.

Compared with bisphosphonate nonuse, bisphosphonate use significantly reduced the overall risk for invasive breast cancer by 32% and the risk of estrogen receptor-positive breast cancer by 30%.³⁸ The reduction in risk for estrogen receptor-negative breast cancer (34%) was not significant primarily because of a low rate of this type of

malignancy. The incidence of *in situ* breast cancer excluding lobular carcinoma *in situ* tumors (i.e., early, noninvasive forms of cancer) was 59% higher in bisphosphonate users than non-users. The investigators viewed these findings as “hypothesis generating and not definitive results.”

In summary, bisphosphonates may or may not decrease the incidence of breast cancer. Additional data from prospective trials are needed to further explore this relationship.

“ Clearly there is a biological link between the bones and the breasts, but the relationship is complex. Although estrogen exposure has long been thought of as the common link between breast and bone health, the relationship might not be explained by estrogen exposure alone. ”

— Laura Boehnke Michaud, Pharm.D., FASHP, BCOP

Emerging News

Pharmacist-initiated Screening Program for Osteoporosis. A recent study published in *Osteoporosis International* showed that a screening program by community pharmacists doubled the number of patients tested for osteoporosis.⁴¹ In this study, 262 patients who met BMD testing guidelines were randomized to receive printed materials, education, and quantitative ultrasound (intervention group) or usual care consisting of printed materials alone (control). The primary endpoint of BMD testing or osteoporosis treatment was achieved by 28 patients who received the intervention compared with 14 patients in the control group. Likewise, a greater percentage of patients receiving the intervention increased their calcium intake compared with controls (30% vs. 19%). Despite the effectiveness of the intervention, however, many patients eligible for BMD screening did not receive appropriate care, and the authors suggested that more intensive interventions are needed.

Denosumab. Denosumab, a fully human monoclonal immunoglobulin G antibody that prevents bone resorption, has been evaluated in clinical trials for the prevention and treatment of postmenopausal osteoporosis and the prevention and treatment of bone loss in patients undergoing hormone ablation for prostate cancer or breast cancer.^{42,43} According to a February 2010 press release, FDA expects to complete its review of denosumab for the treatment of postmenopausal osteoporosis by July of this year.⁴⁴ In August 2009, an FDA advisory committee voted to approve denosumab for the treatment of postmenopausal osteoporosis (not prevention).⁴⁵ In October 2009, however, FDA issued a Complete Response Letter to request additional information needed to complete the review of the application for product approval for this indication.⁴⁶ Additional pre-marketing clinical trials were not deemed necessary, but FDA indicated that a risk evaluation and mitigation strategy (REMS), including a medication guide, communication plan, and timetable for submission of assessments of the REMS, would be necessary. Based on a review of the Complete Response submitted in January 2010, FDA classified it as a Class 2 resubmission and set the July 2010 action date.⁴⁴ The infrequent dosing (once every 6 months) and the positive efficacy results from clinical studies make denosumab a potentially promising new drug in managing postmenopausal osteoporosis.⁴⁷

Amgen continues to work with FDA regarding the review of indications for denosumab in the treatment and prevention of bone loss due to hormone ablation in patients with breast or prostate cancer.⁴⁴

Did you attend the Midyear Symposium on bone health? If so, please complete the post-activity outcomes survey if you haven't done so already. This survey is brief, and it is important because it enables us to document changes in practice as a result of the educational activity.

Take Survey

Coming in March 2010

If you missed the Midyear Symposium, "Looking Beyond the 'Obvious' to Promote Bone Health," at the 2009 ASHP Midyear Clinical Meeting and Exhibition and want to learn more about this topic, a web-based activity based on the symposium will be available in March. It is approved for 2 hours (0.2 CEUs) of continuing pharmacy education. Look for the activity on the bone health initiative Web site (www.ashpadvantage.com/bonehealth).

Planned and coordinated by ASHP Advantage.
This activity is supported by an educational donation provided by Amgen.



References

1. Mauck KF, Cuddihy MT, Atkinson EJ et al. Use of clinical prediction rules in detecting osteoporosis in a population-based sample of postmenopausal women. *Arch Intern Med.* 2005; 165:530-6.
2. The International Society for Clinical Densitometry. General recommendations for non central DXA devices: QCT, pQCT, QUS, and pDXA. <http://www.iscd.org/Visitors/positions/OfficialPositionsText.cfm> (accessed 2010 Jan 21).
3. The International Society for Clinical Densitometry. Position statement: QUS. <http://www.iscd.org/Visitors/positions/OfficialPositionsText.cfm> (accessed 2010 Jan 21).
4. MacLaughlin EJ, MacLaughlin AA, Snella KA et al. Osteoporosis screening and education in community pharmacies using a team approach. *Pharmacotherapy.* 2005; 25:379-86.
5. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ.* 2009; 339:b4229.
6. World Health Organization. FRAX® WHO fracture risk assessment tool. <http://www.shef.ac.uk/FRAX/> (accessed 2010 Jan 27).
7. Gold DT. Medication adherence: a challenge for patients with postmenopausal osteoporosis and other chronic illnesses. *J Manag Care Pharm.* 2006; 12(6 Suppl A):S20-5.
8. Seeman E. To stop or not to stop, that is the question. *Osteoporos Int.* 2009; 20:187-95.
9. Pazianas M, Miller P, Blumentals WA et al. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. *Clin Ther.* 2007; 29:1548-58.
10. Black DM, Schwartz AV, Ensrud KE et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA.* 2006; 296:2927-38.
11. Watts NB, Chines A, Olszynski WP et al. Fracture risk remains reduced one year after discontinuation of risedronate. *Osteoporos Int.* 2008; 19:365-72.
12. Curtis JR, Westfall AO, Cheng H et al. Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday. *Osteoporos Int.* 2008; 19:1613-20.
13. Miller PD. How long should postmenopausal women continue to take bisphosphonate therapy for osteoporosis? *Menopause e-Consult.* October 2008. <http://www.menopause.org/ME1008.pdf> (accessed 2010 Jan 22).
14. Russell RG, Watts NB, Ebetino FH et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int.* 2008; 19:733-59.
15. McEvoy GK, ed. Tamoxifen citrate. In: *AHFS drug information 2009.* Bethesda, MD: American Society of Health-System Pharmacists; 2009:1235-42.
16. Fisher B, Costantino JP, Wickerham DL et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998; 90:1371-88.
17. Evista package insert. Indianapolis, IN: Eli Lilly and Company; 2008 Oct.
18. Cummings SR, Eckert S, Krueger KA et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* 1999; 281:2189-97.

19. MacLean C, Newberry S, Maglione M et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med.* 2008; 148:197-213.
20. Vogel VG, Costantino JP, Wickerham DL et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA.* 2006; 295:2727-41.
21. Liberman UA, Weiss SR, Bröll J et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med.* 1995; 333:1437-43.
22. Black DM, Cummings SR, Karpf DB et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996; 348:1535-41.
23. Cummings SR, Black DM, Thompson DE et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998; 280:2077-82.
24. Chesnut CH III, Skag A, Christiansen C et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004; 19:1241-9.
25. Boonen S, Laan RF, Barton IP et al. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. *Osteoporos Int.* 2005; 16:1291-8.
26. Harris ST, Watts NB, Genant HK et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA.* 1999; 282:1344-52.
27. McClung MR, Geusens P, Miller PD et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med.* 2001; 344:333-40.
28. Reginster J, Minne HW, Sorensen OH et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int.* 2000; 11:83-91.
29. Black DM, Delmas PD, Eastell R et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007; 356:1809-22.
30. Ettinger B, Black DM, Mitlak BH et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* 1999; 282:637-45.
31. Delmas PD, Ensrud KE, Adachi JD et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab.* 2002; 87:3609-17.
32. Reclast package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2009 May.
33. Zometa package insert. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2009 Oct.
34. Gnant M, Mlineritsch B, Schippinger W et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med.* 2009; 360:679-91.

35. Eidtmann H, Bundred NJ, DeBoer R et al. The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36 months follow-up of ZO-FAST. Presented at the 31st Annual San Antonio Breast Cancer Symposium; San Antonio, TX: December 10-14, 2008. Abstract 44.
36. Powles T, Paterson S, Kanis JA et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol*. 2002; 20:3219-24.
37. Brufsky A, Bundred N, Coleman R et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist*. 2008; 13:503-14.
38. Chlebowski RT, Chen Z, Cauley JA et al. Oral bisphosphonate and breast cancer: prospective results from the Women's Health Initiative (WHI). Presented at the 32nd San Antonio Breast Cancer Symposium; San Antonio, TX: December 10, 2009. Abstract 21.
39. Cauley JA, Lucas FL, Kuller LH et al. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures Research Group. *JAMA*. 1996; 276:1404-8.
40. Chen Z, Arendell L, Aickin M et al. Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative. *Cancer*. 2008; 113:907-15.
41. Yuksel N, Majumdar SR, Biggs C et al. Community pharmacist-initiated screening program for osteoporosis: randomized controlled trial. *Osteoporos Int*. 2010; 21:391-8.
42. Popat V. Denosumab efficacy: FDA analysis. Presented at FDA Reproductive Health Drugs Advisory Committee meeting, August 13, 2009. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM179781.pdf> (accessed 2010 Jan 21).
43. Rothstein A. Denosumab safety: FDA analysis. Presented at FDA Reproductive Health Drugs Advisory Committee meeting, August 13, 2009. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM179782.pdf> (accessed 2010 Jan 21).
44. FDA classified Prolia™ (denosumab) complete response submission and targets action date. February 19, 2010. http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1393314 (accessed 2010 Feb 23).
45. Amgen issues statement on outcomes of Advisory Committee for Reproductive Health Drugs (ACRHD) meeting. August 13, 2009. http://www.amgen.com/media/media_pr_detail.jsp?year=2009&releaseID=1320684 (accessed 2010 Feb 11).
46. Amgen provides update on status of Prolia (denosumab) biologics application (BLA) submitted to the U.S. Food and Drug Administration. October 19, 2009. http://www.psa-rising.com/wiredbird/amgen_denosumab-101909.htm (accessed 2010 Feb 11).
47. Cummings SR, San Martin J, McClung MR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009; 361:756-65.