Complete Summary

GUIDELINE TITLE

American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer.

BIBLIOGRAPHIC SOURCE(S)

Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, Cauley JA, Blumenstein BA, Albain KS, Lipton A, Brown S. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003 Nov 1;21(21):4042-57. [67 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Society of Clinical Oncology. Guideline on the role of bisphosphonates in breast cancer. J Clin Oncol 2000 Mar;18(6):1378-91.

At annual intervals, the panel cochairs and two panel members designated by the cochairs will determine the need for revisions to the guideline based on an examination of current literature. The entire panel will be reconvened every 3 years to discuss potential changes or more frequently if new information suggests that more timely modifications may be warranted. When appropriate, the panel will recommend revised guidelines to the American Society of Clinical Oncology (ASCO) Health Services Research Committee and the ASCO Board of Directors for review and approval.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- On April 7, 2005, after concluding that the overall risk versus benefit profile is unfavorable, the FDA requested that Pfizer, Inc voluntarily withdraw Bextra (valdecoxib) from the market. The FDA also asked manufacturers of all marketed prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including Celebrex (celecoxib), a COX-2 selective NSAID, to revise the labeling (package insert) for their products to include a boxed warning and a Medication Guide. Finally, FDA asked manufacturers of non-prescription (over the counter [OTC]) NSAIDs to revise their labeling to include more specific

information about the potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drug. See the FDA Web site for more information.

Subsequently, on June 15, 2005, the FDA requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products. FDA recommended proposed labeling for both the prescription and over-the-counter (OTC) NSAIDs and a medication guide for the entire class of prescription products. All sponsors of marketed prescription NSAIDs, including Celebrex (celecoxib), a COX-2 selective NSAID, have been asked to revise the labeling (package insert) for their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. See the FDA Web site for more information.

Additional Notice

- On March 25, 2005, Novartis and U.S. Food and Drug Administration (FDA) notified healthcare professionals of revisions to the DOSAGE AND ADMINISTRATION and WARNINGS sections of the prescribing information for the drug Zometa (zoledronic acid), to reflect new safety information on management of patients with advanced cancer and renal impairment, whose baseline creatinine clearance is 60 ml/min or lower. The recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are provided in a table. It is recommended that, during treatment, serum creatinine be measured before each dose and treatment should be withheld for renal deterioration. See the FDA Web site for more information.

  Subsequently, on May 18, 2005, Novartis and the FDA notified dental healthcare professionals of revisions to the prescribing information to describe the occurrence of osteonecrosis of the jaw (ONJ) observed in cancer patients receiving treatment with intravenous bisphosphonates, Aredia (pamidronate disodium) and Zometa (zoledronic acid). The prescribing information recommends that cancer patients receive a dental examination prior to initiating therapy with intravenous bisphosphonates (Aredia and Zometa), and avoid invasive dental procedures while receiving bisphosphonate treatment. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. See the FDA Web site for more information.

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SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To update the 2000 American Society of Clinical Oncology (ASCO) guidelines on the role of bisphosphonates in women with breast cancer and address the subject of bone health in these women

TARGET POPULATION

- Women with imaging evidence of bone metastases
- Women with extraskeletal metastases without evidence of bone metastases
- Patients with breast cancer using bisphosphonates as adjuvant therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Bisphosphonates approved for metastatic bone disease: clodronate, pamidronate, and zoledronic acid

MAJOR OUTCOMES CONSIDERED

Major Outcomes

- Length of survival (disease-free or overall)
- Quality of life

- Toxicity (both short- and long-term)
- Cost-effectiveness

Intermediate Outcomes

- Biomarkers
- Radiographic criteria for bony response or progression
- Bone mineral density, in the adjuvant setting
- Skeletal-related events (SREs)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

For the 2000 guideline, pertinent information from the published literature was retrieved and reviewed for the creation of these guidelines. Searches were done of MEDLINE (National Library of Medicine, Bethesda, MD) and other databases for pertinent articles through May 1999 and abstracts presented at the national American Society of Clinical Oncology (ASCO) annual meetings. Additional data collected as part of randomized trials and submitted to the United States (U.S.) Food and Drug Administration (FDA) were also reviewed.

For the 2003 update, the Panel reviewed the published data since 2000. Computerized Medline searches were performed, meeting abstracts were reviewed, and members of the industry were contacted and given the opportunity to provide data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For the 2003 update, the Panel had two meetings to consider the evidence for each of the 2000 recommendations. The guideline was circulated in draft form to the full expert panel and to the American Society of Clinical Oncology Health Services Committee for review and approval.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Commentary: Public Policy and Cost-Utility Implications

Prior cost-effectiveness analyses have suggested that the cost-savings from bisphosphonates and/or radiation in reducing bone complications were insufficient to offset the costs associated with the bisphosphonates and their delivery. Since 2000, there have been new cost-effectiveness assessments of bisphosphonates in breast cancer.

There are new retrospective data indicating that a reduction in medical services is probably the case with intravenous bisphosphonates, but that the initial characteristics of patients receiving pamidronate substantially differ. The chart review study involving 12 community United States oncology sites compared women who initiated pamidronate within 3 months (early) of bone metastasis diagnosis or after 3 months (late) of diagnosis with patients who never (none) received pamidronate between July 1996 and April 1999; 295 patients were identified. Patients receiving early pamidronate were more likely to have multiple bone lesions, a serious initial event, or hypercalcemia. Pamidronate-treated patients needed less radiotherapy and the duration of hospitalizations were about 50% shorter than nonpamidronate patients.

With the recent approval of zoledronic acid in the United States, the decision facing most oncologists will be whether to switch from pamidronate to zoledronic acid. In 2001, generic pamidronate became available. In 2003, there were at least four suppliers of generic pamidronate. In an ideal world, competition would drive down the price of pamidronate; however, current US average wholesale prices of pamidronate have changed minimally since the introduction of generic versions.

Pamidronate's longer infusion time compared with zoledronic acid (2 hours versus 15 minutes) is associated with an opportunity for lower cost to the patient (their time), the cancer location (use of infusion chair), and extra staff time (reflected in common procedural terminology codes). A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid versus pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour, 6 minutes, compared to 2 hours, 52 minutes for pamidronate patients. From the infusion center perspective, the opportunity benefit for zoledronic acid was an average increase in 1.8 chairs per day available for other patients.

The choice of bisphosphonates is broader in number and delivery method (oral versus intravenous) outside the U.S. Where oral clodronate is available, the price difference between available bisphosphonates is commonly minimal, and the absolute cost for any bisphosphonate is much lower per standard treatment interval. Pamidronate and zoledronic acid have acquisition prices in most of Europe that are 40 to 70% less than the U.S. Therefore, each country must make its own relative cost benefit assessment.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

An external review by individuals acknowledged in the guideline document not directly involved in development of the guideline assessed the clarity, utility, and completeness of the document.

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research Committee and by the American Society of Clinical Oncology (ASCO) Board before dissemination.

The 2003 guideline update was adopted on May 30, 2003 by ASCO. It was submitted for publication in a peer-reviewed journal on August 5, 2003 and accepted on August 12, 2003.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The American Society of Clinical Oncology (ASCO) has updated its 2000 recommendations on the role of bisphosphonates and bone health issues in women with breast cancer. Each recommendation from the 2000 guideline is listed below, and is followed by an updated (2003) recommendation, if applicable. "No change" is indicated if a particular recommendation has not been revised.

Bisphosphonate Use in Women With Imaging Evidence of Bone Metastases

Lytic Disease on Plain Radiographs

2000 Recommendation: Intravenous (IV) pamidronate 90 mg delivered over 1 to 2 hours every 3 to 4 weeks is recommended in women with metastatic breast cancer who have lytic destruction of bone on plain radiograph(s) and who are receiving systemic therapy with hormonal therapy or chemotherapy.

2003 Recommendation: For breast cancer patients who have evidence of bone destruction on plain radiographs, IV pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient's general performance status and overall prognosis.

Abnormal Bone Scan, Normal Radiographs but Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) Scan Showing Bone Destruction

2000 Recommendation: Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT scan or MRI showing bone destruction and localized pain, but normal plain radiographs, is considered reasonable by panel consensus based on the findings in women with osteolytic changes on plain radiographs.

2003 Recommendation: Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs.

Abnormal Bone Scan, Normal Radiographs, and No Evidence of Bone Destruction on CT or MRI

2000 Recommendation: Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bony destruction on radiographs, tomograms, CT scans, or MRI, or with localized pain, is not suggested.

2003 Recommendation: Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.

Safety and Adverse Effects

2003 Recommendation: In patients with pre-existing renal disease and a serum creatinine level less than 3 mg/dL (265 micromoles/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with Food and Drug Administration (FDA)-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and

hematocrit/hemoglobin should also be monitored regularly, even though there is no evidence on which to base a recommendation for time intervals. In contrast to multiple myeloma patients, there currently is no data to support routine assessments for albuminuria in breast cancer patients.

Biochemical Markers

2000 Recommendation: The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.

2003 Recommendation: No change

Duration of Therapy

2000 Recommendation: The Panel suggests that, once initiated, IV bisphosphonates be continued until evidence of substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal-related events (SREs).

2003 Recommendation: No change

Role in Control of Pain Secondary to Bone Metastases

2000 Recommendation: The Panel recommends that current standards of care for cancer pain, analgesics, and local radiation therapy should not be displaced by bisphosphonates. IV pamidronate is recommended in women with pain caused by osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2003 Recommendation: The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radiopharmaceuticals, and local radiation therapy. Among other therapeutic options, IV pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2000 Recommendation: There is insufficient evidence to support a role for IV bisphosphonates as an adjunctive therapy to radiation therapy in women with pain caused by metastatic bone disease when systemic chemotherapy and/or hormonal therapy is not being used. The role of bisphosphonates vis-a-vis radiation therapy as the sole therapy in this setting has not been determined. In women already being treated with local radiotherapy who have persistent or recurrent pain, bisphosphonates are an attractive but little-studied salvage therapy.

2003 Recommendation: No change

Role of Bisphosphonates With No Radiographic Evidence of Bone Metastases

Extraskeletal Metastases Without Evidence of Bone Metastases

2000 Recommendation: Starting bisphosphonates in women without evidence of bone metastases, even in the presence of other extraskeletal metastases, is not recommended. This clinical situation has not been studied using IV bisphosphonates and should be the focus of new clinical trials.

2003 Recommendation: No change

Bisphosphonates as Adjuvant Therapy

2000 Recommendation: Inconsistent, evolving data have been found in studies of bisphosphonate use in the adjuvant setting to prevent osseous metastases. Starting bisphosphonates in women at any stage of their nonosseous disease, outside of clinical trials, despite a high risk for future bone metastasis, is currently not recommended.

2003 Recommendation: No change

Bone Health In Women With A History Of Breast Cancer

Osteoporosis Prevention

2000 Recommendation: Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in premenopausal women with treatment-induced (usually secondary to chemotherapy) menopause.

2003 Recommendation: Most women with newly diagnosed breast cancer are at risk of osteoporosis due to either their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of these women's bone health. The Panel recommended an algorithm for patient management to maintain bone health.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Although the Panel reviewed numerous publications on the subject since 2000, the vast majority of reports were reviews revisiting the small current collection of

clinical trials. Since 2000, no major randomized controlled trials in the metastatic setting have been initiated.

- There is insufficient evidence supporting the efficacy of one bisphosphonate over the other.
- There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal-related events (SREs).
- There is insufficient evidence to support a role for intravenous (IV) bisphosphonates as an adjunctive therapy to radiation therapy in women with pain caused by metastatic bone disease when systemic chemotherapy and/or hormonal therapy is not being used.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Bisphosphonates provide a supportive, albeit expensive and non-life-prolonging, benefit to many patients with bone metastases.
- Among other therapeutic options, intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

POTENTIAL HARMS

Short-term use of bisphosphonates, when administered according to recommended infusion doses, infusion times, and dosing intervals, is associated with a low risk of renal dysfunction.

- Although shorter infusion times may be tolerated on a short-term basis, shorter infusion times have been associated with a higher risk of renal toxicity. Intravenous infusions of pamidronate over less than 2 hours, especially those $\leq$1 hour given on a long-term basis (>1 year), have been occasionally associated with renal toxicity including albuminuria followed by azotemia. More serious renal toxicity has also been reported with long-term use of higher doses or more frequent dosing of pamidronate. Most cases occurred among patients with multiple myeloma, although some also occurred among patients with breast cancer. The kidney pathology may show a collapsing focal segmental glomerulosclerosis or tubulointerstitial nephritis.
- Recently, several case reports have been reported relating to adverse renal consequences with prolonged pamidronate use.

The safety and frequency of nonrenal adverse events with zoledronic acid appear to be similar to pamidronate. The latter were well characterized in the pamidronate versus placebo trials and the recent pamidronate versus zoledronic acid studies. The incidence of most adverse effects in patients treated with pamidronate was similar to that observed in the placebo group. Transient myalgias, arthralgias, and flu-like symptoms with fever tend to occur more often in patients treated with pamidronate than placebo. These symptoms usually occur only after the first and/or second infusion of pamidronate and are not an

indication to discontinue treatment of the drug. Ocular side effects from pamidronate are a relatively rare but well-recognized complication, first reported in 1994. An update review of case reports found 17 cases of unilateral scleritis and one case of bilateral scleritis, usually within 6 hours to 2 days after intravenous pamidronate. Six patients had positive rechallenge testing with the scleritis occurring again after a repeat drug exposure.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

American Society of Clinical Oncology (ASCO) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. It cannot be assumed that these guidelines apply to interventions performed in clinical trials, which are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that guideline development involves a review and synthesis of the latest literature, and a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Mar (revised 2003 Nov 1)

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology (ASCO)

GUIDELINE COMMITTEE

Bisphosphonates in Breast Cancer Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: Bruce E. Hillner, MD, Chair, Virginia Commonwealth University, Richmond, VA (Health Services Researcher and Medical Oncologist); James N. Ingle, MD, Co-Chair, Mayo Clinic, Rochester, MN (Medical Oncologist); Kathy S. Albain, MD, Loyola University Medical Center, Maywood, IL (Medical Oncologist); Susan Brown, MS, RN, The Susan G. Komen Breast Cancer Foundation, Dallas, TX (Patient/Advocate Representative); Brent A. Blumenstein, PhD, Tri Arc Consulting, Seattle, WA (Biostatistician); Jane A. Cauley, DrPH, University of Pittsburgh, Pittsburgh, PA (Epidemiologist); Rowan T. Chlebowski, MD, PhD, Harbor UCLA Medical Center, Torrance, CA (Medical Oncologist); Julie Gralow, MD, University of Washington, Seattle, WA (Medical Oncologist); Nora A. Janjan, MD, M.D. Anderson Cancer Center, Houston, TX (Radiation Oncologist); Allan Lipton, MD, Milton S. Hershey Medical Center, Hershey, PA (Medical Oncologist); Gary C. Yee, Pharm D, University of Nebraska Medical Center, Omaha, NE (Pharmacology)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: American Society of Clinical Oncology. Guideline on the role of bisphosphonates in breast cancer. J Clin Oncol 2000 Mar;18(6):1378-91.

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GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

Guidelines are available for Personal Digital Assistant (PDA) download from the ASCO Web site.

PATIENT RESOURCES

The following is available:

- Bisphosphonates for breast cancer. Alexandria (VA): American Society of Clinical Oncology; 2003 Aug. 16 p.

Electronic copies: Available from the Cancer.Net Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC Summary was completed by ECRI on September 21, 2000. The guideline developer was provided with a copy of this NGC summary for review, but to date, NGC has not received any comments from the guideline developer. This guideline was updated by ECRI on February 16, 2004. The updated information was verified by the guideline developer on February 26, 2004. This summary was updated by ECRI on March 28, 2005, following the U.S. Food and

Drug Administration advisory on Zometa (zoledronic acid). This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on May 20, 2005, following the U.S. Food and Drug Administration advisory on Aredia (pamidronate disodium) and Zometa (zoledronic acid). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

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