American Association of Oral and Maxillofacial Surgeons
Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws

Approved by the Board of Trustees September 25, 2006

Introduction

Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) adversely affects the quality of life and produces significant morbidity in afflicted patients. Oral and maxillofacial surgeons have been responsible for counseling, managing and treating a majority of these patients. The strategies set forth in this position paper were developed by a Task Force appointed by the American Association of Oral and Maxillofacial Surgeons (AAOMS). The Task Force was composed of clinicians with extensive experience in caring for these patients, clinical epidemiologists and basic science researchers offering a broad range of experience and background. The strategies are based on an analysis of the existing literature and the clinical observations of the expert Task Force members. AAOMS considers it vitally important that this information be disseminated to other dental and medical specialties. It is understood that the strategies and treatment algorithms outlined in this paper are starting points based on our current understanding of BRONJ. As the knowledge base and experience in addressing BRONJ evolves, future modifications and refinements of the current strategies will necessarily be required.

Purpose

The purpose of this position paper is to provide:

1. perspectives on the risk of developing BRONJ and the risks and benefits of bisphosphonates in order to facilitate medical decision-making of both the treating physician and the patient;
2. guidance to clinicians regarding the differential diagnosis of BRONJ in patients with a history of treatment with intravenous (IV) or oral bisphosphonates; and
3. guidance to clinicians on possible BRONJ prevention measures and management of patients with BRONJ based on the presenting stage of the disease.

Benefits of bisphosphonate therapy

Intravenous bisphosphonates are primarily used and effective in the treatment and management of cancer-related conditions. These include hypercalcemia of malignancy, skeletal-related events associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer and lung cancer, and in the management of lytic lesions in the setting of multiple myeloma. [1-12] The IV bisphosphonates are effective in preventing and reducing hypercalcemia, stabilizing bony pathology and preventing fractures in the context of skeletal involvement. While they have not been shown to improve cancer-specific survival, they have had a significant impact on the quality of life for patients with advanced cancer that involves the skeletal system. Before 2001, pamidronate (Aredia®) was the only drug approved in the United States for treatment of metastatic bone disease. In 2002, zoledronic acid (Zometa®) was approved for this indication by the US Food and Drug Administration (FDA). [12]

Oral bisphosphonates are approved to treat osteoporosis and are frequently used to treat osteopenia as well. [13] They are also used for a variety of less common conditions such as Paget's disease of bone, and osteogenesis imperfecta of childhood. [14-15] By far the most prevalent and common indication, however, is osteoporosis. [16-17] Osteoporosis may arise in the context of other diseases such as inflammatory bowel disease or primary biliary cirrhosis, as the result of medications, most commonly steroids, or as a consequence of postmenopausal aging. [18-20] Whatever the underlying etiology of the osteoporosis, bisphosphonates may play a role, perhaps in conjunction with calcium and vitamin D, in its management.

Risks of bisphosphonate therapy

In 2003-04, oral and maxillofacial surgeons were the first clinicians to recognize and report cases of non-healing exposed, necrotic bone in the maxillofacial region in patients treated with IV bisphosphonates. [21-22] Since these initial reports, several case series and reviews have been published. [23-30] In September 2004, Novartis, the manufacturer of the IV bisphosphonates pamidronate (Aredia®) and zoledronic acid (Zometa®), notified healthcare professionals of additions to the labelling of these products, which provided cautionary language related to the development of osteonecrosis of the jaws. [31] This was followed in 2005 by a broader drug class warning of this complication for all bisphosphonates including the oral preparations. [32-33] See Appendix 1 for list of bisphosphonate medications that are currently available in the United States.

BRONJ Case Definition

To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adopted by the AAOMS:

Patients may be considered to have BRONJ if all of the following three characteristics are present:
1. Current or previous treatment with a bisphosphonate;
2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and
3. *No history of radiation therapy to the jaws*.

It is important to understand that patients at risk for BRONJ or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions may include, but are not limited to, alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology and TMJ disorders.
Estimated Incidence and Factors Associated with Development of BRONJ

IV bisphosphonates and incidence of BRONJ

The clinical efficacy of IV bisphosphonates for the treatment of hypercalcemia and bone metastases is well established. [1-4] Currently, available published incidence data for BRONJ are limited to retrospective studies with limited sample sizes. Based on these studies, estimates of the cumulative incidence of BRONJ range from 0.8%-12%. [34-42] With increased recognition, duration of exposure and follow-up, it is likely that the incidence will rise.

Oral bisphosphonates and incidence of BRONJ

The clinical efficacy of oral bisphosphonates for the treatment of osteopenia/osteoporosis is well established and is reflected in the fact that over 190 million oral bisphosphonate prescriptions have been dispensed worldwide. [43] The specialty's experiences have identified several BRONJ cases related to oral bisphosphonates. [22, 24] Patients under treatment with oral bisphosphonate therapy are at a considerably lower risk for BRONJ than patients treated with IV bisphosphonates. Based on data from the manufacturer of alendronate (Merck), the incidence of BRONJ was calculated to be 0.7/100,000 person/years of exposure. [44] This was derived from the number of reported (not confirmed) cases that were deemed to likely represent BRONJ divided by the number of alendronate pills prescribed since approval of the drug, and converted to number of patient years. While this is the best available data to date, there may be serious underreporting and, as noted above, none confirmed. Correspondence with Alastair Goss, DDSc (September 2006), reported that the estimated incidence of BRONJ for patients treated weekly with alendronate is 0.01-0.04%, based on prescription data in Australia. Following extractions, this rate increased to 0.09-0.34%.

Based on the above cited data, the risk of BRONJ for patients receiving IV bisphosphonates appears to be significantly greater than the risk for patients receiving oral bisphosphonates. Regardless, given the large number of patients receiving oral bisphosphonates for the treatment of osteoporosis/osteopenia it is likely that most practitioners may encounter some patients with BRONJ. It is important to accurately determine the incidence of BRONJ in this population and to assess the risk associated with long-term use, i.e., greater than 3 years, of oral bisphosphonates. The effect of certain comorbidities, e.g., chronic corticosteroid use, also requires further study.

Risk factors

Risk factors for the development of BRONJ can be grouped as drug-related, local risk factors and demographic/ systemic factors.

I. Drug-related risk factors include:
- A. Potency of the particular bisphosphonate: zoledronate (Zometa®) is more potent than pamidronate (Aredia®) and pamidronate (Aredia®) is more potent than the oral bisphosphonates; the IV route of administration results in a greater drug exposure than the oral route. 34-35, 42, 45
- B. Duration of therapy: longer duration appears to be associated with increased risk. 35, 42

II. Local risk factors include:
- A. Dentoalveolar surgery, including, but not limited to 34, 42, 45
  1. Extractions
  2. Dental implant placement
  3. Periapical surgery
  4. Periodontal surgery involving osseous injury

Patients receiving IV bisphosphonates and undergoing dentoalveolar surgery are at least seven times more likely to develop BRONJ than patients who are not having dentoalveolar surgery. 42, 45

- B. Local anatomy
  1. Mandible
     a. Lingual tori
     b. Mylohyoid ridge
  2. Maxilla
     a. Palatal tori

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses and the mylohyoid ridge. 22, 24, 46

- C. Concomitant oral disease

Patients with a history of inflammatory dental disease, e.g., periodontal and dental abscesses, are at a seven-fold increased risk for developing BRONJ. 42

III. Demographic and systemic factors
- A. Age: With each passing decade, there is a 9% increased risk for BRONJ in multiple myeloma patients treated with IV bisphosphonates. 45
- B. Race: Caucasian 45
- C. Cancer diagnosis: Risk is greater for patients with multiple myeloma than for patients with breast cancer; and

those with breast cancer have a greater risk than those with other cancers. [42]
D. Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis [42]

The following factors are thought to be risk factors for BRONJ:

1. Corticosteroid therapy
2. Diabetes
3. Smoking
4. Alcohol use
5. Poor oral hygiene
6. Chemotherapeutic drugs

Further studies are required to accurately determine if these factors are associated with BRONJ risk.

Management Strategies for Patients Treated with Bisphosphonates

Prevention of BRONJ

Prior to treatment with an *IV bisphosphonate*, the patient should have a thorough oral examination, any unsalvageable teeth should be removed, all invasive dental procedures should be completed and optimal periodontal health should be achieved. Based on the experience of two Task Force members with approximately 50 patients, the risk of developing BRONJ associated with *oral bisphosphonates*, while exceedingly small, appears to increase when the duration of therapy exceeds three years. This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. *If systemic conditions permit*, it has been proposed that discontinuation of oral bisphosphonates for a period of three months prior to and three months following elective invasive dental surgery may lower the risk of BRONJ. The risk reduction may vary depending on the duration of bisphosphonate exposure. Modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Treatment Goals

The major goals of treatment for patients at risk of developing or who have BRONJ are:

- Prioritization and support of continued oncologic treatment in patients receiving IV bisphosphonates.Oncology patients can benefit greatly from the therapeutic effect of bisphosphonates by controlling bone pain and reducing the incidence of other skeletal complications.
- Preservation of quality of life through:
  - Patient education and reassurance
  - Control of pain
  - Control of secondary infection
  - Prevention of extension of lesion and development of new areas of necrosis

Treatment Strategies [24, 29, 47-49]

A. Patients about to initiate intravenous bisphosphonate treatment

The treatment objective for this group of patients is to minimize the risk of developing BRONJ. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following dentoalveolar surgery. [34, 42, 45] Therefore *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until dental health is optimized. This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient.

Non-restorable teeth and those with a poor prognosis should be extracted. Othernecessary elective dentoalveolar surgery should also be completed at this time. Based on experience with osteoradionecrosis, it appears advisable that bisphosphonate therapy should be delayed, *if systemic conditions permit,* until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control and conservative restorative dentistry are critical to maintaining functionally sound teeth. This level of care must be continued indefinitely. Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. It is critical that patients be educated as to the importance of dental hygiene and regular dental evaluations, and specifically instructed to report any pain, swelling or exposed bone. Medical oncologists should evaluate and manage patients scheduled to receive IV bisphosphonates similarly to those patients scheduled to initiate radiation therapy to the head and neck. The osteoradionecrosis prevention protocols are guidelines that are familiar to most oncologists and general dentists.

B. **Asymptomatic patients receiving intravenous bisphosphonates**
Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots. [49] Placement of dental implants should be avoided in the oncology patient exposed to the more potent intravenous bisphosphonate medications (zoledronic acid and pamidronate) on a frequent dosing schedule (4-12 times per year). There has been limited information on IV bisphosphonate use for osteoporosis, as this indication is an off-label use. However, the dosing schedule for osteoporosis is far less frequent than for adjunct treatment of oncology patients. A September 16, 2006 media release from Novartis provided information on Phase III trials of a once-yearly infusion of zoledronic acid for the treatment of postmenopausal osteoporosis, which is currently under review by the FDA. [50] Based on the decreased frequency/dosage for this indication, the Task Force believes the risk of developing BRONJ may be equivalent to or possibly less than that of oral therapy for osteoporosis.

C. **Asymptomatic patients receiving oral bisphosphonate therapy**
Patients receiving oral bisphosphonates are also at risk for developing BRONJ, but to a much lesser degree than those treated with intravenous bisphosphonates. [22, 24-25, 46] BRONJ can develop spontaneously or after minor trauma. In general, these patients seem to have less severe manifestations of necrosis and respond more readily to stage specific treatment regimens. (See Table 1.) Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the small risk of compromised bone healing. The risk of BRONJ may be associated with increased duration of treatment with oral bisphosphonates, i.e., > three years, based on experience with 50 such patients by two Task Force members. The risk of long-term oral bisphosphonate therapy clearly requires further analysis and research.

Management Strategies

Sound recommendations based on strong clinical research designs are lacking for patients taking oral bisphosphonates. The Task Force strategies outlined below are based on clinical experience of clinicians involved in caring for these patients, in which it appears that the risk of developing BRONJ associated with oral bisphosphonates increased when duration of therapy exceeded three years. As more data become available, these strategies will be updated and modified as necessary.

For individuals who have taken an oral bisphosphonate for less than three years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary. This includes any and all surgeries common to oral and maxillofacial surgeons, periodontists and other dental providers. It is suggested that if dental implants are placed,

informed consent should be provided related to possible future implant failure and possible osteonecrosis of the jaws if the patient continues to take an oral bisphosphonate. Such patients should be placed on a regular recall schedule. It is also advisable to contact the provider who originally prescribed the oral bisphosphonate and suggest monitoring such patients and considering either alternate dosing of the bisphosphonate, drug holidays or an alternative to the bisphosphonate therapy.

For those patients who have taken an oral bisphosphonate for less than three years and have also taken corticosteroids concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery, *if systemic conditions permit*. The bisphosphonate should not be restarted until osseous healing has occurred. These strategies are based on the hypothesis that concomitant treatment with corticosteroids may increase the risk of developing BRONJ and that a "drug holiday" may mitigate this risk.

For those patients who have taken an oral bisphosphonate for more than three years with or without any concomitant prednisone or other steroid medication, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for three months prior to oral surgery, *if systemic conditions permit*. The bisphosphonate should not be restarted until osseous healing has occurred. These strategies are based on the experience of two Task Force members managing 50 BRONJ patients who had a history of oral bisphosphonate therapy for three or more years, and the hypothesis that a "drug holiday" may mitigate this risk.

D. Patients with an established diagnosis of BRONJ

The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue and minimize the progression or occurrence of bone necrosis. These patients respond less predictably to the established surgical treatment algorithms for osteomyelitis or osteoradionecrosis. Surgical debridement has been variably effective in eradicating the necrotic bone. [22-24, 29] It may be difficult to obtain a surgical margin with viable bleeding bone as the entire jawbone has been exposed to the pharmacologic influence of the bisphosphonate. Therefore, surgical treatment should be delayed if possible. Areas of necrotic bone that are a constant source of soft tissue irritation should be removed or recontoured without exposure of additional bone. Based on the experience of the Task Force members and case reports, loose segments of bony sequestrum should be removed without exposing uninvolved bone. [51] The extraction of symptomatic teeth
within exposed, necrotic bone should be considered since it is unlikely that the extractionwill exacerbate the established necrotic process.

Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, since these surgical sites may result in additional areas of exposed necrotic bone. Symptomatic patients with pathologic mandibular fractures may require segmental resection and immediate reconstruction with a reconstruction plate. The potential for failure of the reconstruction plate because of the generalized effects of the bisphosphonate exposure needs to be recognized by the clinician and patient. Immediate reconstruction of these patients with non-vascularized or vascularized bone may be problematic as necrotic bone may develop at the recipient site.

The effectiveness of hyperbaric oxygen therapy is undetermined. [52] A communication to AAOMS from J. Freiberger, MD, MPH on May 17, 2006, reported that a clinical trial has been funded to establish the efficacy of hyperbaric oxygen therapy in treating patients with BRONJ, and began enrolling patients in August 2006 (August 31, 2006 e-mail).

Staging and Treatment Strategies (See Table 1) Staging In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates, the AAOMS proposes use of the following staging categories:

1. Patients at risk: No apparent exposed/necrotic bone in patients who have been treated with either IV or oral

bisphosphonates.
2. Patients with BRONJ
Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection.
Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection.
Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border

Treatment strategies
At risk - Patients who are at risk of developing BRONJ by virtue of the fact that they have been exposed to a bisphosphonate do not require any treatment. However, these patients should be informed of the risks of developing BRONJ, as well as the signs and symptoms of this disease process.
Stage 1 – These patients benefit from the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No surgical treatment is indicated. Patients who present with Stage 1 disease have done well with this type of conservative treatment.
Stage 2 – These patients benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. It is hypothesized that the pathogenesis of BRONJ may be related to factors adversely influencing bone remodeling. Additionally, BRONJ is not due to a primary infectious etiology. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used with success in those patients who are allergic to penicillin. Microbial cultures should also be analyzed for the presence of actinomyces species of bacteria. If this microbe is isolated, the antibiotic regimen should be adjusted accordingly. In some refractory cases, patients may require combination antibiotic therapy, long-term antibiotic maintenance or a course of intravenous antibiotic therapy.
Stage 3 – These patients typically have pain that impacts the quality of life. Surgical debridement/resection in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain.

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

Discontinuation of bisphosphonate therapy
IV bisphosphonates
Oncology patients benefit greatly from the therapeutic effects of bisphosphonates by controlling bone pain and the incidence of pathologic fractures. Discontinuation of IV bisphosphonates offers no short-term benefit. However *if systemic conditions permit*, longterm discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient.

Oral bisphosphonates
Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Based on the experience of two Task Force members managing 50 BRONJ patients who were treated with oral bisphosphonates, discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Table 1 Staging and Treatment Strategies
BRONJ† Staging Treatment Strategies‡

At risk category No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
- No treatment indicated
- Patient education

Stage 1 Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
- Antibacterial mouth rinse
- Clinical follow-up on a quarterly basis
- Patient education and review of indications for continued bisphosphonate therapy

Stage 2 Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
- Symptomatic treatment with broad-spectrum oral antibiotics, e.g. penicillin, cephalexin, clindamycin, or 1st generation fluoroquinolone
- Oral antibacterial mouth rinse
- Pain control
- Only superficial debridements to relieve soft tissue irritation

Stage 3 Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border
- Antibacterial mouth rinse
- Antibiotic therapy and pain control
- Surgical debridement/resection for longer term palliation of infection and pain

† Exposed, necrotic bone in the maxillofacial region without resolution in 8-12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

‡ Discontinuation of the IV bisphosphonates shows no short-term benefit. However, *if systemic conditions permit*, long-term discontinuation may be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the patient.

‡ Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Based on the experience of two Task Force members managing 50 BRONJ patients who were treated with oral bisphosphonates, discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

Future Research

On July 31, 2006, the National Institutes of Health announced funding opportunities for research on the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw. [53] At least one grant has been awarded for a project titled “Bisphosphonates and Oral Complications of Cancer Chemotherapy: A Pilot Study,” with Dr. Regina Landesberg as the principal investigator. [54] Prospective clinical trials are required so that the present staging system can evolve into a more comprehensive staging system, which would enable clinicians to make accurate judgements about risk, prognosis, treatment selection, and outcome for patients with BRONJ.

the clear understanding that continued research and practice may result in new knowledge or recommendations. AAOMS makes no express or implied warranty regarding the accuracy, content, completeness, reliability, operability, or legality of information contained within the position paper, including, without limitation, the warranties of merchantability, fitness for a particular purpose, and non-infringement of proprietary rights. In no event shall the AAOMS be liable to the user of the position paper or anyone else for any decision made or action taken by him or her in reliance on such information.

Appendix I Bisphosphonate Preparations Currently Available in the US *

Primary
Indication
Nitrogen
Containing
Dose Route Relative
Potency**
Etidronate
(Didronel)
Paget's
Disease
No 300 -750
mg daily for
6 months
Oral 1
Tiludronate
(Skelid)
Paget's
Disease
No 400 mg
daily for 3
months
Oral 50
Alendronate
(Fosamax)
Osteoporosis Yes 10 mg/day
70 mg/week
Oral 1,000
Risedronate
(Actonel)
Osteoporosis Yes 5 mg/day
35 mg/week
Oral 1,000
Ibandronate
(Boniva)
Osteoporosis Yes 2.5 mg/day
150
mg/month
Oral 1,000
Pamidronate
(Aredia)

Bone
Metastases
Yes 90 mg/3
weeks
IV 1,000 –
5,000
Zoledronate
(Zometa)
Bone
Metastases
Yes 4 mg/3
weeks
IV 10,000 +
*A once-yearly infusion of zoledronic acid for the treatment of postmenopausal osteoporosis is under FDA review. 50
**Relative to etidronate

References
1. Nussbaum SR, Younger J, Vandepol CJ, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med*. 1993;95:297-304.
2. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled, clinical trials. *J Clin Oncology*. 2001;19:558-67.
3. Hortobagyi GN, Theriault RL, Porter L, et. al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer study Group. *N Eng J Med*. 1996;335:1785-91.
4. Hortobagyi GN, Theriault RL, Lipton A, et. al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer study Group. *J Clin Oncol*. 1998;16:2038-44.
5. Hillner BE, Ingle JN, Chelbowski RT, et.al. 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;21:4042-57.
6. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94:1458-68.
7. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96:879-82.
8. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with non-small cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind placebocontrolled trial. *Cancer*. 2004;100:2613-21.
9. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med*. 1996;334:488-93.

10. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol. 1998;16:593-602.
14
11. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III double-blind, comparative trial. *Cancer* J 2002; 7:377-87.
12. Berenson JR, Hillner BE, Kyle RA, et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002;20:3719-36.
13. *Physicians' Desk Reference*. 57th ed. Montvale, NJ: Medical Economics; 2003.
14. Delmas PD, Meunier PJ. The management of Paget's disease of bone. *N Engl J Med*. 1997;336:558-66.
15. Letocha AD, Cintas HL, Troendle JF, et al. Controlled trial of pamidronate in children with types III and IV osteogenesis imperfecta confirms vertebral gains but not short-term functional improvement. *J Bone Miner Res*. 2005;20:977-86.
16. Watts NB. Bisphosphonate treatment of osteoporosis. *Clin Geriatr Med*. 2003;19:395-414.
17. Delmas PD. The use of bisphosphonates in the treatment of osteoporosis. *Curr Opin Rheumatol*. 2005;17:462-6.
18. Haderslev KV, Tjellesen L, Sorensen HA, Staun M. Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease. *Gastroenterology*. 2000;119:639-46.
19. Zein CO, Jorgensen RA, Clarke B, et al. Alendronate improves bone mineral density in primary biliary cirrhosis: a randomized placebo-controlled trial. *Hepatology*. 2005;42:762-71.
20. Bone HG, Hosking D, Devogelaer JP, Tucci JR, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350:1189-99.
21. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic [Letter]. *J Oral Maxillofac Surg*. 2003;61:1115-8.
22. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff S. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg*. 2004;62:527-34.
23. Estilo CL, Van Posnak CH, Williams T, et al. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: a retrospective study. *J Clin Oncol*. Proc Am Soc Clin Oncol. 2004;22:8088.
15
24. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis\osteopetrosis) of the jaws: risk factors, recognition, prevention and treatment. *J Oral Maxillofac Surg*. 2005; 63:1567-75.
25. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. *Cancer*. 2005;104:83-93.
26. Purcell PM, Boyd IW. Bisphosphonates and osteonecrosis of the jaw. *Med J Aust*. 2005;182:417-8.

27. Bagan JV, Jimenez Y, Murillo J, et al. Jaw osteonecrosis associated with bisphosphonates: multiple exposed areas and its relationship to teeth extractions. study of 20 cases [Letter]. *Oral Oncol*. 2006;42:327-9.
28. Pires FR, Miranda A, Cardoso ES, et al. Oral avascular bone necrosis associated with chemotherapy and bisphosphonate therapy. *Oral Dis*. 2005;11:365-9
29. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med*. 2006;144:753-61.
30. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaws and bisphosphonates [Letter]. *N Engl J Med*. 2005;353:100.
31. Hohnecker JA. Novartis "Dear Doctor" Precautions added to label of Aredia and Zometa. September 24, 2004.
32. United States Food and Drug Administration Oncologic Drugs Advisory Committee . Combidex briefing information. Available at: http://www.fda.gov/ohms/dockets/ac/05/briefing/2005-4095b1.htm Accessed
33. US food and Drug Administration Office of Drug Safety Postmarketing Safety Review Available at: www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4095B2_03_04-FDA-TAB3.pdf - 03-02-2005 - Accessed August 14, 2006
34. Durie BGM, Katz M, Crowley J. Osteonecrosis of the jaws and bisphosphonates [Letter]. *N Engl J Med*. 2005;353:99.
35. Bamias A, Kastritis E, Bamia C, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol*. 2005;23:8580-7.
36. Dimopoulos MA, Kastritis E, Anagnostopoulos A, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica*. 2006;91 [Epub ahead of print].
16
37. Dimopoulos M, Kastritis E, Moulopoulos LA, Melakopoulos I, et al. The incidence of osteonecrosis of the jaw in patients with multiple myeloma who receive bisphosphonates depends on the type of bisphosphonate. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 2005;106:637.
38. Tosi P, Zamagni E, Cangini D, et al. Bisphosphonates and osteonecrosis of the jaws: incidence in a homogeneous series of patients with newly diagnosed multiple myeloma treated with zoledronic acid. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 2005;106:3461.
39. Pozzi S, Marcheselli R, Sacchi S, et al. Analysis of frequency and risk factors for developing bisphosphonate associated necrosis of the jaw. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 2005;106:5057.
40. Cafro AM, Barbarano LA, Andriani A, et. al. Osteonecrosis of the jaw associated with chroninc bisphosphonates therapy: an Italian experience. *Blood*. (American Society of Hematology Annual Meeting Abstracts) 2005;106:5152.
41. Zavras AI, Zhu S. Bisphosphonate are associated with increased risk for jaw surgery in medical claims data; is it osteonecrosis? *J Oral Maxillofac Surg*. 2006;64:917-23.
42. Hoff AO, Toth BB, Altundag K, et al. Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy. *J Clin Oncol*. 2006 ASCO Annual Meeting Proceedings (post meeting edition). 2006;24:8528. Available at: http://meeting.jco.org/cgi/content/abstract/24/18_suppl/8528. Accessed on August 14,

2006.
43. IMS HEALTH, NPA Plus™ May 2006.
44. Report of the Council of Scientific Affairs. Expert panel recommendations: dental management of patients on oral bisphosphonate therapy. American Dental Association. June 2006. Available at http://www.ada.org/prof/resources/topics/osteonecrosis.asp Accessed June 29, 2006.
45. Badros A, Weikel D, Salama A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol*. 2006;24:945-52.
46. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Path Oral Radiol Endod. 2006 (In press)*
47. Ruggiero SL, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, et al. Practical guidelines for the prevention, diagnosis and treatment of osteonecrosis of the jaw in patients with cancer. *J Clin Oncol Prac* 2006; 2:7-14.
17
48. Migliorati CA, Casiglia J, Epstein J, Siegel, MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis. *J Am Dent Assoc*. 2005;136:1658-68.
49. American Association of Endodontists Position Statement Endodontic implications of bisphosphonate-associated osteonecrosis of the jaws. Available at: http://www.aae.org/dentalpro/guidelines.htm. Accessed on August 14, 2006.
50. Novartis Media Release. New data demonstrate benefits of once-yearly Aclasta® in the treatment of postmenopausal osteoporosis. September 16, 2006. Available at http://cws.huginonline.com/N/134323/PR/200609/1075407_5.html. Accessed on September 22, 2006.
51. Kademani D, Koka S, Lacy MQ, Rajkumar V. Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. *Mayo Clin Proc*. 2006;81:1100-03.
52. Chhoeu AH, Siegel D. Landesberg R, Althoff M, et al. A case series of hyperbaric oxygen treatment for non-radiation induced osteonecrosis of the jaw. *J Oral Maxillofac Surg*. 2006;64(Sup):80-1.
53. National Institutes of Health Program Announcement. Available at: http://grants2.nih.gov/grants/guide/pa-files/PA-06-500.html. Accessed September 15, 2006.
54. National Institutes of Health Computer Retrieval of Information on Scientific Projects. Available at http://crisp.cit.nih.gov/crisp/CRISP_LIB.getdoc?textkey=7145967&p_grant_num=1R21DE017164-
01A1&p_query=(osteonecrosis)&ticket=24536900&p_audit_session_id=133450496&p_audit_score=33&p_audit_numfound=2&p_keywords=osteonecrosis. Accessed September 14, 2006.