

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

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 article 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.

Disclaimer: The AAOMS is providing this position paper on Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) to inform practitioners, patients, and other interested parties. The position paper is based on a review of the existing literature and the clinical observations of an expert Task Force composed of oral and maxillofacial surgeons experienced in the diagnosis, surgical and adjunctive treatment of diseases, injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions, epidemiologists, and basic researchers. The position paper is informational in nature and is not intended to set any standards of care. AAOMS cautions all readers that the strategies described in the position paper are not practice parameters or guidelines and may *not* be suitable for every, or any, purpose or application. This position paper cannot substitute for the individual judgment brought to each clinical situation by the patient's oral and maxillofacial surgeon. As with all clinical materials, the position paper reflects the science related to BRONJ at the time of the paper's development, and it should be used with 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 noninfringement 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.

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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.

Background

BENEFITS OF BISPSPHONATE 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; Novartis, East Hanover, NJ) was the only drug approved in the United States for treatment of metastatic bone disease. In 2002, zoledronic acid (Zometa; Novartis) 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 and 2004, oral and maxillofacial surgeons were the first clinicians to recognize and report cases of nonhealing 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 labeling 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](#) 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 3 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 8 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 as BRONJ. Commonly misdiagnosed conditions may include, but are not limited to, alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint 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% to 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, Whitehouse Station, NJ), 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. Although these are the best available data to date, there may be serious under-reporting 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% to 0.04%, based on prescription data in Australia. After extractions, this rate increased to 0.09% to 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, ie, more than 3 years, of oral bisphosphonates. The effect of certain comorbidities, eg, 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 7 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, eg, periodontal and dental

abscesses, are at a 7-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: Caucasian⁴⁵
 - 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 diagnosis⁴²

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 2 Task Force members with approximately 50 patients, the risk of developing BRONJ associated with *oral bisphosphonates*, although exceedingly small, appears to increase when the duration of therapy exceeds 3 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 3 months prior to and 3 months after 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}

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 after 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.

Nonrestorable teeth and those with a poor prognosis should be extracted. Other necessary 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 osteoradione-

crisis prevention protocols are guidelines that are familiar to most oncologists and general dentists.

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. Nonrestorable 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 who was 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.

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 (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, ie, 3 years or more, based on experience with 50 such patients by 2 Task Force members. The risk of long-term oral bisphosphonate therapy clearly requires further analysis and research.

MANAGEMENT STRATEGIES

Sound recommendations for patients taking oral bisphosphonates that are based on strong clinical research designs are lacking. 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

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	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Symptomatic treatment with broad-spectrum oral antibiotics, eg, penicillin, cephalexin, clindamycin, or first-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, extraoral fistula, or osteolysis extending to the inferior border	<ul style="list-style-type: none"> • 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 to 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 because 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 2 Task Force members managing 50 BRONJ patients who were treated with oral bisphosphonates, discontinuation of oral bisphosphonates for 6 to 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.

associated with oral bisphosphonates increased when duration of therapy exceeded 3 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 3 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.

However, 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 3 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 3 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 3 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 3 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 2 Task Force members managing 50 BRONJ patients who had a history of oral bisphosphonate therapy for 3 or more years, and the hypothesis that a “drug holiday” may mitigate this risk.

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 because it is unlikely that the extraction will exacerbate the established necrotic process.

Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, because 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 nonvascularized 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. Freiburger, 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 (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, extraoral fistula, or osteolysis extending to the inferior border

TREATMENT STRATEGIES

At Risk Patients

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 the disease process.

Stage 1 Patients

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 Patients

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, then the antibiotic regimen should be adjusted accordingly. In some refractory cases, however, patients may require combination antibiotic therapy, long-term antibiotic maintenance, or a course of intravenous antibiotic therapy.

Stage 3 Patients

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 con-

sidered because 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*, 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.

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 2 Task Force members managing 50 BRONJ patients who were treated with oral bisphosphonates, discontinuation of oral bisphosphonates for 6 to 12 months may result in either spontaneous sequestration or resolution after 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 judgments about risk, prognosis, treatment selection, and outcome for patients with BRONJ.

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Appendix. BISPHOSPHONATE PREPARATIONS CURRENTLY AVAILABLE IN THE UNITED STATES*

	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.