

ONJ is uncommon, may be prevented, and can be managed



What is ONJ?

Osteonecrosis of the jaw (ONJ) is characterised by exposed bone in the maxillofacial area with no evidence of healing. It may occur¹

- In association with dental surgery
- Spontaneously

Patients who present with ONJ clinical features should be referred to a dental professional immediately.¹

ONJ is diagnosed by a dental professional when there is¹

- No evidence of healing after 6 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

Potential risk factors for ONJ

Although what causes ONJ is not well understood, uncommon cases have been reported in patients receiving bone-targeted therapies (such as bisphosphonates and RANKL inhibitors). However, a causal relationship has not been established.²⁻⁵

Factors that may increase the risk of ONJ include^{3,4}

- Treatment modalities such as radiation, chemotherapy, and corticosteroids
- Cancer
- Infection
- Periodontal disease
- Dental procedures (eg, tooth extraction)
- Alcohol use and smoking
- Malnutrition
- Coagulation abnormalities and vascular disorders

ONJ is uncommon

A comprehensive review by the MD Anderson Cancer Center revealed that ONJ is uncommon^{6,7}:

- ONJ occurs in 0.73% of all cancer patients treated with bisphosphonates⁶
 - The frequency was 1.2% in patients with breast cancer and 2.4% in patients with multiple myeloma⁶
- A retrospective adjudication process applied to data from the ZOMETA clinical trial program in tumour-induced hypercalcaemia, multiple myeloma, and bone metastases from solid tumours demonstrated a prevalence of 0.1% among 16,900 patients exposed to ZOMETA as of November 2006⁷

ONJ may be prevented

Prior to treatment with ZOMETA^{3,4}

- Patients should get a dental exam
- Maintain good oral hygiene


During treatment with ZOMETA^{1,3,4}

- Patients should avoid invasive dental procedures
- Maintain routine dental cleanings/exams, and avoid soft-tissue injuries to maxillofacial area
- Ensure good fit of dentures
- See a dental professional immediately if ONJ is suspected

Preventive measures have proven to reduce the annual incidence of ONJ by **75%**^{8*}

*Based on a retrospective analysis.

Please see accompanying full Prescribing Information.

ZOMETA[®]
zoledronic acid 
Protect what is essential

ONJ is uncommon, may be prevented, and can be managed



ONJ can be managed

If a patient develops ONJ, steps can be taken to minimise its impact.

ONJ stages* and treatment strategies^{4,7}

Stage 1	Stage 2	Stage 3
<p>Exposed/necrotic bone in asymptomatic patients without evidence of infection</p> <p>Treatment:</p> <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 	<p>Exposed/necrotic bone associated with infection (pain and erythema) in region of exposed bone with or without purulent drainage</p> <p>Treatment:</p> <ul style="list-style-type: none"> • Symptomatic treatment with broad-spectrum oral antibiotics • Oral antibacterial mouth rinse • Pain control • Superficial debridement to relieve soft-tissue irritation 	<p>Exposed/necrotic bone in patients with pain, infection, and ≥ 1 of the following: pathological fracture, extraoral fistula, or osteolysis extending to the inferior border</p> <p>Treatment:</p> <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

*Recommended treatment protocol per American Association of Oral and Maxillofacial Surgeons (AAOMS). AAOMS has defined stage 0 as patients with no clinical evidence of exposed/necrotic bone but with nonspecific symptoms for which symptomatic treatment may be advisable.

Important Product Information

ZOMETA® 4 mg/5 mL concentrate for solution for infusion

Important note: Before prescribing, consult full prescribing information.

Presentation: Zoledronic acid. Vials containing 4 mg of zoledronic acid supplied as a liquid concentrate for further dilution prior to use.

Indications: Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone. Treatment of hypercalcaemia of malignancy (HCM).

Prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors (AIs).

Dosage: Zometra must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs. For "prevention of skeletal related events in patients with advanced malignancies involving bone", the recommended dose is 4 mg (diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution), given as an intravenous infusion of no less than 15 minutes every 3 to 4 weeks. Dose reduction is recommended in patients with pre-existing mild to moderate renal impairment.

For "treatment of HCM", the recommended dose is 4 mg given as a single intravenous infusion of no less than 15 minutes. No dose adjustment in patients with mild to moderate renal impairment.

Patients without hypercalcaemia should also be administered an oral calcium supplement (500 mg calcium and 400 IU vitamin D daily).

For "Prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors (AIs)" the recommended dose is 4 mg (diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution, given as an intravenous infusion lasting no less than 15 minutes every 3 to 4 weeks.

Contraindications: Pregnancy, breast-feeding women, patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of Zometra.

Warnings/Precautions: Patients must be assessed prior to administration of Zometra to ensure that they are adequately hydrated. Monitoring of standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, and particularly, serum creatinine. Severe and occasional incapacitating bone, joint, and/or muscle pain have been reported infrequently in patients taking bisphosphonates. In view of the potential impact of bisphosphonates on renal function, and the lack of extensive clinical data in patients with severe renal impairment with Zometra, its use in this population is not recommended.

Dose reduction in patients with pre-existing mild to moderate renal impairment and/or continuing repeated administration of Zometra, serum creatinine should be evaluated prior to each dose. If renal function has deteriorated, the dose should be withheld. Limited clinical data in patients with severe hepatic insufficiency; no specific recommendations can be given for this patient population. Overhydration should be avoided in patients at risk of cardiac failure. Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving bisphosphonates, including Zometra. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma),

and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Therefore, cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates. Cancer patients should inform their dentist while under dental treatment or if dental surgery is foreseen. Patients treated with Zometra (zoledronic acid) should not be treated with Aclasta. No experience in children. Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

Pregnancy: See contraindications.

Breast-feeding: See contraindications.

Interactions: Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes *in vitro*, but no formal clinical interaction studies have been performed. Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is asked when used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia development during treatment. In multiple myeloma patients, the risk of renal dysfunction may be increased when bisphosphonates are used in combination with thalidomide.

Side effects: Usually mild and transient and similar to those reported for other bisphosphonates:

Common (1% to 10%): reduction in renal calcium excretion is compensated by a fall in serum phosphate (hypophosphataemia);

Common (1% to 10%): flu-like syndrome consisting of fever, fatigue, chills, and bone-, joint, and/or muscle pain, generalised pain, headache; elevation of serum creatinine and blood urea; renal impairment; anaemia; conjunctivitis; gastrointestinal reactions, such as nausea and vomiting, anorexia, serum calcium may fall to asymptomatic or hypocalcaemic levels;

Common (0.1% to 1%): bone myeloma; leucopenia; hypersensitivity reactions; hypertension, hypotension, resulting in syncope or circulatory collapse; shortness of breath, cough, dizziness, paraesthesia, numbness, hypoaesthesia, paresthesia, tremor, anxiety, sleeping disturbances; blurred vision; diarrhoea, constipation, dyspepsia, stomatitis, dry mouth; local reactions at the infusion site such as pain, redness, swelling, asthenia, peripheral oedema, weight increase, chest pain; rash and pruritus; hypocalcaemia, muscle cramps, osteonecrosis (primarily of the jaw); acute renal failure, haematuria, proteinuria, hypomagnesaemia, hypokalaemia;

Rare (0.01 to 0.1%): pancytopenia, confusion, bradycardia, angioneurotic oedema, hyperkalaemia, hypernatraemia;

Very rarely (< 0.01%): uveitis, episcleritis, bronchoconstriction, somnolence, atrial fibrillation, anaphylactic shock/reaction and urticaria.

Packs and prices: Country specific.

Legal classification: Country specific.

References: 1. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients—May 2006. *Crit Rev Oncol Hematol*. 2007;62:148-152. 2. 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 Pathol Oral Radiol Endod*. 2006;102:433-441. 3. Ruggiero S, Gralow J, Marx RE, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract*. 2006;2:7-14. 4. American Association of Oral and Maxillofacial Surgeons. Position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update. http://www.aaoms.org/docs/position_papers/bronj_update.pdf. Accessed 19 July 2011. 5. Xgeva US Prescribing Information. Amgen, Inc. 6. Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008;23:826-836. 7. Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. *Am J Med*. 2009;122:S33-S45. 8. Ripamonti C, Maniezzo M, Cislighi E, et al. Application of preventive measures minimizes the occurrence of the osteonecrosis of the jaw (ONJ) in solid tumors patients (pts) with bone metastases treated with bisphosphonates (BPs): a single institution series. Presented at: 30th Annual San Antonio Breast Cancer Symposium; 13-16 December 2007; San Antonio, TX. Abstract 2056.

Please see accompanying full Prescribing Information.