







# 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 occur<sup>1</sup>

- In association with dental surgery
- Spontaneously

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

ONJ is diagnosed by a dental professional when there is<sup>1</sup>

- 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, cases have been reported in patients receiving bone-targeted therapies (such as bisphosphonates and RANKL inhibitors). However, a causal relationship has not been established.<sup>2-5</sup>

## Additional factors that may increase the risk of ONJ include<sup>3,4</sup>

- 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 has been reported in patients treated with bisphosphonates

A comprehensive review by the MD Anderson Cancer Center revealed that ONJ is uncommon<sup>6,7</sup>:

- ONJ occurs in 0.73% of all cancer patients treated with bisphosphonates<sup>6</sup>
- -The frequency was 1.2% in patients with breast cancer and 2.4% in patients with multiple myeloma<sup>6</sup>
- Data from the ZOMETA clinical trials in tumour-induced hypercalcaemia, multiple myeloma, and bone
  metastases from solid tumours demonstrated an ONJ incidence of 0.55% among 27,204 patients exposed
  to ZOMETA as of August 2012<sup>8</sup>

#### Risk of ONJ can be reduced

Prevention strategies		
Prior to treatment with ZOMETA <sup>3,4</sup>	During treatment with ZOMETA <sup>1,3,4</sup>	
Patients should get a dental exam	Patients should avoid invasive dental procedures	
Maintain good oral hygiene	<ul> <li>Maintain routine dental cleanings/exams, and avoid soft-tissue injuries to maxillofacial area</li> </ul>	
	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 up to

85%

### ONJ can be managed

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

Recommended treatment protocol per AAOMS <sup>4,7†</sup>			
Stage 1	Stage 2	Stage 3	
Patients who are asymptomatic and have no evidence of infection	Associated with infection as evidenced by pain and erythema	Pain, infection, and 1 or more of the following: pathological fracture	
Recommended treatment  Antibacterial mouth rinse	in the region of the exposed bone with or without purulent drainage	extraoral fistula, or osteolysis extending to the inferior border	
Clinical follow-up on a	Recommended treatment	Recommended treatment	
quarterly basis	Symptomatic treatment with oral antibiotics	Antibacterial mouth rinse	
Patient education and review of indications for continued bisphosphonate therapy	<ul> <li>Oral antibiotics</li> <li>Oral antibiotics</li> <li>Pain control</li> <li>Superficial debridement to relieve soft-tissue irritation</li> </ul>	<ul> <li>Antibiotic therapy and pain control</li> <li>Surgical debridement/resection flonger term palliation of infection and pain</li> </ul>	

<sup>1</sup>Recommended treatment protocol per American Association of Oral and Maxillofacial Surgeons (AAOMS). AAOMS has inhed stage 0 as patients with no clinical evidence of exposed/necrotic bone but with nonspetic symptoms for which symptomatic treatment may be advisable.



<sup>\*</sup>Based on a retrospective analysis.

### Important Safety Information

Important note: Before prescribing, consult full prescribing informatio

**Presentation:** Zoledronic acid. Vials containing 4 mg of zoledronic acid supplied as a powder together with ampoules containing 5 mL of water for injections for reconstitution or as a 4 mg/5 mL liquid concentrate for further dilution prior to use. The 'ready to use' presentation contains bottles of Zometa\* 4 mg/100 mL solution for infusion

Indications: Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone. Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy that includes a Gonadotropin Releasing Hormone (GnRH) agonist. Treatment of hypercalcemia of malignancy (HCM, or tumor-induced hypercalcemia, TiHJ) defined as albumin-corrected serum calcium (cCa) ≥12.0 mg/dL [3.0 mmol/L]. Prevention of fracture and bone loss in postmenopausal women with early breast cancer treated with aromatase inhibitors (Als). Treatment of severe osteogenesis imperfecta (OI) in children aged 1 to 17 years.

#### Dosage:

Zometa 4 mg powder should be reconstituted in the vial using 5 mL water for injection from the supplied ampoule. The reconstituted solution or the Zometa 4 mg/5 mL concentrate should be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution before infusion. The final Zometa solution for infusion, should be given as an intravenous infusion of no less than 15 minutes. Zometa must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringers solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

The Zometa 4 mg/100 mL solution for infusion is a "ready to use" presentation and must not be further diluted or mixed with other infusion solutions except for patients with renal impairment. It should be administered as a single intravenous solution in a separate infusion line of no less than 15 minutes. Patients without hypercalcemia should also be administered an oral calcium supplement of 500 mg

For "adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy that includes a GnRH agonist, the recommended dose is 4 mg Zometa infusion given every 6 months. Dose reduction is recommended in patients with pre-existing mild to moderate renal impairment.

- For "prevention of skeletal related events in patients with advanced malignancies involving bone, the recommended dose is 4 mg Zometa infusion given every 3 to 4 weeks. Dose reduction is recommended in patients with pre-existing mild to moderate renal impairment.

- For "treatment of HCM (or TIH), the recommended Zometa dose is 4 mg given as a single infusion. No dose adjustment is necessary in patients with mild to moderate renal impairment.

 For "prevention of fracture and bone loss in postmenopausal women with early breast cancer treated with aromatase inhibitors (Als)" the recommended dose is 4 mg Zometa given every 6 months. Dose reduction is recommended in patients with pre-existing mild to moderate renal impairment.

- For "treatment of severe OI in children" the recommended dose is 0.025 mg/kg or 0.05 mg/kg (up to 4 mg) [diluted with 50 mL or 100 mL 0.996 w/v sodium chloride (or 5% w/v glucose solution)] in children aged 1 to <3 years or 3 to 17 years, respectively, given as an intravenous infusion over 30 minutes (30 to 45 minutes for children aged 1 to <3 years) every 3 months. Pediatric patients without hypercalcemia should also be administered an oral calcium and vitamin D supplement daily starting at least 2 weeks prior to the first administration of zoledronic acid. The recommended calcium dose is 500 mg, 800 mg and 1,300 mg daily for children aged 1 to 3 years, 4 to 8 years and 9 to 17 years, respectively. The recommended vitamin D dose is 5 microgram (200 IU) daily for all pediatric age ranges

**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 Zometa.

Warnings/Precautions: All patients must be assessed prior to administration of Zometa to ensure that they are adequately hydrated.Overhydration should be avoided in patients at risk of cardiac failure.Monitoring of standard hypercalcemia-related metabolic parameters such as serum levels of calcium, phosphate and magnesium, and particularly, serum creatinine.In view of the potential impact of bisphosphonates on renal function, and the lack of extensive clinical safety data in patients with severe renal impairment with Zometa, its use in this population is not recommended. Dose reduction in patients with pre-existing mild to moderate renal impairment. In patients requiring repeated administration of Zometa, 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. Osteonecrosis of the jaw has been reported predominantly in adult patients with cancer receiving

bisphosphonates, including Zometa. Post-marketing experience and the literature suggest a greate frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Therefore, patients should avoid invasive dental surgery during treatment with Zometa, maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment osphonates. Patients should inform their dentist while under dental treatment or if dental surgery is foreseen. Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including Zometa, primarily in patients receiving long-term treatmen for osteoporosis. Discontinuation of Zometa therapy should be considered pending evaluation of the patient. During Zometa treatment patients should be advised to report any thigh, hip or groin pain. Severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking bisphosphonates.Patients treated with Zometa (zoledronic acid) should not be treated with Aclasta. Zometa should also not be given together with other bisphosphonates since the combined effects of these agents are unknown. Asthmatic patients who are sensitive to acetylsalicylic acid should not take Zometa. 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 hypocalcemia, calcium gluconate infusions should be administered as clinically indicated. There are no established data in children with severe OI below 1 year of age, Symptomatic hypocalcemia has occurred with Zometa administration in children with severe OI aged 1 to 17 years. It is recommended that adequate oral daily intake of calcium and vitamin D be initiated at least 2 weeks before the first dose of Zometa and continued throughout the treatment period. The recommended doses of oral calcium and vitamin D are provided in the dosage section "Treatment of severe OI in children" Pre-existing hypocalcemia must be effectively treated by adequate intake of calcium and vitamin D before initiating therapy with Zometa. Physicians should consider clinical monitoring of serum calcium and mineral levels (phosphorus and magnesium) for patients at risk, especially during the 3 days following the first infusion of Zometa. The safety and efficacy of Zometa in other pediatric patients have not been established.

Pregnancy: See Contraindications.

Breast-feeding: See Contraindications

Interactions: Caution is advised when bisphosphonates are administered with aminoglycosides or loop diuretics, 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. Caution is advised when Zometa is administered with anti-angiogenic drugs as cases of ONJ were observed in patients treated concomitantly with these drugs.

Adverse reactions: Common adverse reactions are usually mild and transient and similar to those reported for other bisphosphonates:

In adult patients: Very common (>10%): hypophosphatemia. Common (1 to 10%): acute phase reaction consisting of fever, fatigue, chills and influenza-like illness; bone-, joint, and/or muscle pain, joint stiffness; generalized pain, hypertension; headache; paresthesia; sleep disorder; peripheral edema; hyperhidrosis; constipation, elevation of serum creatinine and blood urea; renal impairment; anemia; asthenia, conjunctivitis; gastrointestinal reactions, such as nausea and vomiting, anorexia, hypocalcemia. Uncommon (0.1 to 1%): thrombocytopenia, leucopenia; hypersensitivity reactions; hypotension, shortness of breath (dyspnea), cough; dizziness, taste disturbance, hypoesthesia, hyperesthesia, tremor; anxiety; blurred vision; diarrhea, abdominal pain, dyspepsia, stomatitis, dry mouth; local reactions at the infusion site such as redness or swelling; , weight increase, chest pain; rash and pruritus;

osteonecrosis of the jaw, muscle cramps; acute renal failure, hematuria, proteinuria, hypomagnesemia, hypokalemia. Rare (0.01 to 0.1%): pancytopenia, confusion, bradycardia, angioneurotic edema, hyperkalemia, hypermatremia. Very rarely (<0.01%) or Unknown: uveitis, episcleritis, bronchoconstriction, somnolence, atrial fibrillation, anaphylactic shock/reaction, urticaria, scleritis and orbital inflammation, interstitial lung disease, severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including Zometa).

In children with severe OI: The type of adverse events observed with Zometa use in children with severe OI were generally consistent with those previously seen in adults treated for hypercalcemia of malignancy or skeletal related events associated with advanced malignancies involving the boneVery common (> 10%): fever, hypocalcemia, vomiting, fatigue, nausea. Common (1 to 10%): headache, pain in extremity, tachycardia, acute phase reaction, pain, arthralgia, musculoskeletal pain, hypohosphatemia, abdominal pain upper and nasopharyngitis. Fractures were observed although their interpretation was difficult since they are common events in patients with severe OI. **Packs and prices**: Country specific.

Legal classification: Country specific.

Please see accompanying full Prescribing Information.





Strategies for the prevention and management of

Osteonecrosis of the jaw (ONJ) in patients with advanced cancer



## نصائح لحصول على صحة جيدة للأسنان خلال علاج السرطان

### نحن نحب أن نذكرك بأهمية مراقبة صحتك العامة خلال فترة علاجك.

### قم بزيارة طبيب الأسنان الخاص بك

علاجات السرطان يمكن أن تؤثر على جسمك كله بما فيها أسنانك ولثتك. أثناء العلاج من السرطان (وإن أمكن قبل البدء في العلاج) يكون من المهم زيارة طبيب الأسنان الخاص بك والتأكد من صحة أسنانك.

#### خطوات يجب مراعاتها قبل بدء العلاج بزوميتا

- أحجز موعد للكشف على أسنانك وتنظيفها
- أبلغ طبيب الأسنان الخاص بك أنك سوف تبدأ العلاح بزوميتا (ZOMETA)
- تناقش معه أن كنت ستحتاج العلاج الأسنان قبل البدء في علاج زوميتا (ZOMETA)
  - أطلب من طبيب الأسنان الخاص بك التأكد من التركيبات الخاصة بالأسنان وضبطها
- أبلغ طبيب الأسنان الخاص بك إذا كان لديك نزف من اللثة أو أي أحساس غريب في اللثة أو الأسنان، أو أن كان لديك إلتهاب بالأسنان.

## الأعراض الجانبية التي يجب إبلاغ طبيبك وطبيب الأسنان الخاص بك عنها

- تغيير في حاسة التذوق
  - تيبس في الفك
- ألم أو عدوى

• تسوس الأسنان

- جفاف الفم

• تورم أو ألم بالأسنان

#### نظافة الأسنان المستمرة هو أمر هام

نظافة الأسنان تصبح لها أهمية أكبر في مرضى السرطان لأن علاجات السرطان يمكن أن تؤثر على الأسنان واللثة.

- إحرص على زيارة طبيب الأسنان الخاص بك بصورة دورية
- نظف أسنانك ولسانك بعد كل وجبة بإستخدام فرشاة أسنان لينة وباستعمال ضربات خفيفة
  - أستخدم خيط تنظيف الأسنان مرة واحدة يوميا
  - تجنب المنطقة الحساسة إذا حدث نزيف من اللثة أو ألم.
    - ترطيب الفم بشكل مستمر بغسيله دائما بالماء.
- العديد من الأدوية تسبب جفاف الفم مما قد يؤدى لتسوس الأسنان ومشاكل أخرى بالأسنان.
  - تجنب أستعمال غسول الأسنان بدون وصفة طبية أو الكحول أو التبغ.
    - كل غذاءا متوازنا
    - إذا كان فمك يؤلمك جرب الأكل اللين والرطب.

أحط طبيب الأسنان الخاص بك علما. التواصل الجيد مهم. يجب أن يعلم طبيب الأسنان الخاص بك بأنك تعالج من السرطان وأنك تأخذ دواء زوميتا (ZOMETA). النموذج التالي يجب استعماله لتسجيل المعلومات حول تشخيصك وعلاجك وينبغي مشاركته مع طبيب الأسنان الخاص بك.

## معلومات هامة تعطى لطبيب الأسنان الخاص بك

- العلاج الكيماوي ـــ
- العلاج المناعي أو أي علاج بيولوجي أخر ــــــــ
  - الكورتيزونات ـــــــــــ البيسفوسفاتينات ــــــــــ

  - علاجات أخرى للسرطان ــــــــــ

#### وسائل الأتصال والمعلومات الطبية

- أسم المريض \_\_\_\_\_\_ أسم طبيب الأورام \_\_\_\_\_ ـ رقم التليفون ــ رو العنوان الإلكتروني \_\_\_\_\_\_
  - - تاريخ تشخيص المرض ــــــــــــ

#### العلاجات السابقة والمستقبلية

- العمليات الجراحية (مكانها) ــــ
- العلاج الأشعاعي (مكانه) ـــــــ



يمكنك الابلاغ عن أي أعراض جانبية أو شكاوى من خلال:
الهيئة العامة للغذاء والدواء المركز الوطني للتيقظ الدوائي
الرقم المجاني: ٨٠٠٢٤٩٠٠٠٠
الفاكس: ٩٦٠١١٢٠٥٢٠٠٠
الايميل: npc.drug@sfda.gov.sa
أو عن طريق الانترنت: /https://ade.sfda.gov.sa
اف عن طريق الانترنت: /١٢٦٥٠٠٠٠
الهاتف: ١٩٦٦١١٢٦٥٨٠٠٠٠
الفاكس: ١٩٦٦١١٢٦٥٨٠٠٠



## $\mathsf{FNTIST}$ معلومات هامة من طبيبك

المريض الذى قام بملئ هذه الورقة هو يعالج من السرطان. تم الإبلاغ عن نخر عظام الفك في المرضى الذين يتلقون بعض أنواع علاجات السرطان بما فيها العقارات المستهدفة للعظام، ومعظم الحلات المبلغ عنها كان ذلك مرتبط بعمليات خاصة بالأسنان مثل "خلع الضرس".

ينبغى على من يتلقون علاجا للسرطان تجنب عمليات الأسنان أثناء تعاطيهم للعلاج أن أمكن. لقد وجد أن عمليات الأسنان تؤدى إلى تفاقم نخر عظام الفك في المرضى النين يصابون به أثناء تعاطيهم العلاج بالأدوية المستهدفة للعظام. إذا كان يجب على هؤلاء المرضى التعرض لعمليات تداخلية بالأسنان فيرجى منهم الإتصال بطبيب الأورام الخاص بهم (المعلومات الخاصة بالأتصال موجودة على خلفية هذه الورقة) لمناقشة طرق منع أو تخفيف خطرها عليه أو عليها.