

## Summary of MHRA Alerts for Bisphosphonates and Denosumab

### Disclaimer

This document is registered at North Central London (NCL) Joint Formulary Committee (JFC) and is intended solely for use by healthcare professionals to aid the treatment of patients within NCL. However, clinical guidelines are for guidance only, their interpretation and application remain the responsibility of the individual clinician. If in doubt, contact a senior colleague or expert. Clinicians are advised to refer to the manufacturer's current prescribing information before treating individual patients.

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Drug(s)	Alert	Summary	Prescriber action	Reference
Bisphosphonates	Atypical femoral fractures	<ul style="list-style-type: none"> <li>• Atypical femoral fracture reported rarely with bisphosphonate therapy, mainly in patients receiving long-term treatment for osteoporosis; atypical femoral fractures are considered a class effect of bisphosphonates</li> <li>• These can occur after minimal or no trauma</li> <li>• May present as thigh or groin pain, weeks to months before presenting with a completed femoral fracture</li> <li>• Poor healing of these fractures have been reported</li> <li>• Overall risk benefit for use in licenced indication remains favourable: the absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented</li> </ul>	<ul style="list-style-type: none"> <li>• Atypical femoral fractures often bilateral; contralateral femur should be examined in bisphosphonate-treated patients with sustained femoral shaft fracture</li> <li>• Consider discontinuation of bisphosphonate if <b>suspected</b> atypical femur fracture while they are evaluated; base this on assessment of treatment benefits and risks for individual</li> <li>• During bisphosphonate treatment, patients should be advised to report any thigh, hip, or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture</li> <li>• Optimum duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of bisphosphonate therapy for individual patients, particularly after 5 or more years of use</li> </ul>	<p>MHRA Drug Safety Update June 2011</p> <p><a href="https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures">https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures</a></p>
Bisphosphonates	Osteonecrosis of the external auditory canal	<ul style="list-style-type: none"> <li>• Osteonecrosis of the external auditory canal has been reported very rarely (&lt;1 in 10,000 patients) with bisphosphonate</li> <li>• Reports are mainly associated with long-term therapy (2 years or longer), and occurred with oral and IV, cancer and osteoporosis indications</li> <li>• The association between bisphosphonates and osteonecrosis of the external auditory canal is believed to be causal</li> <li>• The number of cases of osteonecrosis of the external auditory canal reported in association with bisphosphonates is low compared with the number of cases reported of bisphosphonate-related osteonecrosis of the jaw</li> </ul>	<ul style="list-style-type: none"> <li>• Possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms, including chronic ear infections, or in patients with suspected cholesteatoma</li> <li>• Steroid use and chemotherapy are possible risk factors, these could be with or without local risk factors such as infection or trauma</li> <li>• Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during bisphosphonate treatment</li> <li>• Report any cases of osteonecrosis of the external auditory canal suspected to be associated with bisphosphonates or any other medicines, including denosumab, on a Yellow Card</li> </ul>	<p>MHRA Drug Safety Update December 2015</p> <p><a href="https://www.gov.uk/drug-safety-update/bisphosphonates-very-rare-reports-of-osteonecrosis-of-the-external-auditory-canal">https://www.gov.uk/drug-safety-update/bisphosphonates-very-rare-reports-of-osteonecrosis-of-the-external-auditory-canal</a></p>

Drug(s)	Alert	Summary	Prescriber action	Reference
Bisphosphonates	Osteonecrosis of the jaw (ONJ)	<ul style="list-style-type: none"> <li>• Risk of developing ONJ in association with oral bisphosphonates appears low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease</li> <li>• There is clear evidence to suggest bisphosphonate-specific and indication-specific risk factors such as potency (highest for zoledronate); route of administration (e.g, intravenous ibandronate, pamidronate, and zoledronate); and cumulative dose.</li> <li>• The evidence base is less robust for other proposed risk factors (e.g, duration and type of malignant disease, concomitant treatment, smoking, and comorbid conditions). However, healthcare professionals should consider these risk factors when evaluating an individual's risk of developing ONJ</li> <li>• A history of dental disease—including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures—is associated with an increased risk of ONJ</li> </ul>	<ul style="list-style-type: none"> <li>• All patients with cancer should have a dental check-up before bisphosphonate treatment.</li> <li>• All other patients who start bisphosphonates should have a dental examination only if they have poor dental status</li> <li>• During bisphosphonate treatment, patients should maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain, or swelling</li> </ul>	<p>MHRA Drug Safety Update November 2009</p> <p><a href="https://www.gov.uk/drug-safety-update/bisphosphonates-osteonecrosis-of-the-jaw">https://www.gov.uk/drug-safety-update/bisphosphonates-osteonecrosis-of-the-jaw</a></p>

Drug(s)	Alert	Summary	Prescriber action	Reference
Bisphosphonates (Zoledronic acid, pamidronic acid, alendronic acid)	Atrial fibrillation	<ul style="list-style-type: none"> <li>• The risk of atrial fibrillation in association with bisphosphonate treatment seems to be low, and the balance of risks and benefits for bisphosphonates remains favourable.</li> <li>• To date, clinical trial results have suggested an increased risk of atrial fibrillation for zoledronic acid (Aclasta ▼), pamidronic acid, and possibly for alendronic acid.</li> <li>• The product information for zoledronic acid has been updated to include atrial fibrillation as a possible side-effect (both for Aclasta ▼ and Zometa, a product that contains zoledronic acid that is given every 3–4 weeks as part of cancer treatment). Atrial fibrillation is also being added to the product information for pamidronic acid.</li> <li>• The risk of atrial fibrillation with alendronic acid will be kept under close review. Should further evidence accumulate, the product information for alendronic acid will be updated accordingly.</li> </ul>	<ul style="list-style-type: none"> <li>• No direct action recommended.</li> </ul>	<p>MHRA Drug Safety Update July 2008</p> <p><a href="https://www.gov.uk/drug-safety-update/bisphosphonates-atrial-fibrillation">https://www.gov.uk/drug-safety-update/bisphosphonates-atrial-fibrillation</a></p>

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Oral Bisphosphonates	Oesophageal cancer	<ul style="list-style-type: none"> <li>• After reports of oesophageal cancer in association with oral bisphosphonates, MHRA and the Cancer Epidemiology Unit at the University of Oxford conducted a study</li> <li>• The study suggested a small increase in the risk of oesophageal cancer in patients who had taken oral bisphosphonates for more than 5 years.</li> <li>• Taken together with other Europe-wide reviews of oral bisphosphonates and oesophageal cancer, there is insufficient evidence to confirm a link between oral bisphosphonate use and oesophageal cancer.</li> </ul>	<p>The 2014 guidance advised:</p> <ul style="list-style-type: none"> <li>• Association between bisphosphonates and oesophageal cancer cannot be excluded</li> <li>• Caution should be used when considering nitrogen-containing bisphosphonates for oral use in patients with known Barrett's oesophagus</li> <li>• Physicians should carefully consider the benefits and potential risks of treatment with alendronate, ibandronate and risedronate in these patients.</li> </ul> <p>Also see <b>Oesophageal Reactions</b> below.</p>	<p>MHRA Drug Safety Update November 2010</p> <p><a href="https://www.gov.uk/drug-safety-update/oral-bisphosphonates-oesophageal-cancer-risk-insufficient-evidence-of-a-link">https://www.gov.uk/drug-safety-update/oral-bisphosphonates-oesophageal-cancer-risk-insufficient-evidence-of-a-link</a></p> <p>MHRA Guidance. Bisphosphonates: Use and Safety. December 2014</p> <p><a href="https://www.gov.uk/government/publications/bisphosphonates-use-and-safety/bisphosphonates-use-and-safety">https://www.gov.uk/government/publications/bisphosphonates-use-and-safety/bisphosphonates-use-and-safety</a></p>

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Oral Bisphosphonates	Oesophageal reactions	<ul style="list-style-type: none"> <li>• Oral formulations of the bisphosphonates alendronate, ibandronate and risedronate are associated with serious oesophageal adverse reactions</li> <li>• These reactions include: oesophagitis, oesophageal ulcers, oesophageal strictures and oesophageal erosions</li> </ul>	<ul style="list-style-type: none"> <li>• Alendronate and oral ibandronate should not be given to patients with abnormalities of the oesophagus and/or other factors which delay oesophageal emptying such as stricture or achalasia.</li> <li>• Risedronate should be used with caution in such patients</li> <li>• Alendronate, oral ibandronate, and risedronate should be used with caution in patients with active or recent upper gastrointestinal problems</li> <li>• In patients with known Barrett's oesophagus, prescribers should consider the benefits and potential risks of alendronate and oral ibandronate on an individual basis</li> <li>• Patients should be advised to stop taking the tablets and to seek medical attention if they develop any symptoms of oesophageal irritation such as difficulty or pain upon swallowing, chest pain, or new or worsening heartburn</li> <li>• Patients should be advised about the importance of adhering to dosage instructions (including taking with at least 200 mL water on an empty stomach immediately after getting up in the morning, and to remain upright for at least 30 minutes after taking the tablet, and before taking any food, drink or other medicine.</li> </ul>	<p>MHRA Guidance. Bisphosphonates: Use and Safety. December 2014</p> <p><a href="https://www.gov.uk/government/publications/bisphosphonates-use-and-safety/bisphosphonates-use-and-safety">https://www.gov.uk/government/publications/bisphosphonates-use-and-safety/bisphosphonates-use-and-safety</a></p>

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IV zoledronic acid	Adverse effects on renal function	<ul style="list-style-type: none"> <li>• Zoledronic acid associated with reports of renal impairment and renal failure, especially if pre-existing renal dysfunction or other risk factors</li> <li>• Worldwide reports of renal impairment and renal failure caused by zoledronic acid include fatalities</li> <li>• Majority of cases occurred with first dose and usually in patients with pre-existing renal dysfunction or other risk factors</li> <li>• Some at risk patients have experienced renal failure requiring dialysis or resulting in death</li> </ul>	<p>Consider the following to minimise risk of renal adverse effects:</p> <ul style="list-style-type: none"> <li>• Measure renal function before each infusion</li> <li>• Appropriate patient hydration required before administration, particularly in elderly and those receiving diuretic therapy</li> <li>• Infusion duration should be at least 15 mins</li> <li>• Consider monitoring renal function after infusion, particularly in at-risk patients (e.g. pre-existing renal dysfunction, advanced age, concomitant nephrotoxic drugs/diuretics, dehydrated)</li> <li>• Caution if concomitant drugs that affect renal function</li> </ul> <p><b>Specific advice for Aclasta®</b></p> <ul style="list-style-type: none"> <li>• Single dose for osteoporosis/Paget's disease not to exceed 5 mg</li> <li>• Contraindicated in CrCl&lt;35 mL/min</li> </ul> <p><b>Specific advice for Zometa®</b></p> <ul style="list-style-type: none"> <li>• Recommended dose in normal renal function is 4 mg; reduce in mild-to-moderate renal impairment</li> <li>• Not recommended for cancer treatment if CrCL&lt;30 mL/min.</li> <li>• Evaluate risk and benefits of treatment for hypercalcaemia in cancer if severe renal impairment present</li> <li>• If renal deterioration during treatment period, withhold and only resume when serum creatinine returns to within 10% of baseline</li> </ul>	<p>MHRA Drug Safety Update April 2010</p> <p><a href="https://www.gov.uk/drug-safety-update/intravenous-zoledronic-acid-adverse-effects-on-renal-function">https://www.gov.uk/drug-safety-update/intravenous-zoledronic-acid-adverse-effects-on-renal-function</a></p>

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Denosumab and IV Bisphosphonates	Osteonecrosis of the jaw (ONJ)	<ul style="list-style-type: none"> <li>• ONJ is a known side effect of denosumab and bisphosphonates</li> <li>• In patients treated for osteoporosis (regardless of route of administration), the risk of ONJ is small compared with that in patients treated with the higher doses used for cancer-related conditions.</li> <li>• Other drug-specific risk factors for ONJ include drug potency (higher risk for highly potent compounds such as zoledronate, pamidronate and denosumab), route of administration (higher risk for parenteral administration) and cumulative dose</li> <li>• Patient reminder cards have been introduced for denosumab and IV bisphosphonates to inform patients of the risk of ONJ and precautions to take before/during therapy</li> </ul>	<ul style="list-style-type: none"> <li>• A dental examination and appropriate preventive dentistry is recommended for all patients before starting denosumab 120 mg (cancer indication)</li> <li>• Do not start denosumab 120 mg in patients with a dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery</li> <li>• Check ONJ risk factors before starting denosumab 60 mg (osteoporosis indication). A dental examination and appropriate preventive dentistry are recommended for patients with risk factors</li> </ul> <p>Before prescribing denosumab or IV bisphosphonates:</p> <ul style="list-style-type: none"> <li>• give patients reminder card for their medicine</li> <li>• explain risk of osteonecrosis of the jaw and advise patients on precautions to take—advise patients to: <ul style="list-style-type: none"> <li>• tell their doctor if any problems with mouth or teeth before starting treatment; if they wear dentures they should make sure their dentures fit properly before starting treatment</li> <li>• maintain good oral hygiene and get routine dental check-ups during treatment</li> <li>• tell their doctor and dentist that they are receiving denosumab or IV bisphosphonate if need dental treatment or dental surgery</li> <li>• tell their doctor and dentist immediately if any problems with mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge)</li> </ul> </li> <li>• do not prescribe denosumab 120 mg (cancer indication) to patients with unhealed lesions from dental or oral surgery</li> </ul>	<p>MHRA Drug Safety Update September 2014</p> <p><a href="https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations">https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations</a></p> <p>MHRA Drug Safety Update July 2015</p> <p><a href="https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk">https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk</a></p>



Drug(s)	Alert	Summary	Prescriber action	Reference
Denosumab	Osteonecrosis of the external auditory canal	<ul style="list-style-type: none"> <li>The underlying possible pathological mechanism is considered to be similar to that for denosumab-related osteonecrosis of the jaw.</li> <li>As observed with bisphosphonates, the number of cases of osteonecrosis of the external auditory canal in association with denosumab is low compared with those of osteonecrosis of the jaw.</li> </ul>	<ul style="list-style-type: none"> <li>The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma</li> <li>Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma</li> <li>Advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment</li> <li>Report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a Yellow Card</li> </ul>	<p>MHRA Drug Safety Update June 2017</p> <p><a href="https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal">https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal</a></p>
Denosumab	Atypical femoral fractures	<ul style="list-style-type: none"> <li>The nature of the fractures seen with denosumab 60 mg is similar to the atypical femoral fractures seen with long-term bisphosphonate therapy</li> </ul> <p>Summary points below based on key findings for bisphosphonate atypical femoral fracture:</p> <ul style="list-style-type: none"> <li>These can occur after minimal or no trauma</li> <li>May present as thigh or groin pain, weeks to months before presenting with a completed femoral fracture</li> <li>Poor healing of these fractures have been reported</li> <li>Overall risk benefit for use in licenced indication remains favourable: the absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented</li> </ul>	<ul style="list-style-type: none"> <li>During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain; patients presenting with such symptoms should be evaluated for an incomplete femoral fracture</li> <li>Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur</li> <li>The contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral</li> <li>Discontinuation of denosumab treatment should be considered if an atypical femur fracture is suspected, while the patient is evaluated; an individual assessment of the benefits and risks should be performed</li> </ul>	<p>MHRA Drug Safety Update February 2013</p> <p><a href="https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia">https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia</a></p>

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Denosumab	Hypocalcaemia	<ul style="list-style-type: none"> <li>Denosumab is also associated with a risk of hypocalcaemia.</li> <li>This risk increases with the degree of renal impairment</li> <li>Severe symptomatic hypocalcaemia, including fatal cases, has been reported in patients receiving denosumab 120 mg</li> <li>Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60 mg</li> <li>Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later</li> <li>Denosumab 60 mg is contraindicated in patients with hypocalcaemia (regardless of severity)</li> <li>Denosumab 120 mg is contraindicated in patients with severe, untreated hypocalcaemia</li> </ul>	<ul style="list-style-type: none"> <li>Pre-existing hypocalcaemia must be corrected prior to initiating denosumab</li> <li>All patients receiving denosumab 120 mg require calcium and vitamin D supplementation unless hypercalcaemia is present</li> <li>Patients receiving denosumab 60 mg require adequate intake of calcium and vitamin D</li> <li>Tell all patients to report symptoms of hypocalcaemia to their doctor (eg, muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).</li> </ul> <p><b>Calcium levels should be monitored as follows:</b></p> <p><b>Denosumab 120 mg (cancer indication)</b> Check calcium levels:</p> <ul style="list-style-type: none"> <li>before the first dose</li> <li>within two weeks after initial dose</li> <li>if suspected symptoms of hypocalcaemia occur.</li> </ul> <p>Consider monitoring calcium levels more frequently in patients with hypocalcaemia risk factors (e.g. severe renal impairment, creatinine clearance &lt;30 ml/min, receiving dialysis).</p> <p><b>Denosumab 60 mg (osteoporosis indication)</b> Check calcium levels:</p> <ul style="list-style-type: none"> <li>before each dose</li> <li>within two weeks after initial dose in patients with hypocalcaemia risk factors (e.g. severe renal impairment, creatinine clearance &lt;30 ml/min)</li> <li>if suspected symptoms of hypocalcaemia occur.</li> </ul>	<p>MHRA Drug Safety Update September 2014</p> <p><a href="https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations">https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations</a></p>

## Document control

Date	Version	Amendments
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## Document management

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