



North Central London
Joint Formulary Committee

DENOSUMAB (60mg) (Prolia®) FACT SHEET

FOR THE TREATMENT OF OSTEOPOROSIS IN POST MENOPAUSAL WOMEN

Start date: January 2012

Review date: August 2018

Document Control

Denosumab Factsheet V1 - produced by Camden Medicines Management Team - agreed at CMMC meeting 25.01.12

V1.2 - Factsheet amended October 2012 to include MHRA letter on safety of medicines- "Amgen - Direct Healthcare Communication - Reports of symptomatic hypocalcaemia, including fatal cases reported in patients treated with XGEVA® (denosumab)"

V1.3 – Factsheet amended November 2012 to include "for the treatment of osteoporosis" in document title; and to state "60mg solution for injection (Prolia®▼)" as this is the only strength and brand licensed for osteoporosis.

V1.4 – Factsheet amended January 2013 as follows:

- MHRA Drug Safety Update October 2012 added as an appendix
- Title changed to "for the treatment of osteoporosis in postmenopausal women"
- Clarification that treatment can be initiated in line with NICE guidance by both primary and secondary care
- MHRA yellow card details added
- Addition to 'Actions for GPs' re: ensuring no follow up appointment arranged for treatment
- Addition to 'Administration' section- method of administration
- Addition of NICE references
- Addition of 'Further Information' section
- Addition of cellulitis under 'Special warnings and precautions' section
- Addition of ear infection and drug hypersensitivity to 'Adverse drug reactions reported' section
- Removal of reference to dosing requirements of other drugs listed under 'Associated Risks'
- Minor grammatical and formatting corrections

V1.5 – Factsheet amended April 2013 to include reference to risk of atypical fractures of the femur (under 'special warnings and precautions') and the addition of the MHRA Drug Safety Update February 2013 as an appendix

V2 – Factsheet amended December 2013 to include changes in the SPC (particularly adverse effects) and to highlight brand to be prescribed for this indication. Removal of black triangle status for Prolia®. Increased prominence given to the Actions for GPs so that Denosumab can be safely initiated in primary care.

V2.1 – Factsheet reviewed and updated October 2014 to include updated information to minimise the risk of osteonecrosis and monitor for hypocalcaemia.

V2.2 – Factsheet reviewed and updated August 2015 to include updated information on the introduction of patient reminder cards.

V2.3 – Factsheet amended July 2017 to include reference to risk of osteonecrosis of the external auditory canal (under 'special warnings and precautions') and the addition of the MHRA Drug Safety update June 2017 as an appendix.

v.2.4 – Factsheet amended June 2018 to include recommendations on calcium monitoring as per MHRA Drug Safety update September 2014 (Appendix 5). Approved via Chair's action.

FACTSHEET TO FACILITATE PRESCRIBING

PLEASE NOTE THIS IS NOT A SHARED CARE GUIDELINE, NOR IS IT A FULL SUMMARY OF DRUG INFORMATION. ALWAYS REFER TO THE MOST RECENT BNF AND/OR SUMMARY OF PRODUCT CHARACTERISTICS.

This document is currently under review - as some of the content may be out of date, it should be viewed as an archive document for information only. If you have any queries, please email admin.ncl-mon@nhs.net

Disclaimer

This Fact Sheet 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, this fact sheet is for guidance only, its interpretation and application remains 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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NCL JFC is funded by and provides advice to Acute Trusts and Clinical Commissioning Groups in NCL.

DENOSUMAB (60mg) (Prolia[®]) FACT SHEET - FOR THE TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

*Denosumab (60mg), Prolia[®], can be **initiated and prescribed in either primary or secondary care** if a patient meets the criteria specified in [NICE Technology Appraisal 204](#) (details outlined below). **N.B:** primary care clinicians will usually be asked to continue the administration and monitoring if already initiated by the specialist. Please ensure the licensed brand Prolia[®] is prescribed for this indication. The annual cost of treatment is £366 per patient (cost taken from [MIMS online](#)- accessed 28th September 2017).*

Check List and Actions for GPs

- **Identify patients who are eligible for treatment with denosumab (Prolia[®])** (see below).
- Then **check that the patient meets NICE criteria** for starting denosumab (see below).
- Read the denosumab factsheet and SPC for special warnings and precautions.
- Before prescribing denosumab or intravenous bisphosphonates, give patients the patient reminder card for their medicine, explain the risk of osteonecrosis of the jaw (ONJ) and advise patients on precautions to take.
- Baseline calcium levels should be performed prior to treatment initiation and hypocalcaemia must be corrected by adequate intake of calcium and vitamin D
- **Check calcium levels:**
 - before each dose
 - Within two weeks after the initial dose in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min)
 - if suspected symptoms of hypocalcaemia occur

Patients should be encouraged to report symptoms indicative of hypocalcaemia (eg, muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).
- **Evaluate all patients for ONJ risk factors** prior to treatment with denosumab (Prolia[®]). A dental examination with appropriate preventive dentistry is recommended in patients with concomitant risk factors.
- Remind patients of advice to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.
- Report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a Yellow Card
- Practices will need to **produce and maintain an up-to-date register of patients being treated** and will need to ensure a systematic call and **6-monthly recall of patients on this register** is taking place.
- Practices must **ensure that all staff involved in providing any aspect of care have the necessary training and skills** and must have guidance in place to cover staff training and maintenance of skills.
- Practices need to **have adequate facilities and equipment for the safe provision of a subcutaneous injection.**
- Ensure there is **no duplication in the patient receiving treatment in primary care and secondary care.**

[NICE Technology Appraisal 204](#) (*Denosumab for the prevention of osteoporotic fractures in postmenopausal women issued in October 2010*) states that denosumab 60mg solution for injection (Prolia[®]) is recommended as a treatment option:

1. For the **primary** prevention of osteoporotic fragility fractures **only in postmenopausal women** at increased risk of fractures:
 - Who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments **and**
 - Who have a combination of T-score, age and number of independent clinical risk factors for fracture (refer to NICE guidance for details)
2. For the **secondary** prevention of osteoporotic fragility fractures **only in postmenopausal women** at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

For the purposes of this document, intolerance of alendronate, risedronate or etidronate is defined as persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment, and that occurs even though the instructions for administration have been followed correctly¹.

¹ [NICE Technology Appraisal 161](#): Osteoporosis – secondary prevention including strontium ranelate:guidance (updated May 2012)

Patient reminder cards

MHRA and other EU medicines regulators have reviewed measures to minimise the risk of ONJ in patients taking denosumab. The review recommended introducing patient reminder cards for denosumab and informing patients of the risk of ONJ and precautions to take before and during treatment. Reminder cards are being issued by license holders for individual products separately. The reminder cards can be seen in appendix 7 or downloaded here.

Administration

The recommended dose of denosumab is 60mg² administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.

Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is cloudy or discoloured. Do not shake excessively. To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting and inject slowly. Inject the entire contents of the pre-filled syringe.

Patients must be adequately supplemented with calcium and vitamin D.

Special Warnings and Precautions

Denosumab 60 mg should **not** be used in patients with hypocalcaemia, regardless of severity.

Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiation of therapy.

Check calcium levels:

- before each dose
- within two weeks after the initial dose in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min)
- if suspected symptoms of hypocalcaemia occur.

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).

Osteonecrosis of the jaw (ONJ) has been reported with denosumab or bisphosphonates. Before starting denosumab treatment, a dental examination and appropriate preventive dentistry are recommended to reduce the risk of ONJ.

Patients should be asked to maintain good oral hygiene and report any oral symptoms.

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. 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.

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**. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. The contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral.

² No dose adjustment is required in elderly patients or patients with renal impairment.
<http://www.medicines.org.uk/emc/medicine/23127/SPC/prolia/>

Reviewing / discontinuing denosumab

There is insufficient data to determine the long term safety of denosumab, beyond 6 years¹. An individual assessment of the benefits and risks should be considered duration of treatment, and review of therapy should be carried out by the specialist team after 5 years² of treatment. **Discontinuation of denosumab treatment should also be considered if an atypical femur fracture is suspected, while the patient is evaluated.**

Patients receiving denosumab may develop skin infections (predominantly cellulitis) requiring hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Storage

Denosumab should be stored in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton to protect from light. Denosumab has a shelf life of 3 years. Once removed from the refrigerator, denosumab should be stored at room temperature (up to 25°C) for up to 30 days in the original container. It must be used within this 30 day period.

Adverse drug reactions (ADRs) reported

Very Common (≥ 1/10): Pain in extremity, musculoskeletal pain

Common (≥ 1/100 to < 1/10): Urinary tract infection, upper respiratory tract infection, sciatica, constipation, abdominal discomfort, rash, eczema.

Uncommon (≥ 1/1000 to < 1/100): Diverticulitis, cellulitis, ear infection.

Rare (≥ 1/10,000 to < 1/1,000): Osteonecrosis of the jaw (ONJ), atypical femoral fractures, hypocalcaemia, drug hypersensitivity and anaphylactic reaction.

Unknown: Osteonecrosis of the external auditory canal

Associated risks

- Patients not meeting NICE criteria due to inappropriate interpretation of intolerance and compliance, hence being initiated on denosumab inappropriately.
- Severe symptomatic hypocalcaemia (e.g. altered mental state, tetany, seizures and QTc prolongation) in patients with increased risk of hypocalcaemia have been reported (see appendices below).

(FOR INFORMATION ONLY - XGEVA[®] (Denosumab 120mg) NOT TO BE PRESCRIBED IN PRIMARY CARE)

¹ No dose adjustment is required in elderly patients or patients with renal impairment. <http://www.medicines.org.uk/emc/medicine/23127/SPC/prolia/>

References

1. Bone HG et. Al, The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension, *The Journal of clinical endocrinology and metabolism*, 2013;98:pp 4483-92
2. All Wales Medicines Strategy Group. [Prescribing of Denosumab \(Prolia®\) in Wales: Review](#) October 2013.

Further Information

- Prolia® Summary of Product Characteristics (SPC) <http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/> - accessed 29th September 2017 (text last updated on 25th September 2017)
- NICE Technology Appraisal 204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women. October 2010 <http://www.nice.org.uk/guidance/TA204>

Appendices

Appendix 1 - MHRA Drug Safety Update October 2012 – Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment – monitoring recommended <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560> - accessed 21st January 2013

Appendix 2 - MHRA Drug Safety Update February 2013- Denosumab 60 mg (Prolia): rare cases of atypical femoral fracture with long-term use <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON239411> accessed 2nd April 2013

Appendix 3 - MHRA letter on safety of medicines – “Amgen - Direct Healthcare Communication - Reports of symptomatic hypocalcaemia, including fatal cases reported in patients treated with XGEVA® (denosumab)” – September 2012 <http://www.mhra.gov.uk/home/groups/comms-ic/documents/websitesources/con185672.pdf> - accessed 15th October 2012

Appendix 4 - MHRA letter on safety of medicines – “Amgen - Denosumab 60mg (Prolia®): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia” – August 2014 <http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con454359.pdf> – accessed 15th October 2014

Appendix 5 - MHRA Drug Safety Update September 2014 - Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia—updated recommendations – <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452540> - accessed 15th October 2014

Appendix 6 – MHRA Drug Safety Update July 2015 - 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> - accessed 20th August 2015

Appendix 7 – MHRA Drug Safety Update July 2015 - Amgen: Content of Prolia® (denosumab) patient card https://assets.digital.cabinet-office.gov.uk/media/55a66d9eed915d151b000003/AMGEN_PROLIA_patient_card.pdf

Appendix 8 – MHRA Drug Safety Update June 2017 - 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> - accessed 4/7/2017

A3 Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment – monitoring recommended

Cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (Xgeva ▼) or 60 mg (Prolia ▼); some of these cases were fatal in those receiving the 120 mg dose.

Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypercalcaemia is present. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

Denosumab 120 mg solution for injection (Xgeva ▼) is given once every 4 weeks for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60 mg solution for injection (Prolia ▼) is given once every 6 months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk

Possible risk of fatal hypocalcaemia

Hypocalcaemia is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance <30 mL/min; estimated glomerular filtration rate [eGFR] 15 – 29 mL/min/1.73m²) or receiving dialysis. Severe symptomatic hypocalcaemia, including three fatal cases, has been reported in patients receiving denosumab 120 mg. Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60 mg*.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment

Periodic monitoring of calcium levels (at the discretion of the prescriber) is recommended after use of denosumab in patients predisposed to hypocalcaemia, including those with severe renal impairment. In patients receiving 120 mg denosumab, supplementation of calcium and vitamin D is required unless hypercalcaemia is present; if hypocalcaemia occurs, additional calcium supplementation may be necessary.

See:

Letter sent to healthcare professionals in September 2012:

<http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con185672.pdf>

A letter was sent to healthcare professionals in September 2012 regarding the updated product information for Xgeva ▼.

Further information:

BNF section 6.6: [Drugs affecting bone metabolism](#)

Advice for healthcare professionals:

The following precautions should be followed to minimise the risk of hypocalcaemia with denosumab:

Contraindications:

- Denosumab 120 mg (for cancer indications) should not be used in patients with severe, untreated hypocalcaemia
- Denosumab 60 mg (for osteoporosis indications) should not be used in patients with hypocalcaemia, regardless of severity*

** the contraindications vary between the two doses, because their indications are different.*

Warnings and recommendations:

- Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving 120 mg denosumab unless hypercalcaemia is present.
- Adequate intake of calcium and vitamin D is important in all patients receiving 60 mg denosumab
- Patients with severe renal impairment (creatinine clearance <30 mL; eGFR 15 – 29 mL/min/1.73m²) or receiving dialysis are at greater risk of developing hypocalcaemia, and monitoring of calcium levels in these patients is recommended.

Article citation: Drug Safety Update Oct 2012 vol 6, issue 3: A3.

Drug safety advice

A1 Denosumab 60 mg (Prolia ▼): rare cases of atypical femoral fracture with long-term use

Atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving long-term (≥ 2.5 years) treatment with denosumab 60 mg (Prolia ▼) in a clinical trial.

During denosumab treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated.

Denosumab is a human monoclonal IgG2 antibody. Denosumab 60 mg solution for injection (Prolia ▼) is given once every 6 months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Denosumab 120 mg solution for injection (Xgeva ▼) is given once every 4 weeks for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Possible risk of atypical femoral fracture

Two cases of atypical femoral fracture have been confirmed in patients receiving denosumab 60 mg for 2.5 or more years participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events occurred rarely (in $\geq 1/10\ 000$ to $< 10/10\ 000$ patients), based on 8 928 subjects being exposed to denosumab 60 mg in bone loss studies.

The risk of atypical femoral fractures also exists for denosumab 120 mg (Xgeva ▼).

The nature of the fractures seen with denosumab 60 mg is similar to the atypical femoral fractures seen with long-term bisphosphonate therapy. For further information on this, and a list of clinical and radiographic features of atypical femoral fractures, see Drug Safety Update June 2011.

A letter was sent to healthcare professionals in February 2013, regarding the updated product information for denosumab 60 mg (Prolia ▼)

See:

Drug Safety Update June 2011 [link to:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213>]

Letter sent to healthcare professionals in February 2013 [link to:
<http://www.mhra.gov.uk/home/groups/comms-ic/documents/websitesresources/con241828.pdf>]

Further information:

Bisphosphonates assessment: Drug Safety Update, June 2011 [link to:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON120213>]

BNF section 6.6: Drugs affecting bone metabolism [LINK to:
<http://www.medicinescomplete.com/mc/bnf/current/PHP4691-denosumab.htm>]

Advice for healthcare professionals:

- 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.
- Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur.
- The contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral (as noted from the bisphosphonates assessment).
- 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.



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03 September 2012

Direct Healthcare Communication

Reports of symptomatic hypocalcaemia, including fatal cases reported in patients treated with XGEVA (denosumab)

Dear Healthcare Professional,

This letter is sent to remind you of the risk of severe symptomatic hypocalcaemia associated with the use of denosumab and to inform about the risk of late onset of hypocalcaemia. Hypocalcaemia can occur at any time during therapy.

Summary of the issue

- Severe symptomatic hypocalcaemia, including fatal cases, has been reported in patients treated with denosumab
- Hypocalcaemia can occur at any time during therapy with denosumab
- Signs and symptoms of these cases included altered mental status, tetany, seizures and QTc prolongation,

Healthcare Professionals are reminded of the following recommendations to minimise this risk:

- Pre-existing hypocalcaemia must be corrected prior to initiating therapy
- Supplementation of calcium and vitamin D is required in all patients unless hypercalcaemia is present.
- If hypocalcaemia occurs, additional calcium supplementation may be necessary.
- Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Monitoring of calcium levels in these patients is recommended

This letter is sent in agreement with the European Medicines Agency and the MHRA

Further information on the safety concern

XGEVA is indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours

The risk of severe hypocalcaemia associated with denosumab use is known and is reflected in the current product information and includes the above recommendations on risk minimisation. Following receipt of adverse drug reaction reports, the warnings in the product information have been updated to inform prescribers that severe fatal cases have been reported in the post-marketing period. The product information has also been updated with information on the risk of late onset of hypocalcaemia,

Hypocalcaemia can occur at any time during therapy with denosumab. Most commonly it occurs within the first 6 months of dosing

For more information regarding denosumab refer to the product details available on the EMA website: <http://www.ema.europa.eu>

Call for reporting

Please report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800 731 6789
- or by electronic download through the MHRA website (www.mhra.gov.uk/yellowcard)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Any suspected adverse reactions with XGEVA may also be reported to Amgen Europe B.V by contacting +44 (0) 1223 436712

Contact details

Should you have any questions or require additional information regarding the use of XGEVA, please contact Amgen UK, Medical Information on +44 (0)1223 436712

Yours sincerely,



Dr Steven Bellamy MBChB
Medical Director, UK & Ireland

Annex: Revised copy of the XGEVA Summary of Product Characteristics (SPC).



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26th August 2014

Denosumab 60mg (Prolia®): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia

Dear Healthcare Professional,

Amgen Ltd. in agreement with the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency would like to inform you of updated information and recommendations to minimise the risk of osteonecrosis of the jaw (ONJ) and hypocalcaemia during treatment with Prolia.

Summary

Osteonecrosis of the jaw

- **Doctors should evaluate all patients for ONJ risk factors prior to treatment with Prolia**
- **A dental examination with appropriate preventive dentistry is recommended in patients with concomitant risk factors**
- **Patients should be encouraged to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling during treatment with Prolia**

Hypocalcaemia

- **Hypocalcaemia is an identified risk in patients treated with Prolia, which increases with the degree of renal impairment.**
- **Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Prolia**
- **Adequate intake of calcium and vitamin D is important in all patients, and especially important in patients with severe renal impairment**
- **Monitoring of calcium levels should be conducted:**
 - **prior to each dose of Prolia**
 - **within two weeks after the initial dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min)**
 - **if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient**
- **Tell patients to report symptoms of hypocalcaemia**

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Further information

Osteonecrosis of the jaw

ONJ is a condition in which the jawbone becomes necrotic, exposed, and does not heal within 8 weeks. The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling.

ONJ has been reported rarely in clinical studies and in the post marketing setting in patients receiving Prolia (denosumab at dose 60 mg every 6 months for osteoporosis). ONJ has been reported commonly in patients with advanced cancer treated with denosumab at a dose of 120 mg administered monthly.

Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, and concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck).

While on treatment, patients with risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on Prolia therapy, doctors should develop a management plan for the individual patient in close collaboration with a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated, where possible.

Hypocalcaemia, including severe symptomatic cases

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

In two phase 3 placebo-controlled clinical trials in postmenopausal women with osteoporosis, there were no reported cases of severe symptomatic hypocalcaemia.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported. Renal insufficiency was described in the majority of these cases, with most cases occurring in the first weeks of initiating Prolia therapy but it can occur later.

Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures, and altered mental status. Symptoms of hypocalcaemia observed in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms, and muscle cramps. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

Indication

Prolia is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia reduces the risk of vertebral, nonvertebral and hip fractures.

Prolia is also indicated the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia reduces the risk of vertebral fractures.

Appendix 4 to Denosumab factsheet

Call for reporting

Please continue to report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard. Please report

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website: www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Reports can also be made to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 01223 436712.

Company contact point

Should you have any questions or require additional information regarding the use of Prolia, please contact Amgen UK/Ireland Medical Information on 01223 436441 or by email to gbinfoline@amgen.com.

Yours sincerely,



Dr Steven Bellamy MBChB
Medical Director, UK & Ireland

Prescribing information for Prolia can be accessed at <http://www.medicines.org.uk/emc/medicine/23127> (Summary of Product Characteristics) and <http://www.medicines.org.uk/emc/medicine/23128> (Package Leaflet)



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Drug Safety Update

Volume 8, Issue 2 September 2014

Latest advice for medicines users

Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia—updated recommendations

Article date: September 2014

Summary

Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia. Before starting denosumab treatment, a dental examination and appropriate preventive dentistry are now recommended to reduce the risk of osteonecrosis of the jaw (ONJ). This applies to all patients considered for denosumab 120 mg for cancer and to patients with ONJ risk factors considered for denosumab 60 mg for osteoporosis (see below). Tell patients to maintain good oral hygiene and report any oral symptoms.

The risk of hypocalcaemia increases with the degree of renal impairment. Monitor calcium levels depending on the indication as described below and tell patients to report symptoms of hypocalcaemia (see advice below)

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Denosumab 120 mg solution for injection (Xgeva ▼) is given once every 4 weeks to prevent skeletal related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60 mg solution for injection (Prolia) is given once every 6 months to treat osteoporosis in postmenopausal women at increased risk of fractures. It is also indicated for treatment of bone loss associated with hormone ablation in men with prostate cancer who are at high risk of fractures.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a well-known and common side effect in patients receiving denosumab 120 mg for cancer. Risk factors for ONJ include:

- smoking
- old age
- poor oral hygiene
- invasive dental procedures (eg, tooth extractions, dental implants, oral surgery)
- comorbidity (eg, dental disease, anaemia, coagulopathy, infection)
- advanced cancer
- previous treatment with bisphosphonates
- concomitant treatments (eg, chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck)

In clinical trials, ONJ incidence increased with duration of denosumab 120 mg exposure. The patient-year adjusted incidence of confirmed ONJ was 1.1% in the first year of treatment, 3.7% in the second year, and 4.6% per year thereafter. Patients with certain dental risk factors (eg, history of ONJ, unhealed oral surgery) were excluded from these trials.

There have been rare cases of ONJ in patients receiving denosumab 60 mg for osteoporosis in clinical practice. The most common risk factors were invasive dental procedures, history of bisphosphonate therapy, and being more than 65 years old.

To date, we have received 9 Yellow Card reports ^[1] of ONJ in patients receiving denosumab 120 mg, 12 reports in patients receiving denosumab 60 mg, and 5 reports in patients receiving an unspecified dose of denosumab.

Based on this evidence, the recommendations regarding the need for a dental examination and appropriate preventive dentistry before treatment have been updated as described below.

Hypocalcaemia

Denosumab is also associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment (see [Drug Safety Update article from October 2012](#)). Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later. Therefore the recommendations for calcium monitoring have been updated as described below.

To date, we have received 23 Yellow Card reports ¹ of hypocalcaemia in patients receiving denosumab 120 mg, 37 reports in patients receiving denosumab 60 mg, and 6 reports in patients receiving an unspecified dose of denosumab.

Advice for healthcare professionals

Osteonecrosis of the jaw

The following precautions are now recommended to reduce the risk of ONJ:

Denosumab 120 mg (cancer indication)

- A dental examination and appropriate preventive dentistry before starting denosumab 120 mg are now recommended for all patients.
- 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.

Denosumab 60 mg (osteoporosis indication)

- Check for ONJ risk factors before starting denosumab 60 mg. A dental examination and appropriate preventive dentistry are now recommended for patients with risk factors.

Tell all patients to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.

Hypocalcaemia

Calcium levels should now be monitored as follows:

Denosumab 120 mg (cancer indication)

- Check calcium levels:
 - before the first dose
 - within two weeks after the initial dose
 - if suspected symptoms of hypocalcaemia occur.

Consider monitoring calcium levels more frequently in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min).

Denosumab 60 mg (osteoporosis indication)

- Check calcium levels:
 - before each dose
 - within two weeks after the initial dose in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min)
 - if suspected symptoms of hypocalcaemia occur.

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).

Further information:

Letters to healthcare professionals sent in August 2014 – includes advice on ONJ and hypocalcaemia that was previously in the summary of product characteristics and has not been changed, as well as the new advice above

[Denosumab 60 mg](#)

[Denosumab 120 mg](#)

Article citation: Drug Safety Update volume 8 issue 2, September 2014: A2

[\[1\]](#) Yellow Card reports are reports of suspected adverse drug reactions (ADRs) submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

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Drug Safety Update (<https://www.gov.uk/drug-safety-update>)

Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk

From: Medicines and Healthcare products Regulatory Agency (<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>)

Published:
20 July 2015

Therapeutic area:
Cancer (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=cancer), Dentistry (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=dentistry), Endocrinology, diabetology and metabolism (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=endocrinology-diabetology-metabolism), Obstetrics, gynaecology and fertility (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=obstetrics-gynaecology-fertility), and Rheumatology (https://www.gov.uk/drug-safety-update?therapeutic_area%5B%5D=rheumatology)

Patient reminder cards about the risk of osteonecrosis of the jaw are being introduced; denosumab 120 mg is now contraindicated in patients with unhealed lesions from dental or oral surgery.

1. Indication
2. Osteonecrosis of the jaw
3. Patient reminder cards and denosumab 120 mg contraindication
4. Oral bisphosphonates: reminder of precautions to take
5. Further information

Before prescribing denosumab or intravenous bisphosphonates:

- give patients the patient reminder card for their medicine
- explain the risk of osteonecrosis of the jaw and advise patients on precautions to take—advise patients to:
 - tell their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures they should make sure their dentures fit properly before starting treatment
 - maintain good oral hygiene and get routine dental check-ups during treatment
 - tell their doctor and dentist that they are receiving denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery
 - tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (eg loose teeth, pain, swelling, non-healing sores or discharge)
- do not prescribe denosumab 120 mg (cancer indication) to patients with unhealed lesions from dental or oral surgery

Please continue to report suspected side effects to denosumab, bisphosphonates or any other medicines on a Yellow Card (<https://yellowcard.mhra.gov.uk/>).

Indication

Denosumab and bisphosphonates are used to treat osteoporosis, Paget's disease, and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma. Individual bisphosphonates and denosumab-containing medicines have different indications; please check the summary of product characteristics (<https://www.medicines.org.uk/emc/>) of the medicine in question.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a known side effect of denosumab and bisphosphonates (see Drug Safety Update articles from November 2009 (<https://www.gov.uk/drug-safety-update/bisphosphonates-osteonecrosis-of-the-jaw>) and September 2014 (<https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations>)). To date, we have received 45 Yellow Card reports of ONJ in people taking denosumab (all doses) and 323 reports in people taking a bisphosphonate.¹

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. 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.

Patient reminder cards and denosumab 120 mg contraindication

MHRA and other EU medicines regulators have reviewed measures to minimise the risk of ONJ in patients taking denosumab or bisphosphonates. The review recommended introducing patient reminder cards² for denosumab and intravenous bisphosphonates to inform patients of the risk of ONJ and precautions to take before and during treatment. The review of ONJ and denosumab also recommended that denosumab 120 mg should be contraindicated in patients with unhealed lesions from dental or oral surgery.

Oral bisphosphonates: reminder of precautions to take

All bisphosphonates are associated with a risk of ONJ. Therefore before prescribing oral bisphosphonates, we remind you to tell patients to maintain good oral hygiene, attend routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.

Further information

European Medicines Agency announcement

(http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/03/WC500184865.pdf), March 2015 (accessed 15 July 2015).

Content of reminder card (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/03/WC500184879.pdf) as approved by the European Committee on Medicinal Products for Human Use (accessed 15 July 2015).

Content of Prolia (denosumab) patient card (https://assets.digital.cabinet-office.gov.uk/media/55a66d9eed915d151b000003/AMGEN_PROLIA_patient_card.pdf)

Content of Xgeva (denosumab 120 mg) patient card (https://assets.digital.cabinet-office.gov.uk/media/55a66ed5e5274a6fed000009/AMGEN_XGEVA_patient_card.pdf)

Article citation: Drug Safety Update volume 8 issue 12 July 2015: 1.

1. Yellow Card reports are reports of suspected adverse drug reactions (ADRs) submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug. ←
2. The reminder cards are being sent by licence-holders for individual products separately and will therefore become available at different times. You can view the content of the reminder cards via the links above. ←

This reminder card contains important safety information that you need to be aware of before and during treatment with denosumab (Prolia).

Your doctor has recommended that you receive denosumab (Prolia), which is used to treat osteoporosis and bone loss. These diseases involve thinning and weakening of the bones so they may break more easily.

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported rarely (may affect up to 1 in 1,000 people) in patients receiving Prolia for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try to prevent ONJ developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing ONJ, there are some precautions you should take.

Before starting treatment:

Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.

Your doctor may ask you to undergo a dental examination if you:

- were previously treated with a bisphosphonate
- are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- are a smoker
- have cancer
- have not had a dental check up for a long time
- have problems with your mouth or teeth

While being treated:

- You should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor and tell your dentist that you are being treated with Prolia.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw

Please read the package leaflet that comes with your medicine for further information.

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

By reporting side effects you can help provide more information on the safety of Prolia

Denosumab (Prolia®, Xgeva ▼): reports of osteonecrosis of the external auditory canal
21st June 2017 <https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal>

Denosumab is associated with a risk of osteonecrosis of the jaw, osteonecrosis of the external auditory canal has also been reported with denosumab.

Background

Denosumab is a human monoclonal IgG2 antibody. Denosumab 60 mg solution for injection (Prolia) is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Denosumab 120 mg solution for injection (Xgeva ▼) is indicated for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours, and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

Reports of osteonecrosis of the external auditory canal

In December 2015, we published a Drug Safety Update article about very rare reports of [osteonecrosis of the external auditory canal with bisphosphonates](#). Since then, this possible risk has been kept under close review with denosumab, given that both denosumab and bisphosphonates are known to be associated with [osteonecrosis of the jaw](#).

Worldwide, 5 reports of osteonecrosis of the external auditory canal have now been received for patients treated with 60 mg denosumab for osteoporosis.

The underlying possible pathological mechanism is considered to be similar to that for denosumab-related osteonecrosis of the jaw. 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.

The product information for all denosumab-containing products is being revised to include a warning on the risk of osteonecrosis of external auditory canal. As for bisphosphonates, the risk of osteonecrosis at sites other than the jaw and the external auditory canal continues to be kept under close review.

Advice for healthcare professionals:

- 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
- possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma
- advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment
- report cases of osteonecrosis of any bone suspected to be associated with denosumab or any other medicine on a [Yellow Card](#)