# DENOSUMAB (60mg) (Prolia®) FACT SHEET

**FOR THE TREATMENT OF OSTEOPOROSIS IN POST MENOPAUSAL WOMEN**

**Start date:** January 2012  
**Review date:** January 2015

## Document Control

| V1.1 | 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. |

Comments on this document should be sent to the Medicines Management Team - Tel 0203 317 2748 or email mmt.camdenccg@nhs.net

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**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 18th November 2013).*

### 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.
- **Monitoring of calcium levels** is recommended for patients predisposed to hypocalcaemia (e.g. severe renal impairment or receiving dialysis). **Baseline tests and correction is required before treatment initiation.**
- 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 correctly.

### Administration

The recommended dose of denosumab is 60mg 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.

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*a NICE Technology Appraisal 161: Osteoporosis – secondary prevention including strontium ranelate:guidance ( updated May 2012)*

*b No dose adjustment is required in elderly patients or patients with renal impairment. [http://www.medicines.org.uk/emc/medicine/23127/SPC/prolia/](http://www.medicines.org.uk/emc/medicine/23127/SPC/prolia/)*

Denosumab Factsheet v2- January 2014 - produced by Camden Medicines Management Team

Agreed at CMMC meeting 22 January 2014
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. Monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia e.g. patients with severe renal impairment (creatinine clearance <30 mL/min; eGFR 15 – 29 mL/min/1.73m²) or receiving dialysis.

Osteonecrosis of the jaw (ONJ) has been reported with denosumab or bisphosphonates. Dental examination should be considered prior to treatment with denosumab in patients with concomitant risk factors. Whilst on treatment, good oral hygiene is essential and patients should avoid invasive dental procedures if possible.

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. 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.

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 and may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator it must be used within this 30 day period.

Adverse drug reactions (ADRs) reported

Very Common (≥ 1/10): Pain in extremity
Common (≥ 1/100 to < 1/10): Urinary tract infection, upper respiratory tract infection, sciatica, cataracts, constipation, rash, eczema.
Uncommon (≥ 1/1000 to < 1/100): Diverticulitis, cellulitis, ear infection.
Rare (≥ 1/10,000 to < 1/1000): Osteonecrosis of the jaw (ONJ), atypical femoral fractures, hypocalcaemia, drug hypersensitivity and anaphylactic reaction.

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)

Appendices


Further Information

• NICE Technology Appraisal 204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women. October 2010 http://www.nice.org.uk/guidance/TA204
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.

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

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.


H1 Simvastatin: evidence supporting recent advice on dose limitations with concomitant amlodipine or diltiazem

Summary

In August 2012 we published advice that simvastatin is now contraindicated with concomitant use of certain medicines, such as ciclosporin, danazol, and gemfibrozil, and that the recommendations for the maximum dose of simvastatin have changed when used with a number of other medicines, including amlodipine and diltiazem. These changes were driven primarily by concerns about an increased risk of myopathy and/or rhabdomyolysis at higher plasma concentrations of simvastatin, which may result from such drug interactions.

Following further consideration by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines, this article summarises the evidence underlying the new advice that the maximum recommended dose for simvastatin in conjunction with amlodipine and diltiazem is now 20 mg/day. The prescribed doses of amlodipine and diltiazem need not be changed.

Pharmacokinetic data

Simvastatin is metabolised through the CYP3A4 pathway. Concomitant use of CYP3A4 inhibitors has the potential to increase exposure to simvastatin.² Both amlodipine and diltiazem are substrates and inhibitors of CYP3A4²,³ and therefore increase the plasma concentration (AUC₀-2₄h) and maximum plasma concentration (Cₘₐₓ) of simvastatin when they are co-administered.

Studies have found that after 10 days of amlodipine (10 mg), the AUC₀-2₄h of simvastatin and simvastatic acid following a single dose of simvastatin 80 mg increased by 1.58- and 1.77-fold respectively, compared with that following a single dose of simvastatin 80 mg without prior amlodipine administration⁴. Use of amlodipine 5 mg with simvastatin 5 mg resulted in a proportionally smaller increase in simvastatin plasma concentration⁵.

Similarly, studies with diltiazem 120 mg twice daily for 10 days increased the AUC₀-2₄h of simvastatin and simvastatic acid following a single dose of simvastatin 80 mg by 3.10 and
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 ≥ 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▼).

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.
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](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](http://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](http://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).**