North Central London
Joint Formulary Committee

DENOSUMAB 60mg (Prolia®) FACT SHEET

FOR THE TREATMENT OF OSTEOPOROSIS IN POST MENOPAUSAL WOMEN

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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.
V3.0 – Factsheet reviewed and updated May 2019. All appendices have been removed and added to references. Update includes the addition of skin infections as a precaution, the NCL position for prescribing denosumab to men with osteoporosis and the NCL position for prescribing in men and women with renal impairment.
V3.1 – Added MHRA alert relating to vertebral fractures; added information on managing adverse effects in Primary care.

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.

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.

FACT SHEET - Denosumab 60mg solution for injection pre-filled syringes (Prolia®) – 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 (TA) 204 (details outlined below). N.B. Primary care clinicians will usually be asked to continue the administration and monitoring of denosumab 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 eMC Dictionary of Medicines and Devices Browser accessed 1st April 2019).*

Check List and Actions for GPs

- **Determine whether the patient meets the eligibility criteria set by NICE TA 204 for treatment with denosumab 60mg (Prolia®).**
- Read the denosumab factsheet and Summary of Product Characteristics (SPC) for special warnings and precautions before use.
- The initiating clinician should ensure the following prior to starting treatment (NB. if initiated by secondary care, all baseline information should be shared with primary care clinicians in a timely manner):
    - **Baseline** calcium levels should be performed and hypocalcaemia must be corrected before denosumab 60mg (Prolia®) can be prescribed.
    - **Evaluate all patients for osteonecrosis of the jaw (ONJ) risk factors** (see page 5 for list of risk factors) prior to treatment with denosumab 60mg (Prolia®). A dental examination and appropriate preventive dentistry is recommended for patients with concomitant risk factors.
    - **Ensure patients are provided with a patient reminder card**. This explains the risk of ONJ and advises patients on precautions to take whilst on treatment.
- Whilst on denosumab 60mg (Prolia®) treatment, **check renal function, vitamin D and corrected calcium levels:**
    - Before each dose **AND**
    - Within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance <30 ml/min). NB. Patients with severe renal impairment will only be managed in secondary care.
    - If suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient.
- Adequate intake of calcium and vitamin D is important in all patients receiving denosumab 60mg (Prolia®).
- Patients should be encouraged to report symptoms indicative of hypocalcaemia, e.g. muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth.
- Remind patients of advice to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment due to the risk of osteonecrosis of the external auditory canal.
- Report cases of ONJ suspected to be associated with denosumab or any other medicine via the Yellow Card scheme.
- Ensure there is **no duplication or overlap of timeframes between doses in the patient receiving treatment in either primary or secondary care.** Practices will need to consider having a system in place to ensure there is a systematic recall of patients on denosumab treatment.
- Practices must ensure that any staff involved in the administration of subcutaneous (sc) injections have the necessary training and skills. Guidance must be in place to cover staff training and maintenance of skills.
- As denosumab 60mg (Prolia®) is administered by sc injection, practices need to have adequate facilities and equipment for the safe provision of a sc injection.

NICE Technology Appraisal 204 (1) *(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.

*Etidronate has been discontinued in the UK and is no longer available.

**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. (2)

Dose and Administration (3)

- The recommended dose of denosumab (Prolia®) is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. The denosumab 60mg (Prolia®) solution for injection comes as a pre-filled syringe.
- Please follow the manufacturer's instructions[3] on how to administer the subcutaneous injection.
- Patients must be adequately supplemented with calcium and vitamin D, unless hypercalcaemia is present.
- No dose adjustment is required in elderly patients or patients with renal impairment.
- Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. **NB. These patients should only be managed in secondary care.**
- The safety and efficacy of denosumab has not been studied in patients with hepatic impairment.

Contraindications (3)

- Hypersensitivity to the active substance or to any of the excipients (see SPC).
- Hypocalcaemia.

Monitoring (3) (4)

If a patient is prescribed denosumab 60mg (Prolia®) treatment, it is advised that **corrected calcium levels** are checked as follows:

- Before each dose **AND**
- Within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance <30 ml/min). NB. Patients with severe renal impairment will be managed in secondary care.
- If suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient.
- Monitoring requirements do not change if the patient continues treatment beyond five years (if extended duration of treatment is indicated following review).
- Patients are retained by the specialist for ongoing review every 12-18 months, with a repeat DEXA scan after three years of treatment.

Adverse drug reactions (ADRs) (3)

- ***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):* ONJ, atypical femoral fractures, hypocalcaemia, drug hypersensitivity, anaphylactic reaction.
- ***Not known***: Osteonecrosis of the external auditory canal.

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

For further information on adverse effects, see the SPC or BNF. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

Special Warnings and Precautions

Hypocalcaemia (3) (4) (5)-(6)
Hypocalcaemia is a known risk with denosumab use and can occur at any time during treatment, though most commonly occurs within the first 6 months. It is also a known risk in patients taking concomitant glucocorticoid treatment, with severe renal impairment (creatinine clearance <30ml/min) or in those receiving dialysis. Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. (5) (6)

Denosumab 60 mg (Prolia®) should not be used in patients with any degree of hypocalcaemia. (6)
It is important to identify patients at risk of hypocalcaemia. Pre-existing hypocalcaemia must be corrected prior to initiating denosumab.

Adequate intake of calcium and vitamin D is important in all patients receiving denosumab 60mg (Prolia®). (4) (5) (6)

Tell all patients to report symptoms of hypocalcaemia to their doctor, e.g. muscle spasms, twitches, or cramps, numbness or tingling in the fingers, toes, or around the mouth. (3) (7)

For calcium monitoring requirements, please see 'monitoring' section above.

If any patient presents with suspected symptoms of hypocalcaemia during treatment, calcium levels should be measured and the supervising specialist should be informed. (3)

Further details on the risk of hypocalcaemia can be found in the denosumab 60mg (Prolia®) SPC[3] and following MHRA updates:

- *Amgen Ltd letter to healthcare professionals (August 2014)* (4)
- *Amgen Ltd Direct Healthcare Communication letter (September 2012)* (5)
- *MHRA Drug Safety Update (October 2012)* (6)
- *MHRA Drug Safety Update (September 2014)* (7)

Osteonecrosis of the jaw (ONJ)
ONJ is a well-known adverse effect of denosumab. Risk factors to ONJ include: smoking, old age, poor oral hygiene, invasive dental procedures, comorbidity (e.g. dental disease, anaemia), advanced cancer, previous treatment with bisphosphonates and concomitant therapies (e.g. chemotherapy, antiangiogenic biologics, corticosteroids). (7)

Clinicians should evaluate all patients for ONJ risk factors prior to treatment with denosumab 60mg (Prolia®). (4) Before starting treatment, a dental examination and appropriate preventive dentistry are recommended for patients with risk factors. (3) (4) (7)

Patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups and immediately report any oral symptoms (e.g. dental mobility, pain or swelling) to their clinician and dentist. (4) (7)

While on treatment, patients with risk factors should avoid invasive dental procedures if possible. (4) Expert opinion recommends that patients should wait at least 6-8 months after the last dose of denosumab before undergoing any invasive dental procedures.

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 cards** for denosumab and intravenous bisphosphonates to inform patients of the risk of ONJ and precautions to take before and during treatment. (8) (9)

Before prescribing denosumab, ensure patients are provided with the patient reminder card and are explained the risks with treatment. The reminder cards can be accessed here. (3) Alternatively, to request a copy of the patient reminder card, please contact Amgen Medical Information on +44 (0) 1223 436441.

For patients who develop ONJ whilst on denosumab therapy, clinicians should develop a management plan for the individual patient in close collaboration with a dentist or oral surgeon with expertise in ONJ (therefore; pause

denosumab therapy, refer to oral surgery specialist and inform the treating specialist to either co-ordinate the restart of therapy or consider alternative treatments). Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated, where possible. (3)

Further details on the risk of ONJ can be found in the denosumab 60mg (Prolia®) SPC[3] and following MHRA updates:

- *Amgen Ltd letter to healthcare professionals (August 2014)* (4)
- *MHRA Drug Safety Update (September 2014)* (7)
- *MHRA Drug Safety Update (July 2015)* (9)

Osteonecrosis of the external auditory canal

Osteonecrosis of the external auditory canal has been reported with denosumab use. Possible risk factors include steroid use and chemotherapy and/or local risk factors e.g. infection or trauma. The possibility of this should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections or in those with suspected cholesteatoma. (3) (10)

Patients should be encouraged to report any ear pain, discharge from the ear, or an ear infection whilst on treatment. (10) A prompt referral should be made to ENT and pause denosumab therapy; the supervising specialist should also be informed.

Further details on the risk of osteonecrosis of the external auditory canal can be found in the denosumab 60mg (Prolia®) SPC (3) *and MHRA drug safety update (June 2017)* (10)*.*

Atypical fractures of the femur

Atypical femoral fractures have been reported in patients receiving denosumab. (3) Atypical femoral fractures often occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. (3) The contralateral femur should be examined (i.e. x-ray) in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral. (11)

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 (i.e. x-ray) for an incomplete femoral fracture. (11)

Further details on atypical fractures of the femur can be found in the denosumab 60mg (Prolia®) SPC (3) *and MHRA Drug Safety Update (February 2013)*. (11)

Skin infections

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 (e.g. redness, warmth, swelling, pain etc.). (3) Skin infections can typically be managed in primary care; if skin infections are recurrent, inform the supervising specialist for consideration of ongoing treatment or alternative treatment options.

Reviewing / discontinuing denosumab

A phase 3 trial looking at the long-term safety and efficacy of denosumab treatment in postmenopausal women with osteoporosis, suggested that treatment for up to 10 years was associated with low rates of adverse events and low fracture incidence. (12) However, it is advised that a review of therapy is carried out by the specialist team or GP after 5 years (13) of treatment with an individual assessment of the benefits and risks.

Discontinuation of denosumab treatment should also be considered if an atypical femur fracture is suspected, while the patient is evaluated on an individual risk-benefit assessment. (3) (11)

An MHRA drug safety alert advises that upon stopping or delaying ongoing denosumab treatment, the risk of vertebral fractures increases. Patients with previous vertebral fracture may be at highest risk. Patients should not stop treatment without specialist review. If an injection is missed, it should be administered as soon as possible; the next injection should be re-scheduled six months from the date of the last injection. (14)

Any queries on complications of denosumab should be directed to the supervising specialist (which can be sent via ERS or by emailing the specialist team directly). Where appropriate consider referral to secondary care for specialist input.

Further details on the increased risk vertebral fractures after stopping or delaying ongoing treatment can be found in the MHRA Drug Safety Update (August 2020).

Storage requirements (3)

Denosumab 60mg (Prolia®) should be stored in a refrigerator between 2°C - 8°C. The pre-filled syringe should be kept in the outer carton to protect it from light. Denosumab has a shelf life of 3 years. Once removed from the refrigerator, the pre-filled syringe may 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.

Exclusions to prescribing within North Central London (NCL)

- NCL Joint Formulary Committee (JFC) restricted the use of denosumab 60mg (Prolia®) in women with stage IV or V Chronic Kidney Disease (i.e. creatinine clearance <30ml/min) to **secondary care only** due to the risk of hypocalcaemia.
- The use of denosumab 60mg (Prolia®) to treat osteoporosis in men is restricted in NCL to one subset of patients, namely those men unable to take oral bisphosphonates (either due to intolerance or unable to comply with administration instructions) and unable to receive IV zoledronic acid due to renal dysfunction. Due to the increased risk of hypocalcaemia in these patients with renal impairment, prescribing is **restricted to secondary care,** to enable close monitoring by the specialist.
- Treatment of osteoporosis with denosumab 60mg (Prolia®) in men without renal impairment is **non-formulary.**
- Denosumab is also available as a 120mg preparation (Xgeva®▼) licensed for the prevention of skeletal related events in adults with advanced malignancies involving bone 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. (15) **This preparation should not be prescribed in primary care.**

References

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2. **NICE.** Technology Appraisal Guidance [TA161]: Raloxifene and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. [Online] 7 February 2018 (Originally published 27 October 2008). [Cited: 1 April 2019.] https://www.nice.org.uk/guidance/ta161.

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11. **Medicines and Healthcare products Regulatory Agency (MHRA) - Drug Safety Update.** Denosumab 60mg (Prolia®): rare cases of atypical femoral fracture with long-term use. [Online] 20 February 2013. [Cited: 1 April 2019.] http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON239411.

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