BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE

Denosumab 60mg injection (Prolia®) for Osteoporosis in Post-menopausal Women and Men (over 50 years) in Primary Care

Prescribing and Blood Test Monitoring Requirements – Information for GPs

**Summary of Key points:**

1. Administer denosumab (Prolia®) every 6 months.
2. Set up and check your re-call system to ensure patient are receiving a dose every 6 months (to ensure doses are not delayed or missed).
3. Check calcium levels before each administration (6 monthly).
4. Be mindful of adverse effect profile and counsel patient appropriately (see SPC / electronic BNF and information below for details).

(NB: This information does not cover the other licensed form of denosumab (Xgeva®) which is a different strength (120mg) and is licensed 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.

**Mechanism of action**

Denosumab (Prolia®) is a human monoclonal antibody (IgG2) that inhibits osteclastic activity thereby decreasing bone resorption in cortical and trabecular bone.¹

**Licensed indications supported by NICE**

- Treatment of osteoporosis in postmenopausal women at increased risk of fractures (NICE approved).

**Licensed indications NOT supported or not assessed by NICE**

- Treatment of osteoporosis in men at increased risk of fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (denosumab is not approved locally for use in this indication).¹

It should also be noted that denosumab is not licensed for the management of osteoporosis in pre-menopausal women or glucocorticoid-induced osteoporosis.

**Place in therapy of Denosumab 60mg (Prolia®) as per locally agreed JPC Osteoporosis Guidelines, (updated September 17)**

- **Joint Third line treatment option in appropriate patients**
  Either denosumab s/c or IV zoledronic acid or IV ibandronic acid can be used as a third line treatment option subsequent to the use of first/second line treatment with oral alendronate (generic) or oral risedronate (generic) or oral ibandronic acid (generic). If using denosumab, the initial dose of denosumab is to be prescribed and administered in secondary care, subsequent doses to be prescribed and administered in the primary care setting.²

- **First line treatment in appropriate patients with severe renal failure (GFR <35ml/min)**
  (as oral and IV bisphosphonates should be avoided in severe renal impairment). When denosumab is used in these patients the responsibility for prescribing and monitoring patients should remain with secondary care specialists (not for GP prescribing).
Prescribing Information
This information sheet has been designed to highlight key prescribing information points and blood test monitoring requirements with regards denosumab (Prolia®) however it is not designed to be an exhaustive document. Clinicians should refer to the Summary of Product Characteristics (SPC’s) and the current electronic BNF for full prescribing details with regards dosage, contraindications, side effects, drug interactions etc.

SPC:  http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/#INDICATIONS

BNF: www.bnf.org/products/bnf-online

Denosumab (Prolia®) was previously a black triangle drug although this status has now been removed. Clinicians are reminded however to report any suspected adverse effects via the yellow card scheme. (NB; Please note that the black triangle status still applies to the higher strength preparation of denosumab - Xgeva®, which is used in cancer related indications (NB: This higher strength preparation is not the subject of this information sheet).

In addition to the information provided in the SPC and the electronic BNF, clinicians should note that there have been 5 MHRA Drug Safety Updates (DSU) relating to denosumab published to date. Details of these updates are provided below.

Dose (See SPC¹ for full details)
The recommended dose is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.¹

Renal impairment: No dose adjustment is required.¹

NB: It has been agreed locally that GPs should not prescribe denosumab for patients with severe renal impairment (see Osteoporosis guidelines 2017²) and that the care of such patients should remain with the Specialist team.)

Hepatic impairment: The safety and efficacy has not been studied in this population.¹

Elderly (age ≥ 65): No dose adjustment is required.¹

Supplementation: All patients on treatment for osteoporosis must be prescribed calcium 1-1.2g plus colecaciferol 20mcg (800IU) daily UNLESS clinician is confident that the patient has adequate calcium intake and is vitamin D replete.²

Treatment duration
NICE supports the use of treatment with denosumab for 5 years but local specialists advise that the need for treatment should be re-assessed after 3-5 years and that a repeat DEXA scan is considered an appropriate method of assessing efficacy. The duration of benefit in terms of fracture risk (as opposed to bone mineral density) is unknown after cessation of osteoporosis treatments.³

Contraindications/ Warnings and MHRA Drug Safety Update Information

Hypocalcaemia: Denosumab is contraindicated in hypocalcaemia and should not be used in patients with hypocalcaemia, regardless of severity. The MHRA issued a warning regarding the risk of hypocalcaemia with denosumab use, especially in patients with severe renal impairment or receiving dialysis. (DSU October 2012)⁴ A further Drug Safety update was issued in Sept 2014 ⁶ which contains specific advice regarding calcium monitoring requirements (applies to ALL patients regardless of renal function) – See Blood Test Monitoring Section of this document and click link for full details of the MRHA DSU.


Osteonecrosis of the jaw (ONJ): Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ). The Sept 14 MHRA Drug Safety Update ⁶ identifies the risk factors and precautions that should be followed to minimise the risk
of ONJ when using denosumab 60mg (osteoporosis indication) and denosumab 120mg (cancer indication). The risk factors listed are:

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

In addition to the above, the SPC includes a diagnosis of cancer with bone lesions as a risk factor.

The MHRA DSU update also states that with regards the use of denosumab 60mg (osteoporosis indication), there have been rare cases of ONJ in clinical practice. The most common risk factors were invasive dental procedures, history of bisphosphonate therapy, and being more than 65 years old.

**Dental Examination**

The MHRA advice (DSU Sept 14) specific to the use of denosumab 60mg states:

- Check for ONJ risk factors before starting denosumab 60mg. 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.

The SPC also states:
- while on treatment, patients should avoid invasive dental procedures if possible.
- For patients who develop ONJ while on denosumab 60mg therapy, dental surgery may exacerbate the condition.

**Click link for full details of the MHRA DSU on ONJ.**

The MHRA have issued a further Drug Safety Update (DSU July 15) to inform prescribers that patient reminder cards are being introduced for patients taking denosumab and intravenous bisphosphonates. These cards inform patients of the risk of osteonecrosis of the jaw and precautions to take before and during treatment. These can be accessed at:

https://assets.publishing.service.gov.uk/media/55a66d9eed915d151b000003/AMGEN_PROLIA_patient_card.pdf

**Osteonecrosis of the external auditory canal**

In December 2015, the MHRA published a Drug Safety Update (DSU) article about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates. A DSU specific to denosumab has been published in June 2017. This lists that worldwide, there have been 5 reports of osteonecrosis of the external auditory canal received for patients treated with 60 mg denosumab for osteoporosis.

This update includes the following advice for healthcare professionals:

**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.
Atypical fractures of the femur – In Feb 2013, the MHRA issued a Drug Safety update entitled “Denosumab 60 mg (Prolia▼): rare cases of atypical femoral fracture with long-term use”. This update is regarding the long-term use of Denosumab 60 mg (Prolia▼) and reports of rare cases of atypical femoral fracture.

In summary, the MHRA stated:

“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.”

The MHRA DSU also stated the following 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.

Cellulitis: Patients receiving denosumab may develop skin infections. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis as this may require hospitalisation.

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

Excipients: Denosumab (Prolia®) contains sorbitol. It should not be used in patients who have a rare hereditary problem of fructose intolerance.

Adverse effects (See SPC for full details)
The most common side effects (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity.

Other commonly reported side effects include UTI, upper respiratory tract infections, sciatica, cataracts, constipation, abdominal discomfort, rash and eczema.

Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw atypical femoral fractures and osteonecrosis of the auditory ear have been observed in patients taking denosumab (Prolia®)

Blood Test Monitoring Requirements
The MHRA advice issued (DSU Sept14) regarding the monitoring of calcium levels when prescribing denosumab 60mg (osteoporosis indication) is as follows:

- Check calcium levels:
  - before each dose (6 monthly)
  - within two weeks after the initial dose in patients with risk factors for hypocalcaemia (e.g. 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 (e.g., muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).
Calcium Monitoring – Specialist’s Responsibilities

- The Specialist should check the patient’s calcium level before initiating therapy.
- The Specialist should advise the GP if a further calcium level is required within two weeks after the initial dose has been given in the hospital (i.e. in patients with risk factors for hypocalcaemia.) (To avoid delays, the Specialist should issue the patient with a blood test form and instruct them to have their calcium level checked within 2 weeks and to contact their GP for the result.).
- If denosumab is being used in patients with severe renal failure (or receiving dialysis) the responsibility for prescribing and monitoring patients should remain with secondary care specialists.

Calcium Monitoring – GP’s Responsibilities

- The GP is responsible for checking the calcium level if a further test was taken within 2 weeks after treatment was initiated (as requested by the Specialist).
- The GP should check calcium levels before each dose of denosumab is given.
- The GP should check calcium levels if suspected signs of hypocalcaemia occur. The GP should contact the Specialist for advice if a patient’s blood test indicate hypocalcaemia or if the patient presents with symptoms of suspected hypocalcaemia.

The Importance of Continuing Therapy

Prescribers must ensure that patients are reminded of the need to administer treatment every 6 months to maintain efficacy. Compliance to this regimen is very important. Studies of denosumab suggest a rapid loss of gain in bone density and anti-fracture efficacy upon treatment withdrawal. 2

Next Dose Recall Mechanisms

There are a variety of ways that can be adopted to help ensure that patients attend for their 6-monthly injections. One way is to set a 6-monthly recall on SystmOne.

Amgen, the manufacturer of denosumab (Prolia®), also offer a recall system called “Prolong” which will send a reminder letter to the patient reminding them of when their next dose is due. This service is provided by a third party company and patients are invited to register when denosumab therapy is initiated. Some local Specialists are routinely advising patients of the existence of this service and are issuing registration forms when they initiate therapy in the hospital. Patients can also be registered directly by contacting the Amgen Medicine Information Department on 01223436441.

Additional Information on Denosumab

The following additional information is available on the Bedfordshire GP Ref Website 9:

4. MHRA Drug Safety Update; October 2012, vol 6, issue 3.
5. MHRA Drug Safety Update; February 2013, vol 6, issue 7
6. MHRA Drug Safety Update; September 2014, vol 8, issue 2
7. MHRA Drug Safety Update; July 2015, vol 8, issue 12
8. MHRA Drug Safety Update; June 2017, vol 10, issue 11


Document History