

## BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE

**Denosumab 60mg injection (Prolia®) for the management of osteoporosis in primary care for the following groups:-**

**Post-menopausal women , men over 50 years and patients with glucocorticosteroid - induced osteoporosis (irrespective of age)**

### **Information for GPs: - Prescribing and Blood Test Monitoring Requirements**

#### **Summary of Key points (including COVID – 19 update)**

- 1. Administer denosumab (Prolia®) every 6 months. (NB: Do not postpone ongoing denosumab treatment during covid-19 pandemic\*)**
- 2. Set up and check a GP 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 of denosumab (set up a recall system to request blood tests approx. 2 weeks before denosumab dose is due).**
- 4. Be mindful of adverse effect profile, MHRA recommendations and advice.**
- 5. Counsel patient appropriately (see SmPC / electronic BNF and information below for details).**
- 6. **DO NOT STOP or DELAY ongoing treatment with denosumab without a specialist review (due to increased risk of multiple vertebral fractures reported) (see [MHRA DSU Aug 2020](#) )****
- 7. GPs should request a DXA after 3-5 years of treatment, specifying duration of treatment so far, and any changes in risk factors since treatment started.**
- 8. Specialist advice regarding duration of treatment will be provided in the DXA report or alternatively advice is available via 'Advice and Guidance'.**

**[\\*see advice in NICE RAPID guideline, April 2020](#)**

(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 osteoclastic activity thereby decreasing bone resorption in cortical and trabecular bone.<sup>1</sup>

### **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 long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
- 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).<sup>1</sup>

NB: It should be noted that denosumab is not licensed for the management of osteoporosis in premenopausal women.

### **Place in therapy of Denosumab 60mg (Prolia®) as per locally agreed JPC Osteoporosis Guidelines, (updated September 2020)**

- **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 following the use of a first or second line oral bisphosphonate. 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.<sup>2</sup>)
- **First line treatment choice 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 (SmPC) and the current electronic BNF for full prescribing details with regards dosage, contraindications, side effects, drug interactions etc.

- SmPC: <https://www.medicines.org.uk/emc/product/568/smpc>
- BNF: [www.bnf.org/products/bnf-online](http://www.bnf.org/products/bnf-online)

Clinicians are reminded to report any suspected adverse effects via the yellow card scheme.

In addition to the information provided in the SmPC and the electronic BNF, clinicians should note that there have been **6 MHRA Drug Safety Updates (DSU)** relating to denosumab published to date. Details of these updates are provided below. (see page 4)

### **Dose (See SmPC<sup>1</sup> 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.<sup>1</sup>

### **Renal impairment:** <sup>(1)</sup>

No dose adjustment is required in 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. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients.

No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (GFR < 30 ml/min).

**NB: It has been agreed locally that GPs should not prescribe denosumab for patients with severe renal impairment (see Osteoporosis guidelines <sup>2</sup>) 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. <sup>1</sup>

**Elderly (age ≥ 65):** No dose adjustment is required.<sup>1</sup>

### **Calcium and vitamin D supplementation**

Adequate intake of calcium and vitamin D is important in all patients.

As per local osteoporosis guidelines, All patients on treatment for osteoporosis must be prescribed calcium 1-1.2g plus colecalciferol 20mcg (800IU) daily UNLESS clinician is confident that the patient has adequate calcium intake and is vitamin D replete.<sup>2</sup>

### **Contraindications**

- Denosumab is contraindicated in hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients

**Special warnings and Precautions for Use:**-See SmPC for full details  
[https://www.medicines.org.uk/emc/product/568\(/smpc\)](https://www.medicines.org.uk/emc/product/568(/smpc))

- Hypocalcaemia ( **see MHRA DSU update**)
- Renal Impairment
- Skin Infections
- Osteonecrosis of the jaw (ONJ) (**see MHRA DSU update**)
- Osteonecrosis of the external auditory canal(**see MHRA DSU update**)
- Atypical fractures of the femur(**see MHRA DSU update**)
- Stopping or delaying ongoing therapy increases the risk of multiple vertebral fractures (**see MHRA DSU update , Aug 2020**)
- Unnecessarily long-term antiresorptive treatment (including both denosumab and bisphosphonates) without regular reassessment/re-evaluation
- Concomitant treatment with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).
- Dry natural rubber (The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.)
- Excipients:
  - contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
  - contains less than 1 mmol sodium (23 mg) per 60 mg that is to say essentially 'sodium-free'.

**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<sup>1</sup>

**Allergy:** The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.<sup>1</sup>

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

**Adverse effects (See SmPC<sup>1</sup> 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®)

**Treatment duration**

In line with MHRA advice (Aug 2020), denosumab **should not be stopped or ongoing treatment delayed without a specialist review** (due to increased risk of multiple vertebral fractures reported). Patients should be sent for a repeat DEXA scan around the 3-5 year mark as part of the ongoing review process. Specialists will then issue advice regarding duration of treatment required on the DEXA report or alternatively they can be contacted for advice via 'Advice and Guidance'.

## **MHRA Drug Safety Update (DSU) Information**

There have been **6 MHRA Drug Safety Updates (DSU)** relating to denosumab published to date.

Details of these are provided below. Click the links to access the relevant DSU.

**MHRA DSU, published October 2012**

- **Hypocalcaemia:** In October 2012, the MHRA issued a warning regarding the risk of hypocalcaemia with denosumab use, especially in patients with severe renal impairment or receiving dialysis.

[\(Denosumab: fatal cases of severe hypocalcaemia- monitoring recommendations\)](#)

**MHRADSU, published Feb 2013**

- 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.

[Denosumab: Atypical fracture of the femur](#)

### **MHRA DSU, Published in Sept 2014**

- In Sept 2014, the MHRA published a DSU covering two issues: monitoring for hypocalcaemia and minimising the risk of osteonecrosis of the jaw.  
[Denosumab: monitoring for hypocalcaemia – updated recommendations](#)

[Denosumab: Minimising the risk of osteonecrosis of the jaw](#)

### **MHRA DSU, Published July 2015**

- The MHRA have issued a further Drug Safety Update (DSU July 15) <sup>7</sup> 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 below.

[Denosumab: Further measures to minimise osteonecrosis of the jaw](#)

[Reminder cards](#)

### **MHRA DSU, Published June 2017**

- In June 2017, the MHRA published a DSU detailing 5 reports worldwide, of osteonecrosis of the external auditory canal in patients treated with 60mg denosumab for osteoporosis. 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.

[Denosumab: Osteonecrosis of the external auditory canal](#)

### **MHRA DSU, Published August 2020**

- In August 2020, the MHRA published a DSU article reporting an increased risk of multiple vertebral fractures in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis. Patient's individual benefits and risks should be evaluated before initiating therapy. Treatment for existing patients should not be stopped without specialist review.

[Denosumab: Increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment](#)

### **Blood Test Monitoring Requirements**

The MHRA advice issued (DSU Sept14) <sup>6</sup> regarding the monitoring of calcium levels when prescribing denosumab 60mg (osteoporosis indication) is as follows:

- **Check calcium levels:**
  - before each dose of denosumab is given (NB: sample should be taken within two weeks of the next dose due)
  - 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**

**The MHRA DSU (Aug 2020) advises that Denosumab should NOT be stopped or ongoing treatment delayed without a Specialist review as an increased risk of multiple vertebral fractures in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis has been reported**

**NICE have advised that ongoing denosumab treatment should NOT be postponed during the covid-19 pandemic. Reference :- [NICE RAPID guideline, April 2020](#)**

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. <sup>2</sup>

### **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 SystemOne. (**NB** GPs are required to check a calcium level approx 2 weeks before dose of denosumab is due.)
- 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 BLMK Medicine management website <https://medicines.blmkccg.nhs.uk>

- Osteoporosis Treatment Guidelines, link to MHRA added Sept 2020 (Bedfordshire and Luton JPC approved)
- “Patient information leaflet” regarding blood test monitoring and dental check-up requirements. (Bedfordshire and Luton JPC approved)
- Patient Reminder Card (Prolia®) (for ONJ / Dental information) produced by the manufacturer Amgen.
- A range of supporting resources for denosumab (Prolia®) produced by the manufacture Amgen, such as information sheet for GPs, Patient information leaflet and administration instructions.

### **References**

1. SPC for denosumab (Prolia; Amgen). Originally accessed 20/4/2012. Electronic SPC last updated July 2017. <http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/#INDICATIONS>
  2. Bedfordshire and Luton Joint Prescribing Committee Osteoporosis guidelines for Primary Care. Sept2011, updated Sept 17.
  3. NICE TA 204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010). <http://www.nice.org.uk/guidance/TA204>
  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
  9. MHRA Drug Safety Update, August 2020, vol 14, issue 1
- The above MHRA Drug Safety Updates are available at: <https://www.gov.uk/government/publications/drug-safety-update-monthly-newsletter>
9. BLMK Medicine management website <https://medicines.blmkccg.nhs.uk>

### **Document History**

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