Prescribing support document for denosumab (Prolia®) for primary and secondary fracture prevention in osteoporotic men and postmenopausal osteoporotic women

This document provides prescribing and monitoring guidance for denosumab (Prolia®) therapy. It should be read in conjunction with the transfer of care letter from the specialist, the Summary of Product Characteristics (SmPC) and the BNF.

Prescribe denosumab by brand name.

This document is for adult only: Denosumab 60mg (Prolia®): should not be used in patients under 18 years due to the risk of serious hypercalcaemia MHRA May 2022[1]

BACKGROUND FOR USE

Denosumab is a monoclonal antibody that inhibits osteoclast formation, function and survival thereby decreasing bone resorption. Denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis.[2,3,4,5] There is evidence that denosumab also increases the bone mineral density in men.[6] Denosumab is recommended in patients who have adverse effects, contraindications or have not responded to treatment with oral bisphosphonates (alendronic acid and risedronate) or IV zoledronic acid. See the Hertfordshire and west Essex ICB Prescribing, Policies and Pathways website for *Prescribing guidelines for women and men over 50 years with or at risk of osteoporosis* here.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to the active substance or to any of its excipients e.g. fructose	Do not use
Allergy to latex	Not recommended
Hypocalcaemia	Calcium and 25(OH) vitamin D should be checked before starting the treatment. **Vitamin D deficiency and hypocalcaemia must be corrected by ensuring adequate intake of calcium and vitamin D before initiating therapy. This will usually require the use of supplements.** Denosumab should not be used in patients with any degree of hypocalcaemia.[7] Check calcium levels before each dose, and within 2 weeks of each dose in patients with eGFR <30ml/min (local guidance is more stringent than MHRA advice) and/or if suspected symptoms of hypocalcaemia occur.
Patients with impaired renal function	Denosumab has no direct nephrotoxic effect. No dose adjustment required in patients with mild or moderate renal impairment, eGFR>30ml/min. Patients with severe renal impairment (eGFR < 30 ml/min) and/or receiving dialysis are at greater risk of developing **hypocalcaemia** (see above). Renal function should be checked regularly. There is very limited data on denosumab use in patients with eGFR<15ml/min. **These patients should stay under the care of the hospital.**
Liver impairment	Metabolism is unlikely to be affected by hepatic impairment. No dose adjustment required.

Cellulitis	Although uncommon, patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
Prevention of jaw osteonecrosis[8,9]	Dental examination with appropriate preventative dentistry is recommended in patients with risk factors (corticosteroids, radiotherapy to head and neck, chemotherapy, pre-existing dental disease, periodontal infections) BEFORE starting treatment. Patients on treatment should be advised to maintain good oral hygiene, avoid invasive dental procedures where possible, attend for regular dental check-ups and report any oral symptoms such as dental mobility, pain or swelling to a doctor or dentist.
Osteonecrosis of the external auditory canal[10]	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.
Pregnancy and lactation	Not recommended
Atypical fractures of the femur	Atypical femoral fractures have been reported in conjunction with denosumab use. During 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

DOSAGE

- Patients must be calcium and vitamin D replete before and during treatment with denosumab. They should therefore be prescribed or agree to buy calcium and vitamin D supplements equivalent to 1 to 1**.**2 grams calcium and 20 micrograms (800 IU) vitamin D. Guidance on vitamin D supplementation is available on the Hertfordshire and west Essex ICB Prescribing, Policies and Pathways website. Guidance on appropriate calcium and vitamin D supplementation will be provided by the specialist.
- The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of the arm. Administration should be performed by an individual adequately trained in injection techniques which includes a patient or carer who has received adequate training.
- It is important that patients receive their 6 monthly injections in a timely manner, preferably within 2 weeks of the due date either side due to the potential for rebound bone loss if the injection is delayed more than this. Patients who fail to attend for an injection should be contacted actively to ensure this.
- The treatment cycle is for 5 years (10 injections) – see table on page 4/5 for treatment schedule.
- Avoid unplanned cessation of denosumab because it can lead to increased vertebral fracture risk, hence it must not be stopped without considering an alternative therapy (NOGG)

TIME TO RESPONSE

- In trials, initial suppression of bone turnover marker occurred after 3 days.
- Clinical trials demonstrated fracture risk reduction after the first year of treatment.

SPECIALIST RESPONSIBILITIES

Before starting treatment the specialist will:

- Review prior treatments for osteoporosis, concomitant medical problems and allergies (including latex).

- Arrange DXA scan if appropriate.
- Organise baseline blood tests: U&Es, Ca, 25(OH)vitamin D, PO_4 if clinically indicated.
- Advise on calcium and vitamin D supplementation.
- Check for risk factors for osteonecrosis of the jaw before starting denosumab; advise on dental examination and appropriate preventative dentistry for patients with risk factors.[8,9]
- Explain the risk of osteonecrosis of the jaw and advise patients on precautions to take:[8,9]
    - 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 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 (e.g. loose teeth, pain, swelling, non-healing sores or discharge).
- Advise that an increased risk of multiple vertebral fractures has been reported in patients within 18 months of stopping or delaying ongoing denosumab therapy for osteoporosis and that patients with a previous vertebral fracture may be at highest risk. Evaluate a patient's individual factors for benefits and risks before initiating treatment with denosumab, particularly in patients at increased risk of vertebral fractures for example those with previous vertebral fracture. **Advise not to stop denosumab without specialist review**.[11]
- Discuss the benefits and possible side-effects of treatment as listed in the patient information leaflet including the risk of hypocalcaemia, cellulitis, eczema and osteonecrosis of the external auditory canal.[10]
- 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] Also advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.[10]
- Provide patient information leaflet and encourage patient to enrol on the PROLONG patient support programme (specialists can obtain registration forms direct from Amgen) to access further support and to ensure that they are reminded when their next injection is due. A registration form needs to be completed. The form can be requested by emailing prolong.support@nhs.net .

Beginning treatment:

1. The first injection will be administered in secondary care.
2. Specialist to organise calcium level check 2 weeks after injection for patients with eGFR 15-30ml/min and manage as necessary.
3. Specialist will review patient approximately 3 months after the injection to assess for possible adverse effects.
4. If, following the initial review visit, the patient is stable and free from adverse reactions, specialist will contact the GP to arrange transfer of care.
5. The due date for the second injection must be stated clearly on the letter from the specialist to the GP and patient.

- After the 10th injection, the specialist will review the patient following referral back by the GP and provide ongoing management advice.
- Advise patient of importance of having a plan for ongoing treatment following 10th injection

PATIENT RESPONSIBILITIES

- Take calcium and vitamin D tablets regularly before and during denosumab treatment.

- Organise a dental check-up and undergo any corrective dentistry before starting denosumab.
- Avoid invasive dental procedures if possible whilst on treatment with denosumab.
- Tell your doctor if you have any problems with your mouth or teeth before starting treatment; if you wear dentures you should make sure their dentures fit properly before starting treatment.
- Maintain good oral hygiene and get routine dental check-ups during treatment.
- Tell your doctor and dentist that you are receiving denosumab if you need dental treatment or dental surgery.
- Tell your doctor and dentist immediately if you have any problems with your mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge).
- Inform the GP if groin or thigh pain or rash is experienced after starting treatment**.**
- Report any symptoms that could suggest hypocalcaemia (low calcium levels) to your doctor (e.g. muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).
- Report any ear pain or discharge, or an ear infection during denosumab treatment.
- At the 2nd injection appointment with the practice nurse, learn to self administer the 3rd to 10th injection, OR identify a friend or family member to attend the 2nd injection appointment with the patient, so the practice nurse can teach them how to administer the injection.
- Attend for a blood test approximately four weeks prior to each injection and two weeks afterwards if required.
- Ensure that a denosumab prescription is requested in time to be able to give the injection on the due date. If there is a two week or more delay in receiving a dose, the treatment may be less effective.
- **Do not stop denosumab treatment without talking to your doctor**. This is because there have been reports of increased risk of multiple fractures in the spine after stopping or delaying ongoing treatment. If you miss a prescribed dose of denosumab, the missed injection should be administered as soon as possible. After this, your next injection will be scheduled 6 months from the date of your last injection.
- Ensure that denosumab is appropriately refrigerated between collection from pharmacy and administration.
- Continue to regularly review your treatments for osteoporosis with your doctor.
- Be aware of the need to have a plan for ongoing treatment following the 10th injection

GP RESPONSIBILITIES

- Transfer of care, in line with this guideline and transfer of care letter, will occur only when the patient has had the first injection and is stable and free from adverse reactions.
- Ensure the patient continues calcium and vitamin D supplementation throughout treatment with denosumab unless the specialist states that this is not needed and explains rationale.
- Ensure that denosumab is added to the patient record and other osteoporosis treatments such as bisphosphonates and strontium are removed.
- Add to first prescription written/electronic prescribing system that patient ‘will need review by secondary care on xx/yy/zzzz’. This should be 5 years from the first injection or 4.5 years from the first GP prescription (i.e. within 6 months of the 10th injection of denosumab).
- Ensure systems are in place to alert when the next blood tests and injections are due. Doses must be given every 6 months or within a week before or after the planned date or there may be rebound bone loss.
- Organise and check blood tests for calcium, vitamin D and U&Es approximately 4 weeks prior to every injection (2 weeks prior in patients with eGFR less than 30ml/min). A normal result should be seen before giving the next denosumab injection/issuing the

prescription for self-administration. Check calcium 2 weeks after every injection in patients with severe renal failure (eGFR 15-30ml/min). Refer to side effects section on page 5/6 for management advice.

Ongoing monitoring by GP	
Calcium, vitamin D and U&Es	• In patients with normal renal function, check serum calcium and vitamin D level within the 4 week period prior to each injection. Serum calcium and vitamin D level must be normal and renal function tests normal or unchanged before the next injection is given. If serum calcium and renal function abnormal, seek urgent advice from the patient's specialist. If vitamin level <40nmol/L, please check patient compliance with oral supplements and seek specialist advice. • In patients with eGFR less than 30ml/min, check serum calcium and vitamin D level and U&Es 2 weeks prior to each injection. • In patients with severe renal failure, eGFR 15-30ml/min, check serum calcium 2 weeks after each injection.

- Prescribe denosumab, by brand on an FP10 in the 2 weeks prior to denosumab due date, once calcium and U&Es are confirmed as normal.
- If blood test result shows hypocalcaemia and/or the eGFR has dropped below 15ml/min, DO NOT prescribe/administer denosumab, but seek urgent advice from the osteoporosis specialist to decide on-going management.
- Arrange for the second injection of denosumab to be administered by the practice nurse who will teach the patient or their carer to administer future injections.
- If patient misses a prescribed dose of denosumab, the missed injection should be administered as soon as possible. After this, the next injection should be scheduled 6 months from the date of the last injection.
- Continue treatment in primary care for 5 years unless adverse effects occur, the eGFR drops below 15 ml/min or the patient start dialysis, in which case there should be a secondary care review.
- Please seek advice from or refer back to secondary care if:
  1. DXA scan shows decline in bone density after the 5th injection despite uninterrupted therapy;
  2. the patient has a fragility fracture whilst on treatment.

<table>
<tr><th colspan="2">Denosumab treatment schedule</th><th>Given by</th></tr>
<tr><td rowspan="3">Year 1</td><td>1st injection</td><td>Secondary care</td></tr>
<tr><td colspan="2">Transfer care from secondary to primary care</td></tr>
<tr><td>2nd injection</td><td>Administer in primary care. Train the patient/carer how to give subsequent injections. See specialist letter for due date</td></tr>
<tr><td rowspan="2">Year 2</td><td>3rd injection</td><td rowspan="4">Prescribed by primary care. Administered by patient/carer or practice nurse.</td></tr>
<tr><td>4th injection</td></tr>
<tr><td rowspan="2">Year 3</td><td>Following 5th injection – GP to arrange DXA</td></tr>
<tr><td>6th injection</td></tr>
</table>

Year 4	7th injection	
	8th injection	
Year 5	9th injection	
	Following 10th injection: GP to arrange DXA scan and review by secondary care. GP to contact specialist for advice if ongoing treatment plan has not been received from specialist within 6 months of 10th injection.	

- Following the 5th injection (i.e. 2 years after commencing treatment), request a DXA scan. This is to ensure the bone density is stable or has improved midway through the 5-year treatment period. Seek advice/refer to secondary care if DXA scan shows decline in bone density despite uninterrupted therapy.
- Following the 10th injection (i.e. 5 years after commencing treatment), request a further DXA scan and secondary care review for further management advice. The patient will need to see the specialist within 6 months of the 10th injection of denosumab and the DXA scan result must be available to the specialist.
- Inform the secondary care specialist if the patient on denosumab:
    - has a new fragility fracture
    - develops any adverse effects possibly related to treatment
    - declines further treatment
    - discontinues treatment for any other reason

SIDE EFFECTS

Very common	Action to be taken
Musculoskeletal pain	Treat symptomatically
Pain in extremity	Treat symptomatically
Common (1/100 to < 1/10):	
UTI	Treat UTI appropriately. If patient is due for the injection – defer until treatment completed.
Upper respiratory tract infection	Treat appropriately. If patient is due for the injection – defer until treatment completed.
Sciatica	Treat symptomatically
Cataracts	If patient presents with accelerated cataracts and no other cause found discuss with the osteoporosis specialist.
Constipation	Treat appropriately. Continue treatment.
Rash	In case of a new rash following denosumab injection discuss with the specialist before the next dose is given.
Eczema	Consider benefits versus risks – if eczema is mild it is reasonable to continue to treat with denosumab, if more severe then seek specialist advice.
Uncommon (1/1,000 to < 1/100):	
Cellulitis	Treat appropriately. Discuss with the osteoporosis specialist before next injection is given.
Diverticulitis	Treat appropriately. If patient is due for the injection – defer until symptoms resolved.
Ear infection	Treat appropriately. If patient is due for the injection – defer until treatment completed.

Rare side effects (1/10,000 to < 1/1,000):	
Osteonecrosis of the jaw	Stop denosumab and seek osteoporosis specialist advice.
Hypocalcaemia. Severe symptomatic hypocalcaemia has been reported in patients receiving denosumab 60 mg. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment.[7]	Do not give denosumab to patients with hypocalcaemia as this will make it worse. Check if patient is taking adequate calcium and Vitamin D supplementation. Seek specialist advice.
Hypersensitivity to denosumab	Stop treatment and seek advice from osteoporosis specialist.
Atypical femoral fracture	Suspect in a patient complaining of thigh or groin pain especially if it is bilateral. Request urgent AP and lateral X-ray of the whole femur. If the radiograph reports insufficiency fracture or localized periosteal reaction, the patient should be made non-weight bearing and referred urgently to the local trauma team and the osteoporosis specialist informed. If the radiograph is normal but the patient has persistent groin or thigh pain discuss with the specialist in osteoporosis.
Osteonecrosis of the external auditory canal	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. Stop denosumab and seek osteoporosis specialist advice.

NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC)

No interaction studies have been performed. There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however, the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

SOURCES OF ADDITIONAL INFORMATION / ADVICE

Contact Details	**West Hertfordshire Hospitals NHS Trust**	**East and North Hertfordshire NHS Trust**	**Royal Free London NHS Foundation Trust**	**Royal National Orthopaedic Hospital NHS Trust**	**The Princess Alexandra Hospital Trust**
Rheumatology	Watford General Hospital: Tel 01923 217520 Specialist nurse contact number: 01923 217798	Dr Marianayagam Consultant Rheumatologist contact number 01438 284128	Dr Jeffrey Lee Specialist nurse contact number Barnet and Chase Farm Hospital contact - 020 8216 4523	0208 954 2300 ask for rheumatology secretaries	Dr Sarah Farrow Lead for Osteoporosis Rheumatology Consultant 01279 827803

	St Albans City Hospital: Tel 01727 897859 Specialist nurse contact number: 01923 217798 Hemel Hempstead Hospital: Tel 01442 287049, Specialist nurse contact number: 01923 217798		Royal Free Hospital Contact - 02037582042		
Endocrinology		Dr Winocour, Consultant Endocrinologist 01438 288324			
Hospital Pharmacy Medicines information	01923 217853	01438 284969	0207 830 2983	020 8954 2300 use option for pharmacy	01279 827054
Hospital switchboard	01923 244366	01438 314333	020 3758 2000	020 8954 2300	01299 444455

REFERENCES:

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11. MHRA, Drug safety update, Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment, August 2020 https://www.gov.uk/drug-safety-update/denosumab-60mg-prolia-increased-risk-of-multiple-vertebral-fractures-after-stopping-or-delaying-ongoing-treatment

NOGG Clinical Guideline for the prevention and treatment of osteoporosis: https://www.nogg.org.uk/full-guideline

Version	11.1 Harmonisation of Hertfordshire Medicines Management Committee (HMMC) guidance and West Essex Medicines Optimisation Programme Board (WEMOPB) guidance updates include: • Rebadging with HWE ICB and removal of Herts CCG headers • Review date removed and replaced with standard statement • Replacement of CCG website links to HWE Prescribing, Policies and Pathways website • Addition of PAHT contact details and update references
Developed by	Document adapted by HMMC from a version produced by Buckinghamshire Healthcare NHS Trust and NHS Buckinghamshire, Sept 2013. Updated by HMMC Sept 2014. Updated July 2020 and March 2021 by: Dr Leena Patel, Consultant Rheumatologist, WHHT Rupinder Witts, Lead Formulary & Medicines Information Pharmacist, WHHT Dr Cathy Geeson, Interface Pharmacist, HVCCG
Date approved/updated	Version 8.0 September 2014 Herts Medicines Management Committee Version 9.0 July 2020 Herts Medicines Management Committee Version 10.0 March 2021 Herts Medicines Management Committee Version 11.0 June 2024 HWE APC
Review date	The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	Version 11.0 amendments to specialist nurse contact details at WHHT (Oct 2024) Version 10.0 amendments: • Update in line with MHRA DSU May 2022 - Denosumab 60mg (Prolia): should not be used in patients under 18 years due to the risk of serious hypercalcaemia. MHRA requirement for biosimilar medicines to be prescribed by brand. • Emphasis on need for continuation of treatment until review • Addition of Osteonecrosis of the external auditory canal to Contraindications and Precautions and Side effects sections. • Vitamin D levels prior to injection • Addition *of Ensure systems are in place to alert when the next blood tests and injections are due. Doses must be given every 6 months or within a week before or after the planned date or there may be rebound bone loss* from legacy WEMOPB denosumab guidance.