The Princess Alexandra Hospital NHS NHS Trust

NHS West Essex Clinical Commissioning Group

Guideline for denosumab for primary and secondary fracture prevention in men and postmenopausal osteoporotic women

Prolia® 60 mg denosumab

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

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] The National Osteoporosis Foundation has stated that up to 25% of men over the age of 50 years will experience a fracture due to osteoporosis. Men who suffer from a major fracture have higher mortality rates than women. Pharmacologic therapy options for treating osteoporosis are limited for men as compared with women. There is evidence that denosumab increases bone mineral density in men[8]

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 West Essex management of osteoporosis guidelines on the West Essex CCG website,
Osteoporosis prevention and treatment guidelines - West Essex CCG

Denosumab is included within the West Essex CCG Blood Monitoring for Specialised Drugs SLA, therefore qualifies for payment to help resource the additional responsibilities within Primary Care

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	Hypocalcaemia is an identified risk in patients treated with denosumab, which increases with the degree of renal impairment. Monitoring of calcium levels should be conducted: • prior to each dose of denosumab • within two weeks after the initial dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min) • if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient[7] Calcium and 25(OH) Vit 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[6].
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** and calcium levels should be checked two weeks after each injection. 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 ONJ	Doctors should evaluate all patients for ONJ risk factors prior to treatment with denosumab.[7] 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 should be advised to maintain good oral hygiene while on treatment.
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 1-1.12g calcium and 20 micrograms (800 IU) vitamin D (2 tablets once daily of Adcal D3 or equivalent). 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 upper 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 injections every 6 months. There is a potential for rebound bone loss if the injection is delayed, so patients who discontinue, or who fail to attend for an injection should be followed up to try and ensure they get their injection within 2 weeks of the due date. The treatment cycle is for 3 years (6 injections) – see table on page 3 for treatment schedule

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, PO_4, 25(OH) vitamin D.
- Advise on calcium and vitamin D supplementation and symptoms of hypocalcaemia.
- Evaluate patient for ONJ risk factors prior to treatment
- Discuss the benefits and possible side-effects of treatment as listed in the patient information leaflet including the risk of cellulitis, eczema and advice on dental treatment.
- Provide patient information leaflet and encourage patient to enrol on the PROLONG patient support programme by post/phone (020 7627 0990) to access further support and to ensure that they are reminded when their next injection is due.

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 6th injection, the specialist will review the patient following referral back by the GP, and provide ongoing management advice

PATIENT RESPONSIBILITIES

- Take calcium and vitamin D tablets regularly before and during denosumab treatment.
- Report symptoms of hypocalcaemia
- Organise a dental check-up and undergo any corrective dentistry before starting denosumab.
- Maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling during treatment with
- Inform the GP if groin or thigh pain or rash is experienced after starting treatment**.**
- At the 2nd injection appointment with the practice nurse, learn to self administer the 3 to 6th injections, 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.
- Ensure that denosumab is appropriately refrigerated between collection from pharmacy and administration.

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 systems are in place to alert when the next blood tests and injections are due. If there is a two week or more delay in receiving a dose, the treatment may be less effective.
- Ensure other osteoporosis treatments such as bisphosphonates and strontium are removed.
- Organise and check blood tests for calcium and U&Es approximately 4 weeks prior to every injection. 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 4 for management advice.

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

- Prescribe denosumab (Prolia®) 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.

- Continue treatment in primary care for 3 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.

Denosumab treatment schedule		**Given by**
Year 1	1st injection	Secondary care
	Transfer care from secondary to primary care	
	2nd injection	Administer in primary care. Train the patient/carer how to give subsequent injections. See specialist letter for due date
Year 2	3rd injection	Prescribed by primary care. Administered by patient/carer or practice nurse.
	4th injection	
Year 3	5th injection	
	6th injection	
	Following 6th injection: GP to request a DXA scan and arrange review by secondary care.	

- Following the 6th injection, request a DXA scan and request secondary care review for further management advice. The patient will need to see the specialist within 6 months of the 6th 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

Common (1/100 to < 1/10):	Action to be taken
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.
Pain in extremity	Treat symptomatically
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	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

with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment.[6]	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. If the radiograph is normal but the patient has persistent groin or thigh pain discuss with the specialist in osteoporosis.

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	**Dr S.J. Farrow** Consultant Rheumatologist 01279 827420
Hospital Pharmacy Medicines information	01279 827054
Hospital switchboard	01279 444455

REFERENCES:

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7. Denosumab 60mg (Prolia®): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia, August 2014, letter from Amgen, EMA and MHRA. http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con454359.pdf
8. Orwoll et al, A Randomized, Placebo-Controlled Study of the effects of Denosumab for the Treatment of Men with Low Bone Mineral Density, J Clin Endocrinol Metab, September 2012, 97(9):3161–3169 https://www.ncbi.nlm.nih.gov/pubmed/22723310

Transfer of Care Agreement Form

for use when transferring prescribing of denosumab from specialist to GP

1. Specialist to use transfer of care letter to summarise rationale for treatment, document pre-treatment counselling and that patient responsibilities have been discussed and understood.
2. Specialist to complete and sign the transfer of care agreement form below.
3. Copy to be filed in patient's hospital notes.
4. Specialist to fax/email signed agreement form, denosumab guideline and transfer of care letter to the GP practice in good time to allow the GP to consider.
5. If willing to accept transfer of care GP will complete and sign agreement form and contact patient to make arrangements for future tests and prescriptions.
6. If unwilling to accept care, GP will provide reason on the form, and contact patient to let them know that care will remain with the hospital specialist.
7. Whichever decision transfer of care agreement letter should be sent to the Specialist and ANONYMISED copy to PAH Pharmacy tpa-tr.ClinicalPharmacy@nhs.net
   Sending a copy of this form to the PAH pharmacy will help to identify any inappropriate requests.
8. GP to file copy of agreement form and denosumab guideline in patient's notes.
9. GP to fax/email transfer of care agreement form back to specialist.

For completion by specialist

Drug: Denosumab (Prolia®) 60mg subcutaneous injection

Indication: Primary and secondary fracture prevention in men
OR
Treatment of postmenopausal osteoporosis in women (delete as appropriate)

Date injection first administered by specialist:

Date for administration of second injection in primary care (must provided within 2 weeks before or after this date):

Does calcium need checking after each injection as well as before each injection? ☐YES/ ☐NO

I accept:

- **the West Essex transfer of care responsibilities and**
- **the requirements defined in the denosumab guideline**

Patient name, NHS number & address or sticker:		**Signature and date**
Specialist name and designation:	Tel. Fax email	**Signature and date**

To the GP: If you are not willing to accept prescribing responsibility, please give rationale:

GP Name & Practice:	I am / I am not willing to take over the prescribing and monitoring for denosumab treatment	**Signature and date**

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The Princess Alexandra Hospital NHS
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Tel: 01279 444455

Information for patients:

SHARED CARE:
Agreement information and confirmation

Patient name:

.....

Medicine:

.....

We would be grateful if you would take time to read this information as it will help us work with you to manage your condition and ensure safe prescribing of the specific medicine listed above.

What is a Shared Care Agreement?

A Shared Care Agreement (SCA) enables the care you have for a specific condition to be shared between the hospital and your GP.

The agreement means that the medicine the hospital has started, can be continued by your GP, so you won't have to visit the hospital to collect your medicine.

The SCA gives information on your medicine, guidance on the prescribing and monitoring responsibilities for your consultant (in the hospital), your GP and you. For an SCA to work everyone involved must understand it and communicate effectively.

Your consultant and your GP will need to sign the agreement and if you agree to this approach we would ask you to sign this letter, to indicate your agreement to have your care managed in this way.

How does Shared Care work?

Your consultant and GP share responsibility for your care.

The consultant is a specialist in your condition and will start prescribing your medicine, making sure it is suitable for you. There will come a point in your treatment when you may not need to be monitored by the consultant as often and this monitoring can be done by your GP.

Once your GP has agreed to the SCA, they will be able to prescribe the same medicine for you at the dose recommended by the consultant.

The organisation which regulates GPs, the General Medical Council, says that 'when a GP prescribes a medicine, the GP needs to satisfy themselves that the prescription is needed, appropriate for the patient and within the limits of their competence'.

So, your GP can only issue a prescription if the consultant and you keep to the responsibilities you have agreed (see below). If responsibilities are not kept or if the GP no longer feels it is safe to prescribe the medicine he/she will explain the reasons to you and your consultant, then prescribing responsibilities will be transferred back to the hospital.

What do I need to do to ensure the SCA can continue?

- **Attend hospital outpatients**
  You must still attend the hospital for regular reviews as directed by your consultant (these maybe less frequent than before). If you do not attend your hospital appointments your GP will not be able to continue issuing prescriptions for this medication.
- **Attend GP appointments**
  You must attend any appointments you have with your GP in relation to this medicine, so they can look after you effectively

continued overleaf

With thanks and acknowledgement to Buckinghamshire Healthcare NHS Trust and NHS Buckinghamshire, **and** Hertfordshire Pharmacy and Medicines Optimisation Team. Approved by MOPB July 2016 review date July 2018

- **Have blood tests as you have been advised to**
  Your consultant should have informed you if and how often you need to have blood monitoring tests. You can usually have your blood taken at an appropriate clinic and not need to go to the hospital.

  If you do not have the blood monitoring tests as advised by your consultant, your GP will no longer be able to issue you with prescriptions as it would not be safe to do so.

What do I do if I am having side effects to the medicine?

Your consultant should have informed you of the common side effects to expect and what to do if you experience them. If you think you may be having side effects from a medicine discuss these with your pharmacist and GP. Your GP may need to seek advice from your consultant before issuing you with another prescription; this is to ensure it is safe for you to continue on the medication.

What if my disease symptoms change or get worse?

Report any changes in disease symptoms or circumstances that could affect management of your disease to your GP.

What about the other medicines I take?

Inform your GP and the consultant of all other medicines you are taking, including those you may have bought yourself. Do not take new medicines (including those you could buy) until you have discussed this with your pharmacist, GP or consultant.

If you would like to go ahead with a shared care agreement for the specific medication identified on page 1, please sign below to confirm that you:

- Understand the shared care agreement
- Are happy to have your care for this aspect of your health managed by a shared care agreement
- You agree to attend regular review appointments as requested
- You agree to have blood tests as required

Patient's signature .....

Date .....

Print name .....

If at any point in time you would like this shared care agreement to stop, please talk to your GP.