NHS
Herts Valleys
Clinical Commissioning Group

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East and North
Hertfordshire
Clinical Commissioning Group

Transfer of care guideline for denosumab for primary and secondary fracture prevention in osteoporotic men and postmenopausal osteoporotic women

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 (SmPC) 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]. There is evidence that denosumab also increases the bone mineral density in men.[9] 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 management of osteoporosis guidelines on the Herts Valleys CCG website, Endocrine recommendations or the East and North Hertfordshire CCG website, Endocrine system recommendations).

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) 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] 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	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.
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 – 1.2 grams calcium and 20 micrograms (800 IU) vitamin D (2 tablets once daily of Adcal D3 or equivalent). Guidance on vitamin D supplementation is available on the Herts Valleys CCG website, nutrition and blood recommendations and on the East and North Hertfordshire CCG website, nutrition and blood recommendations. 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. There is a potential for rebound bone loss if the injection is delayed more than this and 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 5 years (10 injections) – see table on page 4/5 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.
- 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.[10]
- Explain the risk of osteonecrosis of the jaw and advise patients on precautions to take:[11]
    - 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).
- 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.

- 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).[10] Also advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.[12]
- 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.

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.

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.
- 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 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).
- Organise and check blood tests for calcium 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.
- Serum vitamin D monitoring is **not** routinely required. In patients at risk of vitamin D deficiency e.g. low baseline serum vitamin D, poor compliance with oral supplements or if there has been intermittent hypocalcaemia), it should be checked annually (preferably at time of performing pre-denosumab blood tests for patient convenience); the need for such monitoring will be indicated in the transfer of care letter. If the vitamin D is <40nmol/L, please check patient compliance with oral supplements and seek advice from the patient's specialist. If the calcium levels are normal, the denosumab injection should not be delayed in order to replace vitamin D.

Ongoing monitoring by GP	
Calcium and U&Es	• In patients with normal renal function, check serum calcium level 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 eGFR less than 30ml/min, check serum calcium 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.
Vitamin D **NB not routinely required. If required, this will be indicated in the transfer of care letter**	• Annually in patients at risk of vitamin D deficiency (e.g. low baseline serum vitamin D, poor compliance with oral supplements or if there has been intermittent hypocalcaemia). • If <40nmol/L, please check patient compliance with oral supplements and seek specialist advice.

- Prescribe denosumab 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 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.

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	Following 5th injection – GP to arrange DXA	
	6th injection	
Year 4	7th injection	
	8th injection	
Year 5	9th injection	
	Following 10th injection: GP to arrange DXA scan and review by secondary care.	

- 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.[6]	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.

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
Rheumatology	Watford General Hospital: Tel 01923 217520 Maria Cunningham/ Claudia Ciufu, Specialist nurse contact number: 01923 217798 St Albans City Hospital: Tel 01727 897859 Annie Seymour, Specialist nurse contact number: 01727 897912. Hemel Hempstead Hospital: Tel 01442	Dr Marianayagam Consultant Rheumatologist contact number 01438 284128	Dr Jeffrey Lee Specialist nurse contact number Barnet and Chase Farm Hospital contact - 020 8216 4523 Royal Free Hospital Contact - 02037582042	0208 954 2300 ask for rheumatology secretaries

	287049 Margaret Brown, Specialist nurse contact number: 01442 287049			
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
Hospital switchboard	01923 244366	01438 314333	020 3758 2000	020 8954 2300

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