Using Denosumab for Osteoporosis in Primary Care

Denosumab (Prolia® ▼) is a monoclonal antibody drug for the treatment of **osteoporosis** administered as 6 monthly subcutaneous injection. Until now practices have been administering the second and subsequent doses of denosumab. This guidance describes how the initial and all subsequent doses can be administered in primary care.

Denosumab will not be prescribed under a shared care arrangement and so does not require a shared care protocol.

Current NICE guidance supports treatment duration of five years followed by clinical review.

Which patient groups should I consider for denosumab based on NICE TA 204:

Denosumab remains third line choice in the treatment of osteoporosis with generic alendronic acid or risedronate being first line.

1) Secondary prevention of osteoporotic fragility fractures in postmenopausal women and men who:

- are unable to comply with the special instructions for administering alendronate or risedronate
- have an intolerance of, or a contraindication to, those treatments.

Intolerance is defined as: 'persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment and that occurs even though the instructions for administration have been followed correctly.'

2) Primary prevention of fragility fractures in postmenopausal women: For patients who are unable to comply or are intolerant of risedronate and alendronic acid and have a T score as outlined below:

T score* cutoffs for using denosumab in primary prevention of fragility fracture

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	Not recommended	-4.5	-4.0
70–74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

*Use the lowest T scores at either lumbar spine or hip DXA for using denosumab.
Clinical risk factors: a) parental history of hip fracture, b) alcohol intake of 4 or more units per day, c) rheumatoid arthritis diagnosis
For example a 73 years old with no risk factors the lowest BMD has to be -4.5 or worse for denosumab to be recommended.

Who <u>cannot</u> have denosumab:

1) Hypocalcaemia patients
2) Chronic Renal Failure patients:

   Whilst bisphosphonates cannot be prescribed to patients with an eGFR <35 ml/min. Denosumab can be prescribed only with secondary care advice for those with an eGFR between 20 and 35 ml/min.

3) Patients with rare hereditary problems of fructose intolerance should not use denosumab (see SPC).

Whilst from trials there was an increased risk of skin and lung infections, this has not been found in subsequent trials nor is it the experience of the Oxford service. If further advice is needed please discuss with the Metabolic Bone Service. Benefits: Denosumab has been shown to produce a 70% reduction in vertebral fracture and a 40% reduction in hip fractures compared with no treatment. This compares with an 87% reduction in vertebral fracture and a 54% reduction in hip fracture with bisphosphonate treatment versus placebo.

Risks: The most common reported side effects in trials were constipation, urinary tract infection, upper respiratory tract infection, pain in extremity, sciatica.

- Patients receiving denosumab may develop skin infections (predominantly cellulitis). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- There have been rare cases of osteonecrosis of the jaw (ONJ) in patients receiving denosumab 60 mg for osteoporosis. The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

•cumulative dose of bone resorption therapy.
•cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
•concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
•poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures
During denosumab treatment patients should avoid invasive dental procedures if possible and maintain good oral hygiene practices. If dental implants are required it is best to do this elective surgery after 5 months from last denosumab injection and WAIT/DELAY next denosumab injection for jaw healing to occur.

- The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause allergic reactions.
- Atypical femoral fractures have been reported in patients receiving denosumab. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment.

Drug interactions

- No interaction studies have been performed with denosumab.
- Other bone therapies such as bisphosphonates should be discontinued prior to starting denosumab. There is low potential for drug–drug interactions.

Risk of vertebral fractures following discontinuation:

A paper published in November 2017[1] looked at vertebral fractures after patients had discontinued denosumab and raises some important questions. This paper whilst having limitations highlights that among participants who discontinued denosumab, the risk of new and worsening vertebral fractures quickly increased to levels similar to the risk in untreated participants; about half of participants who sustained a vertebral fracture sustained more than one. Furthermore, the risks of single and multiple vertebral fractures were higher among participants who had a history of vertebral fracture before or after the FREEDOM trial or Extension. The authors conclude that clinicians should "keep careful track of the dates when a patient's next dose of denosumab is due. If a patient discontinues denosumab, particularly if she has had a vertebral fracture, the patient should promptly receive a bisphosphonate or another antiresorptive agent to prevent the increased risk of vertebral fractures, especially multiple vertebral fractures, that develop soon after stopping denosumab."

The SPC for denosumab states "the optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use"

Clinicians and patients should be aware of the risk of increased multiple vertebral fracture after discontinuation of denosumab. It should be noted that there is a lack of evidence in this area and clinicians should think carefully before initiating denosumab as to whether denosumab is the best treatment for their patient and should also consider when and how denosumab should be discontinued in each patient. Secondary care should be consulted before denosumab is discontinued.

Ten Responsibilities of clinician initiating treatment

1. Ensure that the patient meets the above eligibility criteria for treatment including housebound patients.
2. Discuss benefits and side effects of treatment (see below) with the patient and provide patient information leaflet on denosumab (available here) and patient reminder card (available here).
3. In last 4 weeks of each dose check: (for housebound patients request blood test via community phlebotomy if available or District Nurse)

a) Vitamin D level >50 nmol/l {send in a yellow top bottle! Like sunshine}
b) eGFR>30 ml/min

c) normal serum calcium in each case **and** within 2 weeks after the initial dose in patients predisposed to hypocalcaemia (eg patients with severe renal impairment, creatinine clearance <30ml/min). Check calcium levels at any time if suspected symptoms of hypocalcaemia occur. 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.

- ❖ If low vitamin D <50 nmol/l: prescribe Fultium D3 3200 IU od for 12 weeks and then OCCG recommend 800 IU od OTC. Can give denosumab after 4 weeks of starting supplements.
- ❖ If hypocalcaemia or low eGFR email Metabolic Bone Unit ox.GPosteop@nhs.net for further information

4. Ensure that the patient has at least intake of 700mg calcium / day :
   For example daily intake should include half a pint of milk and either 2 match box sizes of cheese or 2 pots of yoghurt.

If not enough calcium from milk/cheese/yogurt from diet prescribe: od or bd to get above 700mg per day on repeat prescription (Adcal = 600 mg calcium) or recommend OTC calcium.

5. Evaluate all patients for ONJ risk factors prior to treatment and advise dental examination for all patients with concomitant risk factors. Patients should be encouraged to maintain good oral hygiene and receive routine dental check-ups (*see SPC for further details*).
6. Add prescription to patient record and book next blood test in 5 months and injection in 6 months. **Optional** enroll patient in Prolong reminder system [see end for details].
7. Initiate first denosumab injection and ensure that the patient understands the plan for follow-up care (blood test in 5 months and repeat injection in 6 months). For housebound patients provide direction to administer to District Nurse team for each administration
8. Report any adverse events to the Medicines and Health Care Regulatory Agency (MHRA) using yellow card system.
9. In patients with eGFR < 35 ml/min, check calcium 2 weeks after injection.
10. Review denosumab treatment in the event of any new fractures or after five years. If two or more fractures on treatment then discuss with metabolic bone service.

Five Responsibilities of patient

1. Report to the doctor if there is not a clear understanding of the treatment and share any concerns in relation to treatment.
2. Report any adverse effects or warning symptoms whilst on treatment with denosumab.
3. Ensure good oral hygiene, e.g. regular 6 monthly dental checks and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment. Tell their dentist they are receiving denosumab.
4. Remember to have the blood test one month BEFORE the denosumab injection, twice a year. They will have a 'Prolong' reminder letter if the doctor has enrolled them.
5. Keep taking calcium + vitamin D tablets OR if there is enough dietary calcium [eg 1 pint skimmed milk/day] continue taking 800 IU vitamin D3 daily to avoid becoming vitamin D3 deficient. Report any symptoms of hypocalcaemia such as paresthesias, muscle stiffness, twitching or cramps.

Role of District Nurse if Patient Housebound

- Complete blood test as requested by GP (This should be done by the Community Phlebotomy service if you have one in your locality)
- Complete administration of denosumab as requested by GP, as per "**Dosage & Administration"** section
- Be aware of **"risks"** section (as below), checking with patient and escalating any concerns to GP before administering
    - Hypocalcaemia – Adequate intake of calcium and vitamin D is essential. Ensure that patient is actually taking any prescribed supplements. Report any symptoms of hypocalcaemia, e.g. muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth.
    - Osteonecrosis of the Jaw (ONJ) – Check that patient is maintaining good oral hygiene and receiving routine dental check-ups. Escalate any oral symptoms such as dental mobility, mouth ulcers, pain or swelling.
    - Cellulitis – Patients may develop cellulitis or other skin infections most commonly in the lower leg.

Escalate any swollen, red area of skin that feels hot and tender, possibly with symptoms of fever.

- Update the Primary Care Record by recording the fact of administration as a consultation (or as agreed with the patient's practice)

Dosage & Administration
60mg of denosumab (in a 1 ml solution) administered by subcutaneous injection into the thigh, abdomen or back of arm once every 6 months. Administration should be performed by an individual who has been adequately trained in injection techniques.

Storage Denosumab has a shelf life of 30 months. Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Do not shake excessively. Denosumab may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, it must be used within this 30 day period.

Procurement
There are two ways in which Prolia can be sourced in primary care:
1. A GP practice can have an account with Movianto and orders can be placed by telephone, fax or email
Telephone: 01234 248631
Fax: 01234 248705
Email: orders.uk@movianto.com
If a GP practice is a new customer an account can be set up by telephoning the number above. Prolia will be delivered direct within 24 hours via refrigerated vehicles to the premises free of charge. Cut off time for orders is 1630 Monday-Friday.
The product code is 900320.
2. Alternatively, the patient can collect their prescription from a local pharmacy via the GP using and writing an FP10.

HELP LINE: Bone Metabolic Service (Nuffield Orthopaedic Hospital): 01865 227647
Fax: 01865 227524; Email: ox.GPosteop@nhs.net
Practices will be paid under the near patient testing for monitoring the patient from the time of the first dose administration and subsequent doses.
PROLONG is the manufacturers patient information service. Details can be found in product insert.

References

1. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension, Cummings et Al, American Society for Bone and Mineral Research, Nov 2017. DOI: 10.1002/jbmr.3337
TA 204: **Denosumab for the prevention of osteoporotic fractures in postmenopausal women**
MOBBB Policy Statement 232: **Pharmacological treatments for the secondary prevention of osteoporotic fragility fractures in men**