

Using Denosumab 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

Age (years)	Number of independent clinical risk factors for fracture		
	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 can't have denosumab:

1) Hypocalcaemia

2) Chronic Renal Failure:

Whilst biphosphonates 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](#)).

While from the trials there was an increased risk of skin and lung infections, this has not been found in subsequent trials nor is 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 a 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.
- Osteonecrosis of the jaw (ONJ) has been reported rarely in osteoporosis studies. Known risk factors for the development of ONJ such as cancer should be taken into consideration before prescribing. 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 patient 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.

Ten Responsibilities of clinician initiating treatment

1. Ensure that the patient meets the above eligibility criteria for treatment
2. Discuss benefits and side effects of treatment (see below) with the patient and provide patient information leaflet on denosumab (available [here](#)).
3. In last 4 weeks check:
 - a. Vitamin D level >50 nmol/l {send in a yellow top bottle! Like sunshine}
 - b. eGFR>30 ml/min
 - c. normal serum calcium.

- ❖ If low vitamin D <50 nmol/l: prescribe either:
- ❖ Fultium D3 3200 IU od for 12 weeks and then 800 IU od . Can give denosumab after 4 weeks of starting supplements.
- ❖ OR: InVita D3 25,000 iu {in 1 ml of Olive oil} one ampoule's liquid on a teaspoon by mouth weekly for 6 weeks as loading dose, THEN one ampoule [25,000 iu] by mouth monthly thereafter as maintenance
- ❖ If hypocalcaemia or low eGFR email Metabolic Bone Unit ox.osteo@nhs.net

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.

If the patient is on a calcium and Vit D3 preparation and their Vit D is <50 nmol/l: the likelihood is they are not taking it !!!!! Check concordance with medication: they may prefer to drink milk and have Vit D3 supplements which are better tolerated

5. Assess the patient to ensure they have good oral hygiene and consider dental examination for patients with concomitant risk factors in the community ([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).
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. 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
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. They should keep taking their calcium + vitamin D tablets OR if they have enough dietary calcium [eg 1 pint skimmed milk/day] continue taking 800 IU vitamin D3 daily to avoid becoming vitamin D3 deficient.

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.osteo@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

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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**

National Osteoporosis Guidelines on Vitamin D and Bone Health 2013

<https://www.nos.org.uk/document.doc?id=1352>

NICE guidelines: Vitamin D: increasing supplement use among at-risk groups Issued: November 2014

NICE public health guidance 56 : guidance.nice.org.uk/ph56