Denosumab for Osteoporosis – Adults

Bath and North East Somerset, Swindon and Wiltshire Together

BSW Formulary positioning: AMBER recommended

Denosumab may be recommended in a clinic letter or via advice and guidance from a rheumatology or care of the elderly specialist. The GP can then initiate the medication.

1. Summary of condition and treatment aims

Postmenopausal osteoporosis is a condition that mainly affects older women and is characterized by a decrease in bone mass. Denosumab is a licensed and NICE-approved option for women with this condition. Denosumab is also licensed for use in men at increased risk of fractures.

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to receptor activator of nuclear factor-K B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

NICE TA204 (October 2010) sets out how this drug should be used in primary & secondary prevention in postmenopausal women.

2. Usual dose and frequency

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.

Treatment Duration:

Trial evidence from 10 years of denosumab treatment demonstrated ongoing improvement in bone density, low fracture rates and low rate of adverse events. Stopping denosumab results in a rebound increase in bone turnover markers and rapid decline in bone density reaching pre-treatment levels within 12 months. Vertebral fractures have been reported in patients who stop denosumab, particularly if they have had prior vertebral fractures. Bone loss following denosumab cessation can be attenuated (but not stopped) by changing to another treatment such as another bisphosphonate. **Denosumab should therefore not be stopped without specialist review and consideration of an alternative treatment to prevent rapid bone loss and reduce risk of rebound vertebral fractures.**

The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. It is suggested that where fracture risk remains high, denosumab is continued for at least 10 years (based on existing data). In older patients (e.g. those aged over 75 at the time of commencing treatment), denosumab should be regarded as a lifelong treatment unless complications arise.

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 10 or more years of use. **Given the rebound increase in bone turnover on stopping treatment do NOT stop or delay denosumab without prior specialist advice**. Use 'Advice and Guidance' via cinapsis.

The MHRA Drug Safety update about increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment, is found here.

3. Details of medication - Product choice (see individual SPC for further information)

Route of administration	Subcutaneous injection
Formulation	Solution for injection in pre-filled syringe
Administration details	Single subcutaneous injection once every 6 months
Other important information	Store in a refrigerator (2°-8°c).

4. Investigations & monitoring

Monitoring parameters	Frequency of monitoring	Action (adjustment &/or referral back to hospita
For patients with a Creatinine Clearance of ≥ 30ml/min. *This is calculated using the Cockcroft-Gault Equation.*	Check creatinine clearance, serum calcium and vitamin D prior to 1st dose. Correct any low calcium / vitamin D before proceeding. Check creatinine clearance and serum calcium	Should the Creatinine Clearance fall to <30ml/min, during treatment, please follow additional monitoring guidance below. Hypocalcaemia advice below

	Before each dose (if adjusted calcium is below reference range, check compliance with supplements and do not give dose until corrected). A post-injection calcium check is not necessary, providing patient is asymptomatic.	
For patients with a Creatinine clearance of < 30ml/min who are NOT on dialysis. *This is calculated using the Cockcroft-Gault Equation.*	Check creatinine clearance, serum calcium and vitamin D prior to 1st dose. Correct any low calcium / vitamin D before proceeding. Check creatinine clearance and serum calcium before each subsequent dose. If there is any concern re: possible non-adherence to supplements, also check vitamin D. If adjusted calcium / vitamin D is below reference range, check compliance with supplements and do not give dose until corrected. Check serum calcium at 2 and 4 weeks post each injection (or sooner if symptomatic).	Hypocalcaemia advice below
For patients on dialysis/ under renal care	The treating specialist will usually advise an individualised monitoring regime. This may require weekly calcium monitoring for the first four weeks post denosumab.	Hypocalcaemia advice below

NOTE: All patients receiving denosumab should be on calcium and vitamin D supplementation, unless otherwise directed by specialist team.

Post injection hypocalcaemia advice:

- If adjusted serum calcium <2 mmol/l, check for symptoms of hypocalcaemia** and seek urgent specialist advice (contact rheumatology team by telephone during working hours, or acute medicine out of hours)
- If adjusted serum calcium 2 – 2.2 mmol/l, check for symptoms of hypocalcaemia. If symptomatic, seek urgent specialist advice. If asymptomatic:
    - Check if patient is taking calcium supplements and address any non-adherence
    - Consider stopping any proton pump inhibitors (as they can lower magnesium and worsen hypocalcaemia) and switching to Gaviscon or H2 blocker.
    - If adherent to calcium supplement, then double dose for 2-4 weeks (revert to normal dose once calcium level has normalised)
    - Inform patient to call back if new persistent symptoms of hypocalcaemia
    - Recheck serum calcium within one week and repeat the above as necessary (once calcium level returns to normal, maintenance calcium dose can usually be resumed)

If a patient has become significantly hypocalcaemic after receiving denosumab (even if managed in primary care), please inform osteoporosis clinic so that additional investigations can be done as necessary (e.g. checking vitamin D / magnesium / PTH), and advice given on supplements prior to next dose.

**Symptoms of hypocalcaemia

muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes or around the mouth, fits, palpitations.

5. Cautions and contra-indications (see individual SPC for further information):

• Hypocalcaemia

• Hypersensitivity to the active substance or to any of the excipients.

This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be considered.

Adequate calcium & vitamin D intake is important for all patients. Hypocalcaemia and insufficient/deficient serum vitamin D levels must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia. Patients with renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended

for patients predisposed to hypocalcaemia (see monitoring guidelines above). **Patients with advanced chronic kidney disease (e.g. creatinine clearance ≤20ml/min) should generally be reviewed in an osteoporosis clinic prior to being commenced on denosumab.**

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. 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 in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however, some have occurred in patients with osteoporosis. MHRA July 2015 Patient reminder cards about the risk of osteonecrosis of the jaw should be used.

Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (e.g., pre-existing dental disease, anaemia, coagulopathy, infection) and previous treatment with bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible.

Good oral hygiene practices should be maintained during treatment with denosumab. For patients who develop ONJ while on denosumab therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with denosumab, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation.

Atypical femoral fractures have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. 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. During denosumab 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.

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.

Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment (MHRA 2017).

6. Drug interactions

In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolised by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is 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).

7. Adverse effects

Adverse Effect	Action to be taken if detected
• Very common (≥ 1/10): pain in extremity, musculoskeletal pain. • Common (≥ 1/100 to <1/10): Urinary tract infection, Upper respiratory tract infection, sciatica, constipation, rash, eczema. • Uncommon (≥ 1/1,000 to <1/100): Diverticulitis, cellulitis, ear infection. • Rare (≥ 1/10,000 to < 1/1,000): Hypocalcaemia.	• Refer patient back to the specialist if any of these side-effects cause concern.

8. Advice to patients and carers

- Denosumab (Prolia®) patient reminder card (safety information) can be found here: https://www.medicines.org.uk/emc/product/568/rmms

9. Pregnancy & breastfeeding

There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity.

Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. Any effects of denosumab are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, considering the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.

10. Specialist contact information

All 3 local acute trust rheumatology departments should be contacted via Cinapsis ideally.

	Telephone	**E-mail:**
SFT		
Dr Zoe Cole	01722 336262 ext 4791 (secretary)	Zoe.cole@nhs.net
RUH		
Dr Sarah Hardcastle	01225 821644	sarahhardcastle@nhs.net
Dr Tehseen Ahmed	01225 821644	tehseen.ahmed@nhs.net
RUH osteoporosis specialist nurse	01225 826770/01225 824083	Ruh-tr.osteoporosisflscnsteam@nhs.net
Dr Celia Gregson	01225 821267	celia.gregson@nhs.net
Dr Veronica Lyell	01225 821267	v.lyell@nhs.net
GWH		
Dr David Collins	01793 604317 (secretary)	david.collins@nhs.net
Care of the elderly contact details		
GWH		
Dr Nicola Watson	01793 605108 (secretary)	nicola.watson12@nhs.net
Dr Sarah Woods		Sarah.woods6@nhs.net
Dr Sarah White		Sarah.white33@nhs.net
RUH		
Dr Matthew Brown		Matthew.brown28@nhs.net
SFT		
Dr Johnny Drayson	01722336262 ext 2163 (secretary)	Johnny.drayson@nhs.net

Dr Hugo Powell		Hugo.powell@nhs.net

13. References & useful information

- Summary of Product Characteristics for Denosumab (Prolia®) via https://www.medicines.org.uk/emc/product/568/smpc
- BNF online via https://bnf.nice.org.uk/
- NICE TA 204 October 2010. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. https://www.nice.org.uk/Guidance/TA204
- MHRA Drug Safety Update 25/9/14. Denosumab: Updated recommendations. https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations
- MHRA Drug Safety Update 20/7/15. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk - GOV.UK (www.gov.uk)
- MHRA Drug Safety Update 21/6/17. https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal?UNLID=917937221202112311297
- MHRA Drug Safety Update 26/8/20. Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment - GOV.UK (www.gov.uk)

Written by (Author Name, Organisation & Role):	Dr Rachel Hobson, Lead Clinical Effectiveness Pharmacist, NHS BSW ICB
Contributors:	Consultant rheumatologists: Dr Tehseen Ahmed, Dr Sarah Hardcastle (RUH)/Dr Zoe Cole (SFT)/Dr David Collins (GWH)
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