SHARED CARE GUIDELINE

Drug: Denosumab 60mg injection
Indication: treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture

Introduction

Background:

Denosumab (Prolia®)[1] is a human monoclonal IgG2 antibody to the receptor activator of nuclear- κB ligand (RANKL) licensed for the:

1. Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.
2. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Denosumab is also recommended in NICE TA204 within its licensed indication as an option for treatment of osteoporosis in postmenopausal women at increased risk of fractures.[2]

According to the CHMP guideline on the evaluation of medicinal products in the treatment of primary osteoporosis,[3] no WHO definition for osteoporosis exists for men. In clinical practice, the same diagnostic cut-off values for BMD can be applied to men and women since observational studies indicate that the absolute risk of fracture for any given BMD and age is similar in men and women.[4] Epidemiological studies have also shown a similar relationship between BMD and fracture risk in men and in postmenopausal women.[5]

In April 2018, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for denosumab (Prolia) to include treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.[6]

Indications:

1. **Denosumab is recommended within the Lancashire Health Economy for the treatment of osteoporosis in both postmenopausal women and in men at increased risk of fracture providing the following limitations are observed**:

-Primary Prevention

Only in patients at increased risk of fractures:

- who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contraindication to, those treatments **and**
- who have a combination of T-score, age and number of independent clinical risk factors (parental history of hip fracture, alcohol intake of 4 or more units per day, rheumatoid arthritis) for fracture as indicated below:

<u>T-scores (SD) at (or below) which denosumab is recommended when alendronate and risedronate are unsuitable</u>

Age (in years)	Number of Independent Clinical Risk Factors for Fracture		
	0	1	2

Date: February 2019
Date of Review: February 2022

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

-Secondary Prevention

Only in patients at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and risedronate, or have an intolerance of, or a contraindication to, those treatments.

2. Denosumab is recommended within the Lancashire Health Economy for the treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Patients with any of the following clinical features may be considered for treatment with denosumab:

- Upper gastrointestinal abnormalities, including oesophageal stricture, achalasia, abnormalities which delay oesophageal emptying, dysphagia, oesophageal disease (oesophagitis, ulcers, erosions), gastritis, duodenitis, gastric ulcers, previous upper GI surgery.
- Inability to sit or stand upright for at least 30 minutes.
- Renal impairment (eGFR <35ml/min). (Denosumab's SPC states there is no data for patients with eGFR < 30ml/min. Many clinicians are happy to use if eGFR > 20ml/min, provided serum calcium is closely monitored after each injection).
- Concerns about compliance with treatment – may include patients with cognitive impairment.

Hypocalcaemia (adjusted calcium < 2.2mmol/l) is a contraindication to denosumab therapy.

The patient must also meet all the following criteria to be eligible:

- Have a diagnosis of osteoporosis.
- Be calcium and vitamin D replete **(adjusted calcium between 2.2 – 2.6mmol/l and 25(OH) vitamin D > 50nmol/l)**
- Have eGFR $\geq$30mL/min/1.73m^2.

Dose & Administration	**Dose** The recommended dose of denosumab is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Patients must have adequate levels of calcium and vitamin D before treatment is started and must continue to be adequately supplemented with calcium and vitamin D i.e.1g elemental calcium and 20mcg (800IU) vitamin D. No dose adjustment is required in patients with renal impairment. No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (GFR < 30 ml/min). No dose adjustment is required in elderly patients. The safety and efficacy of denosumab have not been studied in patients with hepatic impairment. Denosumab is not recommended in paediatric patients (age < 18) as the safety and efficacy of denosumab in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption. **Method of administration** For subcutaneous use. Administration should be performed by an individual who has been adequately trained in subcutaneous injection techniques. The injection solution should not be used if it contains particles, or is cloudy or discoloured. It must not be mixed with other medicinal products. To avoid discomfort at the site of injection, the pre-filled syringe should be allowed to reach room temperature (up to maximum of 25°C) before injecting slowly. **Storage** Store in a refrigerator between 2°C and 8°C. Once removed from the refrigerator, denosumab **(**Prolia**)** may be stored at room temperature (up to 25°C) for up to 30 days in the original container. It must be used within this 30 days period.
Secondary Care Responsibilities	1. Confirm the diagnosis of osteoporosis. 2. Assess the need for and appropriateness of denosumab, in line with licence and LMMG criteria. 3. Discuss the benefits and side effects of treatment with the patient and provide written information to the patient. 4. Ensure patients are aware that they should report symptoms of hypocalcaemia e.g. paraesthesia (tingling), muscle cramps, carpopedal spasms, tetany & neuromuscular excitability. 5. Perform pre-treatment screening (Serum calcium, 25(OH) Vitamin D, creatinine clearance/ eGFR) NB. Patients with a CrCl <30ml/min are not eligible for treatment under this shared care guidance and would remain under secondary care. 6. If calcium or vitamin D deficiency or insufficiency (30-50nmol/l) identified, the deficiency must be corrected and assurance gained that patient is calcium and vitamin D replete before start of denosumab. Secondary care may treat patients with 25(OH) Vitamin D > 45nmol/l. 7. All patients should be screened for ONJ (osteonecrosis of the jaw) risk factors prior to starting treatment. 8. A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with concomitant risk factors for developing osteonecrosis of the jaw (see contraindications, below). 9. Stop other drugs affecting bone metabolism e.g. bisphosphonates, parathyroid hormone. 10. Prescribe and administer the first injection of denosumab to establish tolerability and assess adverse effects.

	11. Re-check serum calcium within two weeks of the initial dose for those patients predisposed to hypocalcaemia. 12. If patient meets criteria for shared care, write to the patient's GP to ask if they are willing to take part in shared care and forward the patient treatment plan. 13. The consultant will give the patient appropriate advice about dental hygiene and regular dental check-ups. 14. Advise patients or their carers how to recognise signs of cellulitis, osteonecrosis of the jaw (ONJ) and atypical femoral fractures, directing them to seek immediate medical attention if symptoms occur. 15. Promptly inform the GP of any changes in treatment or treatment plan within 14 days. 16. Review the patient at a minimum after five years to assess the need for ongoing therapy. The consultant will ensure that the patient is given the appropriate appointments for secondary care follow up and that defaulters from follow-up are contacted to arrange alternative appointments. If this is not practically possible, the specialist must contact the primary care provider and ensure arrangements for follow-up or re-referral are made. 17. If during treatment the patient then falls outside the criteria for the shared care agreement, the consultant will accept prescribing responsibilities for the patient.
Primary Care Responsibilities	1. Provide the patient with prescriptions for denosumab 60mg injection after the initial minimum 6 months treatment or first injection. 2. Ask the patient to report symptoms of hypocalcaemia e.g. paraesthesia (tingling), muscle cramps, carpopedal spasms, tetany & neuromuscular excitability. 3. Administration should be performed by an individual who is competent or has been trained in the administration of subcutaneous injections. 4. It is important that treatment with denosumab is administered on time every 6 months; timely reminders and repeat appointments will need to be arranged. 5. Provide the patient with prescriptions for calcium and vitamin D supplements. If the patient has previously required high dose vitamin D supplementation, consider a maintenance dose of vitamin D in addition to standard calcium and vitamin D supplementation. 6. Undertake falls risk assessment of patient. 7. Monitor the patient's overall health and well-being and report signs of disease progression to the consultant or the specialist nurse. 8. Arrange ongoing monitoring at the recommended frequencies (see MONITORING below). 9. Where a patient's test results are considered abnormal (see MONITORING below) and the abnormality cannot be corrected using routine measures, either contact the specialist for advice or refer patient back to secondary care and relinquish prescribing responsibility. 10. Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises. 11. Inform consultant if patient declines further treatment. 12. Report any serious suspected adverse events to the MHRA. 13. Advise patients and their carers on how to recognise signs of cellulitis, osteonecrosis of the jaw (ONJ) and atypical femoral fractures, directing them to seek immediate medical attention if symptoms occur. 14. Ensure patient is scheduled for review by secondary care specialist at a minimum after five years to monitor the patient's response to assess the need for ongoing therapy. This may include re-referral to specialist.

Monitoring	**Primary care** • Measure creatinine/ eGFR 1-3 weeks before each denosumab injection to ensure ≥30mLs/min/1.73m^2. • Measure corrected calcium and vitamin D 1-3 weeks before each denosumab injection (denosumab can cause hypocalcaemia usually within the first 6 months of treatment but can also cause late onset of hypocalcaemia). • Patients should be asked to report symptoms of hypocalcaemia e.g. paraesthesia (tingling), muscle cramps, carpopedal spasms, tetany and neuromuscular excitability. Serum calcium should be measured if suspected symptoms occur. • Gain regular assurances of compliance with calcium and vitamin D supplements. • Gain assurances of good oral hygiene and regular dental checks. • Regular falls risk assessments. **Secondary care** • Repeat DXA scan as appropriate; the specialist to advise when the DXA scan should be reviewed. • Re-check serum calcium within two weeks of the initial dose for those patients predisposed to hypocalcaemia. • Review and assess risks and benefits of continued prescribing after 5 years and then at clinically appropriate intervals – GP to be advised.
Adverse Effects	The most common side effects are: - • Infections (urinary tract and upper respiratory tract). • Nervous system disorders (sciatica). • Gastrointestinal disorders (constipation, abdominal discomfort). • Skin and subcutaneous tissue disorders (rash, eczema). • Musculoskeletal and connective tissue disorders (pain in extremities, musculoskeletal pain – very common). In addition: • The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. • Patients receiving denosumab may develop skin infections leading to hospitalisation (predominantly cellulitis). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. • Rarely, patients, may develop hypocalcaemia. • Unlike bisphosphonates, denosumab has no effect on renal function and no increased risk of atrial fibrillation. • Atypical femoral fractures have been reported rarely in patients on long-term (≥2.5 years) treatment with denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Patients should be advised to report any new or unusual thigh, hip or groin pain during treatment with denosumab. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered as part of the evaluation. An individual assessment of the benefits and risks should be performed.[7] **Always consult the latest version of the Summary of Product Characteristics (SPC) at www.medicines.org.uk for full details.**

Common 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 pharmacodynamic interactions is considered to be low. In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy.

Contraindications[2]	**Contraindications**
	
	Denosumab should not be given to patients with:
	• Hypersensitivity to the active substance or to any of the excipients.
	• Hypocalcaemia (adjusted calcium <2.2mmol/l).
	• Rare hereditary problems of fructose intolerance.
	
	Cautions
	
	Caution is advised when prescribing denosumab:
	
	• In severe renal impairment (creatinine clearance < 30 ml/min) or in patients receiving dialysis (because they are at greater risk of developing hypocalcaemia).
	• Hypocalcaemia must be corrected before initiating therapy.
	• Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.
	• Patients being treated with denosumab should not be treated concomitantly with other denosumab-containing medicinal products.
	• With risk* factors for developing osteonecrosis of the jaw (ONJ) – prior dental check recommended to check for risks.
	  ○ While on treatment avoid invasive dental procedures if possible.
	  ○ Good oral hygiene practices should be maintained during treatment.
	  ○ For patients who develop ONJ while on therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment, refer patients to oral surgeon and inform specialist initiating the treatment for advice on further osteoporosis treatment. Do not give any further denosumab injections. The management plan of patients who develop ONJ should be set up in collaboration with the treating physician and a dentist or oral surgeon with expertise in ONJ.
	• Osteonecrosis of the external auditory canal has been reported with denosumab. Patients should be advised to report any ear pain and/or discharge or an ear infection to their GP. The possibility of osteonecrosis of the external auditory canal should also be considered in denosumab treated patients with suspected cholesteatoma.[8] **
	
	*Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck).
	** Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma.

This guidance does not replace the SPC, which should be read in conjunction with this guidance.

RELEVANT CONTACT LIST

The consultant or representative will be available for information or advice to the GP.

Speciality	
Name and Title.	Tel. No.

References

[1] Summary of Product Characteristics, Prolia®, last updated June 2018. https://www.medicines.org.uk/emc/product/568 (accessed online January 2019)
[2] NICE Technology Appraisal Guidance 204, October 2010: Denosumab for the prevention of osteoporotic fractures in postmenopausal women. https://www.nice.org.uk/guidance/ta204
[3] Committee for medicinal products for human use (CHMP), Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis; CPMP/EWP/552/95 Rev. 2; 16 November 2006. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003405.pdf
[4] National Osteoporosis Guideline Group (NOGG) 2017, Clinical guideline for the prevention and treatment of osteoporosis. https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf
[5] EMA/CHMP/267934/2014 Committee for Medicinal Products for Human Use (CHMP) Assessment report Prolia, International non-proprietary name: denosumab http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001120/WC500169764.pdf
[6] European Medicines Agency EMEA/H/C/001120/II/0068. Variation assessment report Prolia, 26 April 2018, accessed on 23 January 2019 at https://www.ema.europa.eu/documents/variation-report/prolia-h-c-1120-ii-0068-epar-assessment-report-variation_en.pdf.
[7] AMGEN UK limited, Direct Healthcare Communication to all Healthcare Professionals, February 13th 2013 “Risk of Atypical Femoral Fractures with Prolia®▼” (denosumab)
[8] MHRA Drug Safety update Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal, 21 June 2017. https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal