Shared Care Guideline (SCG) for Denosumab (Prolia®)

Denosumab (Prolia® 60mg solution for injection in pre-filled syringe

Executive Summary/ Critical Information.

Indication	Route & Dose	Key aims of treatment in the long term	Monitoring undertaken by specialist before requesting shared care	Ongoing monitoring to be undertaken by GP	Duration of treatment	Stopping criteria (advice should be sought from the specialist rheumatology team in the event that any of these occur as specialist review/re-referral may be necessary)	Follow up (weeks/ months)
Treatment of osteoporosis in post- menopausal women at increased risk of fractures (in line with NICE TA 204)	60mg subcut into thigh, abdomen or upper arm every 6 months	Significantly reduce the risk of vertebral, non-vertebral and hip fractures Treatment of bone loss associated with long – term systemic glucocorticoid therapy	FBC, LFTs, U&Es Bone profile, calcium and vitamin D levels (and supplementation as necessary prior to 1st dose denosumab) DEXA scanning as indicated FRAX scores Assessment to determine if dental examination required prior to initiation of therapy PLEASE NOTE – FIRST DOSE WILL BE GIVEN BY SPECIALIST TEAM	Safety blood monitoring - FBC, LFTs, U&Es – every 6 months (before each dose) Bone profile, calcium and vitamin D levels – every 6 months (before each dose) GP to supplement calcium and vitamin D as required	Up to 10 years (specialist will review after each 3 - 5 year period with DEXA and determine if should continue, if yes, GP can continue treatment for up to 10 years)	Hypocalcaemia and / or low vitamin D levels persistently (i.e. refractory / unable to correct with usual supplementation) Significant / unmanageable side effects Pregnancy and breast feeding Osteonecrosis of the jaw (ONJ) or external auditory canal New diverticulitis Severe skin infections / cellulitis Worsening renal / hepatic impairment New fractures (including atypical femoral fractures) Patient choosing to discontinue treatment	Specialist - 3 - 5 years GP – every 6 months

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Key Safety Notice (for instance: notification if prescribing must be brand specific or BNF cautionary and advisory warnings).
Prescribe as Prolia® brand (currently the only brand available for the indication(s) specified in this SCG but will likely be biosimilar versions available in future). **Increased risk of ONJ with denosumab treatment - Patients should counselled to immediately report oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge and be referred for dental assessment as necessary. This should be done before initiating treatment by the specialist team and reiterated by the GP as necessary. Patients will also be given a "Patient Reminder Card" from Prolia® manufacturer, Amgen. Specialist advice should be sought if ONJ suspected or confirmed and discontinuation of denosumab considered.** **Increased risk of osteonecrosis of the external auditory canal with denosumab treatment – Patients should be counselled to report any symptoms such as ear pain, discharge from the ear, ear infections or hearing changes whilst taking denosumab and specialist advice should be sought and discontinuation considered.** **Risk of atypical femoral fracture increased with denosumab treatment – If suspected then specialist advice should be sought and discontinuation considered.** **The needle cover of the pre-filled syringe of Prolia® contains dry natural rubber (a derivative of latex), which may cause allergic reactions.**
Exclusion criteria (note, these exclusion criteria relate to this SCG only, patients may still be able to receive denosumab treatment in secondary/tertiary care centres)
Patients who do not meet criteria specified in NICE TA 204 **Patients with severe renal impairment (CrCl <30ml/min) or on dialysis** **Patients with active cancer or receiving treatment for cancer** **Patients who are pregnant or breastfeeding** **Paediatric patients (i.e. <18 years old)**
Other
The specialist rheumatology team will give the first dose of denosumab and then GP to continue as per this SCG. **The specialist rheumatology team should be contacted for advice regarding calcium and vitamin D supplementation if required for refractory cases.**

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All drug-specific information for questions 1-7 is as per the Prolia® Summary of Product Characteristics (SPC). Full details can be found at: https://www.medicines.org.uk/emc/product/568/smpc .

1. Background

Denosumab is a human monoclonal antibody (IgG2) licensed for the treatment of osteoporosis in postmenopausal women (and in men at increased risk of fractures). It is also licensed for prevention of bone loss in patients receiving systemic glucocorticoid therapy (and in men receiving hormone treatment for prostate cancer but this will not be discussed here). It acts by preventing activation of RANK receptors on osteoclasts (and osteoclast precursors)

Currently denosumab prescribing is undertaken completely in a secondary / tertiary care environment and the purpose of this SCG is to provide a tool for primary care practitioners / clinicians to enable them to undertake routine prescribe of denosumab for patients identified as suitable by specialist rheumatology clinicians.

2. Important information

Prescribe as Prolia® brand only. In the event that a more cost-effective "biosimilar" agent becomes available then this will need to be re-addressed.

Monitoring requirements and referral criteria as documented in table(s) above.

3. Drug name, form, and licensed indications

Prolia® 60 mg/1 ml solution for subcutaneous injection in pre-filled syringe.

Licensed indications:

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

This SCG covers only "Treatment of osteoporosis in postmenopausal women at increased risk of fracture" in line with NICE TA 204.

4. Dose and Administration

It is recommended that 60 mg denosumab (Prolia®) be administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

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5. Contraindications/Cautions

Cautions:

- Hypocalcaemia – Must be corrected (with appropriate calcium and vitamin D supplementation) prior to initiation of denosumab treatment and should continue to be monitored and supplemented throughout treatment with denosumab as needed.
- Renal impairment – Patients with severe renal impairment (CrCl <30 ml/min) are at increased risk of hypocalcaemia when taking denosumab. These patients are excluded from this SCG.
- Skin infections – Denosumab usage has been linked to skin infections. Patients should be advised to seek medical advice / assistance if they develop and signs or symptoms of cellulitis.
- Osteonecrosis of the jaw (ONJ) – Denosumab use as been linked with ONJ - dental examination may be required prior to initiation of treatment and at regular intervals throughout treatment.
- Osteonecrosis of the external auditory canal – Caution in patients with ear symptoms including recurrent infections.
- Atypical femur fractures – Specialist team should review suitability of continuation of denosumab if patient presents with atypical fracture(s) of the femur.
- Long-term denosumab usage can lead to increased risk of adverse events – Suitability of continuation of treatment should be regularly reviewed.
- The needle cover for Prolia® contains dry natural rubber (latex derivative) – Caution should be exercised before prescribing to patients with latex allergies
- Concomitant treatment with other denosumab-containing products should be avoided.
- Contains 47mg sorbitol in each 1 mls of injection, dietary intake of sorbitol (or fructose) should be taken into account.

Contraindications:

- Hypersensitivity to active ingredient or excipient
- Hypocalcaemia (untreated)

For complete list and full details of contraindications and cautions, please refer to the SPC: https://www.medicines.org.uk/emc.

6. Drug interactions

Nil specific drug interactions. For full details, please refer to the SPC: https://www.medicines.org.uk/emc.

Denosumab can cause hypocalcaemia and so co-administration with other medications that that may reduce serum calcium levels should be avoided.

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7. Side effects which require managing

The table below has been adapted from the SPC for Prolia® (available at: https://www.medicines.org.uk/emc).
The following frequency classification has been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Please see section 8 for guidance around situations where advice may need to be sought from secondary care/specialist team.

edDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common Common Uncommon Uncommon Uncommon	Urinary tract infection Upper respiratory tract infection Diverticulitis Cellulitis Ear infection
Immune system disorders	Rare Rare	Drug hypersensitivity Anaphylactic reaction
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]
Nervous system disorders	Common	Sciatica
Gastrointestinal disorders	Common Common	Constipation Abdominal discomfort
Skin and subcutaneous tissue disorders	Common Common Common Uncommon	Rash Eczema Alopecia Lichenoid drug eruptions
Musculoskeletal and connective tissue disorders	Very common Very common Rare Rare Not Known	Pain in extremity Musculoskeletal pain Osteonecrosis of the jaw Atypical femoral fractures Osteonecrosis of the external auditory canal

8. Process for Referral Back to (or to Seek Advice From) Secondary Care

Patient will be reviewed by specialist rheumatology team after 3 - 5 years and so formal re-referral is not necessary. The rheumatology specialist team can be contacted using the details provided below for advice or if an additional review or appointment is required. Some specific situations in which seeking specialist advice required / prescribing denosumab in primary care may no longer be appropriate:

Hypocalcaemia and / or low vitamin D levels persistently (i.e. refractory / unable to correct with usual supplementation)

Significant / unmanageable side effects (see section 7 and SPC for full list of potential side effects)

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Pregnancy and breast feeding

Osteonecrosis of the jaw (note – may need to be referred for dental assessment if develops oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. If dentist concerned regarding continuing denosumab following assessment then seek specialist advice).

Osteonecrosis of the auditory canal

New diverticulitis

Severe skin infections /cellulitis

Worsening renal / hepatic impairment

CrCl <30ml/min

New fractures

Patient choosing to discontinue treatment

9. Monitoring and Responsibilities

a. Hospital specialist:

- To assess the suitability of the patient for denosumab (including performing initial DEXA scan as indicated) & give the first dose.
- To discuss the benefits and side effects of treatment with the patient, including guidance over dental surgery, ensuring that the patient / carer is an informed recipient in therapy.
- Ensure baseline investigations are normal before commencing treatment (including initiating supplementation of vitamin D and calcium prior to commencement if required).
- Explain to the patient that the treatment is 6 monthly injections for 3 - 5 years (they will then be reviewed and may continue for up to 10 years total).
- Discuss the shared care arrangement with the patient and ensure he / she understands the plan for their follow-up 6 monthly injections at their GP surgery.
- Explain to the patient that they will be recalled for follow-up in the osteoporosis clinic after 3 - 5 years (and will likely have a repeat DEXA at that time)
- Send a letter to the GP requesting shared care for this patient.
- Assess the patient to ensure he / she has good oral hygiene and use clinical judgement to determine if dental examination is required prior to initiating therapy.
- Counsel patients to immediately report oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge so that they can be referred for dental assessment as necessary.
- Supply patient with “Patient Reminder Card” from Prolia® manufacturer, Amgen.
- Evaluation of any reported adverse effects by GP or patient.
- Report any adverse events to the MHRA.
- Supply GP with a summary of the patient review and a copy of the local guidelines on use of denosumab.
- Ensure that backup advice is available at all times.
- Identify patients that require monitoring for hypocalcaemia.

b. General Practitioner:

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- Reinforce the patients understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate, including guidance over dental surgery.
- Monitor patient's overall health and well-being.
- To ensure that denosumab is added to the patient's drug record.
- To ensure that other osteoporosis treatments (e.g. alendronate, strontium) are stopped and removed from the patient's repeat prescription.
- To ensure that calcium and vitamin D supplements are continued if appropriate.
- To ensure 6-monthly blood test monitoring (FBC, U&Es, LFTs, vitamin D, calcium, bone profile)
- Ensure that prior to injection the denosumab prefilled syringe must be kept in its outer carton, in order to protect from light, and stored in a refrigerator.
- Prescribe and administer the denosumab injection at six monthly intervals for time period as specified by the initiating specialist.
- Report any adverse events to the MHRA and discuss with the consultant if action is uncertain.
- Refer back to specialist if any concerns

c. Patient or parent/carer:

- Compliance with blood monitoring
- Regular 6 monthly dental checks and good oral hygiene
- Compliance with calcium and vitamin D supplements as recommended and / or prescribed
- Reporting of side effects and new symptoms
- Keeping active as per government lifestyle guidelines
- To attend for their injections

10. Contact Information

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11. References

https://www.medicines.org.uk/emc/product/568/smpc

NICE TA 204 Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Technology appraisal guidance Published: 27 October 2010 (available at: https://www.nice.org.uk/guidance/ta204/resources/denosumab-for-the-prevention-of-osteoporotic-fractures-in-postmenopausal-women-pdf-82600189194949)

12. Document Management

Document ratification and history	
Produced by:	Barts Health NHS Trust
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Approved by:	Waltham Forest and East London Medicines Optimisation and Commissioning Committee (WELMOCC)
Date approved:	24/03/2021
Ratified by:	Barts Health Drugs and Therapeutics Committee
Date ratified:	07/04/2021
Review date:	3 years - or sooner if evidence or practice changes
Obsolete date:	March 2024
Version number:	1.2 (version 1.1 updated 12/02/2021)

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Appendix 1.

Shared Care Guideline: Prescribing Agreement	
Section A: To be completed by the hospital consultant initiating the treatment	
GP Practice Details: Name: Tel No: Email (nhs.net):	**Patient Details:** Name: DOB: NHS Number (10 digits):
Consultant Details: Consultant Name: Secretary Contact Details: Tel No: Email (nhs.net):	
Diagnosis:	**Drug Name (to be prescribed by GP):** **Dose:** **Frequency:**
I will review the patient in clinic in weeks / months (*Delete as appropriate)*.	

Dear

Your patient started treatment with the above drug for the above diagnosis on (insert date) and in my view; his/her condition is now stable.

The patient has given consent to treatment under a shared care prescribing agreement and has agreed to comply with instructions and follow up requirements.

I am requesting your agreement to sharing the care of this patient from (insert date) in accordance with the attached Shared Care Prescribing Guideline.

This patient was reviewed on (insert date). These are the results relevant for the drug and/or condition, as outlined in the shared care document:

Test	Baseline	Date

Please continue to monitor the patient as outlined in the shared care guidelines. Refer to the attached guidelines for monitoring criteria.

Other relevant information:

Consultant Signature:	Date:

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above [If returned via e-mail, use NHS.net email account ONLY]

Please sign and return your agreement to shared care within 14 days of receiving this request.

☐ Yes, I accept sharing care as per shared care prescribing guideline.

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☐ No, I am not willing to undertake shared care for this patient for the following reason: (Please give reason)		
GP Name:	GP Signature:	Date:

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