Working in partnership

SHARED CARE PRESCRIBING GUIDELINE

Denosumab (Prolia®) For The Treatment Of Osteoporosis In Post-Menopausal Women And Adult Males At Increased Risk Of Fractures

NOTES to the GP

The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing this drug.

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility and reply to specialist request to share patient's care as soon as possible.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with the appropriate Milton Keynes Hospital specialist service, who will be willing to provide training and support.

The overall clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

"Shared care" occurs when a secondary care specialist retains a responsibility for the on-going monitoring or review of a patient after the point in time when they consider it clinically appropriate for the patient's General Practitioner (GP) to take over the responsibility of routine prescribing. This usually only applies to long-term treatment with drugs that are not part of most GPs' routine practice.

Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.

Patients will only be referred to the GP once the GP has agreed in each individual case and the hospital will continue to provide prescriptions until successful transfer of responsibilities
The patient's best interests are always paramount.

Approved by (date approved): Milton Keynes Prescribing Advisory Group – MKPAG (May 2017)
Original Authors: Dr. Anne Jenkins and Debbie Morrison
Review Author: This updated guidance has been reproduced by Dupe Fagbenro, Principal Pharmacist, Formulary Services and Prescribing Advisory Lead in collaboration Dr Anne Jenkins. It has been subject to consultation and endorsement by MKPAG.

Introduction and reason for shared care

This shared care guideline outlines the sharing of responsibilities between secondary care specialists, primary care clinicians (GPs) and the patient/carer where appropriate and covers the use of Denosumab for:

- Treatment of osteoporosis in postmenopausal women at increased risk of fractures as specified within NICE TA 204 guidance. **And**
- Treatment of osteoporosis in men aged 50 years and over for secondary prevention, where alendronate and risedronate have been tried and not tolerated or are contra-indicated.

Criteria for Use
Denosumab has been approved by NICE - TA 204

Primary Prevention
Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures:

- who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, 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 for fracture as indicated in the following table.

T-scores at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

Age (years)	**Number of independent clinical risk factors for fracture**		
	0	1	2
65-69	Treatment with denosumab is not recommended	-4.5	-4.0
70-74	-4.5	-4.0	-3.5
75 and older	-4.0	-4.0	-3.0

For the purposes of this guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

Secondary Prevention
Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in

A) **Postmenopausal women** at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments.

B) **Men** with osteoporosis over the age of 50 who have had a fragility fracture and a diagnosis of osteoporosis only when alendronate and risedronate have been tried and not tolerated or are contra-indicated, according to the same criteria as for women.

Important Clinical Information For All Prescribers
PROLIA® - Denosumab for the Prevention of Osteoporotic Fractures

Denosumab (Prolia®)
The initial injection of denosumab should be prescribed and administered by a secondary care specialist. If the patient is subsequently stable and free from adverse reactions, care can be transferred to the primary care clinician who may administer the second and subsequent injections.

Missing an injection by more than 2 weeks (before or after that 6-month target date) can lead to increased risk of osteoporotic fracture. **Due to the potential reduction in BMD with cessation of denosumab, the dosing frequency of every six months plus or minus two weeks needs to be maintained.** Treatment effect reverses rapidly, so NOT suitable for 'drug holidays' as can be considered for bisphosphonate treatment

The manufacturer therefore offers a patient-reminder system called Prolong. Details of how patients can register for Prolong support are in the Prolia® packs.

Not to be administered to patients with a known latex allergy

1. AREAS OF RESPONSIBILITY

Consultant

1. To discuss treatment options with the patient and ensure that the patient is suitable for treatment with denosumab according to NICE guideline and local agreement.

2. Provide the first dose, monitor the patient's response to the drug and when assessed as suitable for GP prescribing, request the sharing of care with the GP.

3. Secondary care specialist to confirm absence of:
   a) **Hypocalcaemia** must be corrected by ensuring adequate intake of calcium and vitamin D (serum 250H vitamin D level of greater than 50nmol/L) before initiating therapy. Patients with severe renal impairment (eGFR < 30 ml/min) or receiving dialysis or vitamin D deficient are at greater risk of developing hypocalcaemia and, only in these patients, clinical monitoring of calcium levels two weeks after injection is recommended. Calcium and Vitamin D supplementation: Adequate intake of calcium (> 800 mg/day) and vitamin D from diet or supplements is important in all patients.
   b) **Hypersensitivity** to the active substance or to any of its excipients e.g. fructose
   c) **Pregnancy, lactation, latex allergy** (the needle cover on the pre-filled syringe contains a derivative of latex).
   d) **Severe renal impairment**

4. **Baseline renal function (eGFR**) prior to initiation of denosumab. Obtain patient's baseline renal function (eGFR) prior to initiation of denosumab. Confirm absence of severe renal failure, i.e. where eGFR is <30 ml/min. No dose adjustment is required in patients with renal impairment (SPC).

5. **Oral Hygiene**. Specialist to assess the patient to ensure that he / she has good oral hygiene and to use clinical judgment to determine if a dental examination is required prior to initiating denosumab.

6. Discuss the benefits and possible common and uncommon **side-effects** of treatment.

Please discuss the importance of notifying the doctor immediately if the patient develops a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), possibly with symptoms of fever.

7. **Compliance**: Ensure the patient understands the importance of compliance and the potential detriment from non-compliance.

8. Prior to Initiation: Secondary-care specialist to inform the GP that a shared care guideline (SCG) is available and to send a copy of the SCG with a request to share care.

9. Initiation: Secondary care specialist to initiate first denosumab injection and discuss the shared care arrangement with the patient and ensure he/she understands the plans for follow-up care. This should be documented in the patient's notes.

10. Medicine Information on Prolia is provided to patient, including advice to register for Prolong reminder service

11. On-going treatment: Ensure that the GP understands the rationale for subsequent doses of denosumab to be given within two weeks either side of the 6 month subsequent treatment date. Secondary care to write to both the patient and their GP to notify them of the date window for the next (i.e. second) injection and to advise GP to check serum adjusted calcium and vitamin D are normal and eGFR is > 30 ml/min within the 4 weeks before each injection.

Ensure that the patient is encouraged to enrol in the PROLONG Patient Support programme online,by post or fax to access further support and to ensure that they are reminded when their next injection is due.

12. Adverse Events. Secondary care specialist to report any adverse events to the MHRA http://yellowcard.mhra.gov.uk/. Prolia® is a black triangle product.

13. Changes to treatment. Secondary care specialist to communicate promptly (within 14 days of patient appointment) in writing/by e-mail with the GP when/if treatment is changed.

14. Review of treatment. Secondary care specialist to review patient at 5 years (after 10 doses) to assess the need to continue treatment or sooner if GP has concerns.

GP

1. Prior to accepting the patient for shared care, discuss the patient's management should there be a need for denosumab to be discontinued. Once it has been confirmed that treatment is to continue the GP practice to identify and confirm who will be responsible for administering the denosumab injection i.e. the GP or nurse, and that they are familiar with the SPC requirements for administration.
2. Ensure the patient knows to respond in a timely manner to recall for appointment for checking of blood before each injection and for administration of denosumab to ensure it is received at a six monthly interval +/- 2 weeks. Monitor patient's compliance with ALL oral treatment
3. GP to take following actions in the following timely manner

Month 1

- Encourage/support patient to register for the Prolia reminder service (referred to as "Prolong Patient Support Programme"). Prolong registration form can be found here: http://prolia.snapwebsitepreview.com/wp-content/uploads/2014/08/Prolong-Registration-Form.pdf

- Add Prolia (Denosumab 60mg) every 6 months to patient record
- Ensure that repeat prescriptions for bisphosphonates are stopped, but calcium/vitamin D remain on repeat as advised by the hospital
- Practice arrangements to be made to ensure that denosumab is stored in a vaccine refrigerator and the temperature monitored daily.
- Practices are advised to use a robust recall system to ensure patients receive timely treatment

Month 5 (and every 5 months from the date of the last injection)

Ensure patient has an appointment booked for the following 3 blood tests in preparation for second and subsequent injections in the practice:

A. Adjusted calcium levels

IF serum calcium below normal, supplement with calcium and vitamin D for 4 weeks then re-test

B. 25OH vitamin D

IF serum vitamin D below 50nmol/L, but calcium normal, load as appropriate according to clinical guideline for management of vitamin D deficiency (which is appended to the SCG) then recall patient for re-test at 4 weeks.
IF levels remain below normal check compliance with therapy and seek advice on further treatment of risk factors for osteoporotic fracture

C. eGFR

IF patient has an eGFR <30ml/min/1.73m² measured 4 weeks before repeat injection, DO NOT GIVE Prolia (Denosumab 60mg) and REFER to hospital rheumatologist for review

Month 6 (and every 6 months from the date of the last injection)

- Treatment needs to be given within a one-month window around each 6-month time point i.e. (+/- 2 weeks)
- Check calcium and vitamin D levels and eGFR are within normal range for ALL patients before each dose
- Check patient is taking calcium and vitamin D as advised by hospital and practice
- Confirm with patient that they are aware of potential adverse reactions to report to the practice.
- IN ALL PATIENTS ON DENOSUMAB - Check for new or unusual symptoms of hip, thigh or groin pain. If present, consider whether evaluation is required to look for atypical femoral fracture.
- Batch number administered and injection site used to be recorded in the patient's notes. Calcium must be normal, ADMINISTER SC INJECTION
- Check renal function and calcium levels 2 weeks after injection

Useful sources of information for prescriber

Prolia® Summary of Product Characteristics - http://www.medicines.org.uk/emc/medicine/23127
Prolia® Patient Information Leaflet available from pack
Prolia® Patient Information Leaflet available available online. You can download a copy from http://www.medicines.org.uk/emc/PIL.23128.latest.pdf

- GP to make arrangements to contact the secondary care specialist if patients discontinue denosumab or are lost to follow-up.
- GP to report any adverse events to the MHRA http://yellowcard.mhra.gov.uk/ Denosumab is a black triangle product.

Patient's role (or that of carer)

1. Report to the specialist or GP if patient does not have a clear understanding of the treatment.
2. Patient to immediately report any adverse events to the doctor who last administered denosumab, particularly if patient develops a swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis); symptoms of fever, muscle aches, dizziness and any dental problems.
3. Patient to notify the GP or secondary care specialist if he/she:

- has an allergy to latex
- has ever had severe kidney problems, kidney failure or has needed dialysis
- has cancer, is undergoing chemotherapy or radiotherapy,
- is taking steroids,
- is pregnant, thinks they may be pregnant, or is planning to get pregnant. (Also, if they are breast-feeding or planning to do so.)

4. Patient to present rapidly to the GP or secondary care specialist should their condition significantly worsen or they experience any adverse reactions.
5. Patient to inform GP if they do not receive routine dental care, or have gum disease. Patient to maintain good oral hygiene. If currently under dental treatment or planning to undergo dental surgery, the patient should tell the dentist that they are being treated with denosumab.
6. Patient to take adequate calcium and vitamin D supplements, as appropriate, to ensure they are replete.
7. Patient to make appropriate appointments with GP: for a blood test 1 month BEFORE the injection (calcium, eGFR and vitamin D), AND for the 6 monthly injections. Only if kidney function (eGFR) is <30ml/min, the patient will also need a blood test 2 weeks **after** the injection (for calcium, eGFR) as well.

COMMUNICATION AND SUPPORT

Hospital contacts:	**Out of hours contacts & procedures:**
Dr Ioanna Papadaki - Consultant Rheumatologist Rheumatologist Tel: 01908 996601 E-mail: Ioanna.Papadaki@mkuh.nhs.uk	Accident and Emergency

Specialist support/resources available to GP including patient information:

1. Prolia® Summary of Product Characteristics - http://www.medicines.org.uk/emc/medicine/23127
2. Prolia® Patient Information Leaflet available from pack
3. Prolia® Patient Information Leaflet available available online. You can download a copy from http://www.medicines.org.uk/emc/PIL.23128.latest.pdf

CLINICAL INFORMATION

Indication(s):	Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Place in Therapy:	Please see details on page 2 of this document
Therapeutic summary:	Denosumab is a monoclonal antibody drug for the treatment of osteoporosis in limited circumstances.
Dose & route of administration:	Denosumab is administered as a single subcutaneous injection into the thigh, abdomen or back of the arm. The recommended dosage is 60 mg once every 6 months (twice a year) by sub-cutaneous injection. It is important that patients receive their 6 monthly injection in a timely manner, preferably within 2 weeks of the due date either side. Denosumab should be administered by an individual who has been adequately trained in sub-cutaneous injection technique. There is a potential for rebound bone loss if the injection is delayed more than this and so patients who discontinue or are lost to follow up should be alerted to the osteoporosis secondary care specialist where appropriate.
Duration of treatment:	Review of treatment: • Current guidance supports prescribing for up to 5 years. • Secondary care specialist to review patient at 5 years (after 10 doses) to assess the need to continue treatment or sooner if GP has concerns.
Preparations available (Manufacturer)	Prolia 60 mg solution for injection in a pre-filled syringe By Amgen Limited
	NB: There is an alternative denosumab product, XGEVA® used for the prevention of skeletal related events in adults with bone metastases from solid tumours. This product is **not** covered by this shared care guideline.
Adverse effects	See summary of product characteristics (SPC) for full list https://www.medicines.org.uk/emc/medicine/23127#UNDESIRABLE_EFFECTS

Monitoring
Patients with severe renal impairment (eGFR < 30ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia.
Clinical monitoring of calcium levels is recommended for patients pre-disposed to hypocalcaemia.

Timing of Interventions in relation to date of denosumab injection	Monitoring	Responsible Clinician
-4 weeks **Month 5 (and every 5 months from the date of the last injection)**	In all patients 1. Adjusted serum calcium level 2. 25OH vitamin D 3. eGFR - patients with an GFR<30ml/min measured at -4 weeks should be referred to secondary care and not given	GP

	denosumab.	
0 **Month 6 (and every 6 months from the date of the last injection)**	Denosumab given – assess for ADRs	GP/ Nurse
+ 2 weeks	Calcium level (only in those with an eGFR of 15-30 ml/min) & creatinine clearance <30ml/min)	GP/ Nurse
Yearly	Routine follow-up with specialist to assess for suitability for continuation	Specialist

Clinically relevant drug interactions:	Interaction with other medicinal products and other forms of interaction Access up-to-date SPC information here
Clinically relevant Precautions and Contraindications:	**Special warnings and precautions** ***Skin infection*** 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. ***Calcium and vitamin D supplementation*** Adequate intake of calcium and vitamin D is important in all patients. ***Hypocalcaemia*** Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (eGFR < 30ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia. Monitoring of calcium and vitamin D status to be undertaken in accordance with local guidelines/practice in patients with severe renal impairment. ***Osteonecrosis of the jaw (ONJ)*** ONJ has been reported in patients treated with denosumab The risk of ONJ increases with increasing duration of treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with denosumab in patients with concomitant risk factors. Whilst on treatment, these patients should avoid invasive dental procedures unless necessary.

	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, refer to secondary care specialist. ***Osteonecrosis of the external auditory canal*** 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
Practical issues: **Source of denosumab in primary care**	There are two ways in which denosumab can be sourced in primary care. **Practices are encouraged to order this themselves rather than issue an FP10.** **1)** A GP practice can have an account with Movianto and orders can be placed by telephone, fax or e-mail. Telephone: 01234 248631 Fax: 01234 248705 E-mail: orders.uk@movianto.com If a GP practice is a new customer an account can be set up by telephoning the number above. Denosumab (Prolia®) will be delivered within 24 hours via refrigerated vehicles to the premises free of charge. The cut-off time for orders is 16:30 hours Monday to Friday. Product Code: 900320 Stock is then held at the surgery until required. Alternatively **2)** The patient can receive the drug from a Community Pharmacy through an FP10 written by the GP. Patients are likely to have to return to the pharmacy after 2 working days to collect the injection, as most pharmacies will not stock this drug, as patient numbers will be small. Please note: Store denosumab 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, denosumab must be used within this 30 day period.

Key references:

1. SPC. Prolia®. December 2016. Available at: https://www.medicines.org.uk/emc/medicine/23127 Accessed <15.05.17>
2. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. Available at: https://www.nice.org.uk/guidance/ta204 Accessed <15.05.17>
3. MHRA Drug Safety Update. Denosumab: monitoring recommended. October 2012; Available at: https://www.gov.uk/drug-safety-update/denosumab-monitoring-recommended Accessed <15.05.17>
4. MHRA Drug Safety Update. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk. July 2015; Available at: https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk Accessed <15.05.17>
5. BNF 2017 May 2017. Available at: www.bnf.org.uk Accessed <15.05.17>

Shared Care Guideline: Denosumab Prescribing Agreement
(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)

Section A: To be completed by the hospital consultant initiating the treatment

GP Practice Details: Name: …… Address: …… Tel no: …… Fax no: …… NHS.net e-mail: ……	**Patient Details:** Name: …… Address: …… DOB: ……/……/…… Hospital number: …… NHS number (10 digits): ……

Consultant name: ……..; **Clinic name:** ……
Contact details:
Address: .....
Tel no: …… NHS.net e-mail: ……

Diagnosis: Osteoporosis	**Drug name & dose to be prescribed by GP:** Denosumab (Prolia®) 60 mg, administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm..

Next hospital appointment: ……/……/……..

Dear Dr. ……..,

Your patient was seen on …../…../……and I have started Denosumab injection for the above diagnosis.
Denosumab is to be administered as a single subcutaneous injection into the thigh, abdomen or back of the arm. The recommended dosage is 60 mg once every 6 months (twice a year). It is important that patients receive their 6 monthly injection in a timely manner, preferably within 2 weeks of the due date either side.
The date the patient received their first injection was: ……;
The next injection is due on …….

I am requesting your agreement to sharing the care of this patient from …../…../…….. in accordance with the (attached) Shared Care Guideline.
Please take particular note of Section 2 where the areas of responsibilities for the consultant, GP and patient for this shared care arrangement are detailed.

Patient information has been given outlining potential aims and side effects of this treatment.

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

Letter has been sent to GP, copied to patient, with date of first injection and results of baseline tests. Please carry out further monitoring as detailed on page 7.

Thank you and kind regards

Consultant Signature: ……Date: ……/……/……...

Section B: To be completed by the GP and returned to the hospital consultant as detailed in Section A above
Please sign and return your agreement to shared care within 14 days of receiving this request Tick which applies: □ I accept sharing care as per shared care prescribing guideline and above instructions □ I would like further information. Please contact me on:……. □ I am not willing to undertake shared care for this patient for the following reason: ……. GP name: ……..……. GP signature: …… Date: …/…/…..

(Note: Sections A and B MUST be forwarded to GP and returned by GP back to the hospital together)