Guidelines for the initiation and on-going treatment of osteoporosis in men and postmenopausal women with denosumab

Denosumab (Prolia®) is a monoclonal antibody drug indicated for the treatment of osteoporosis in men and postmenopausal women at increased risk of fractures, administered as a 6-monthly subcutaneous injection.

Indications for Denosumab

1. Secondary prevention of osteoporotic fractures in men and post-menopausal women who
   - are unable to comply with the special instructions for administering alendronic acid and risedronate OR
   - 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.'* **Treatment is not recommended for patients who have failed (i.e. have subsequent fractures) or had an unsatisfactory response on previous treatment with other agents i.e. bisphosphonates**. Alendronic acid remains the first line treatment for the prevention of osteoporotic fragility fractures in men and postmenopausal women.

See also Treatment Algorithm for Secondary Prevention of Osteoporosis

2. Primary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with or are intolerant of or have a contra-indication to alendronic acid and risedronate, and have a of T-score and risk factors for fracture as indicated in the following table:

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69		-4.5	-4.0
70–74	-4.5	-4.0	-3.5
75 or older	-4.0	-4.0	-3.0

Use the T scores at either lumbar spine or hip DXA for denosumab.
Clinical risk factors: parental history of hip fracture, alcohol intake of 4 or more units per day, rheumatoid arthritis

Treatment with denosumab may be initiated in either primary or secondary care; if initiated in secondary care the initiating clinician should ensure the GP is informed to ensure on-going prescribing.

Responsibilities of clinician initiating treatment

1. Ensure the patient meets the criteria for treatment with denosumab by checking full details of patient's medical records and medication history (i.e. G.P. records)
2. Discuss benefits and side effects of treatment with the patient and provide patient information leaflet (PIL) on denosumab (Manufacturers patient information leaflet) and the **patient reminder card** **about the risk of osteonecrosis of the jaw (ONJ), whilst explaining the risk of ONJ and advice on precautions to take**.
3. Assess the patient to ensure they have good oral hygiene and consider dental examination for patients with concomitant risk factors (*see prescribing information*).
4. In the last 4 weeks check:
   a. eGFR>30ml/min
   b. normal serum calcium

- Patients should stop any calcium and Vitamin D supplement
- Start Vitamin D loading dose (*see Appendix A*). If initiated in secondary care the full supply should be supplied by Worcestershire Acute Hospitals NHS Trust.
- If hypocalcaemia, hypercalcaemia or eGFR <30ml/min discuss with secondary care before proceeding.

5. Four weeks after starting Vitamin D loading dose, initiate the first dose of treatment with denosumab injection and ensure that the patient understands the plan for follow-up care.
6. Start or advise patient to recommence calcium and Vitamin D supplementation at the end of the chosen Vitamin D loading regimen (*see Appendix A*).
7. In patients with eGFR <35ml/min, check calcium two weeks after denosumab injection.
8. Ensure that arrangements for continued prescribing are in place for denosumab and calcium and Vitamin D supplementation.

Responsibilities of clinician prescribing on-going denosumab treatment

1. Monitoring of calcium levels should be conducted:
    - prior to each dose
    - if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient.
2. Check patient is taking calcium and vitamin D supplementation regularly.
3. Ensure a system is in place to recall the patient after six months. GPs may wish to see Guide to adding denosumab to EMIS web.
4. Prescribe and administer denosumab at the dose recommended, at six monthly intervals after initial administration. See prescribing information below for details of ordering and administration.
5. Ensure good oral hygiene and routine dental check-ups are being maintained.
6. GPs who are providing on-going treatment should report to, and seek advice from, the specialist on any aspect of patient care that is of concern and may affect treatment.
7. GPs who are providing on-going care should refer back to specialist if the patient's condition deteriorates.
8. Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
9. If denosumab is to be **administered** by another practitioner complete, checklist in **Appendix B** and attach to referral to request administration.

Responsibilities of the 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 including oral symptoms (e.g. dental mobility, pain or swelling) or symptoms of hypocalcaemia whilst on treatment with denosumab.
3. Adhere to any calcium and vitamin D treatment prescribed.
4. Inform specialist or GP of any medication being taken, including over-the-counter products.
5. Ensure good oral hygiene practices are maintained and routine dental check-ups are received.

This information should be read in conjunction with the current BNF and manufacturer's SPC.

Licensed indications
Treatment of osteoporosis in men and postmenopausal women at increased risk of fractures.
(*Also licensed for bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures - not covered by this guideline*).

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. Please see Denosumab training guide for how to administer
If training is required on administering the injection please contact the current Amgen local representative Richard Hudson on 07852 574322 or Amgen Ltd. on 01223 420305.

Storage
Denosumab has a shelf life of 36 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 denosumab (Prolia®) can be sourced in Primary Care:

1. A GP practice can have an account with Movianto and orders placed by telephone, fax or email
   Telephone: 01234 248631 (8.30am-4.30pm Monday to Friday)
   Fax: 01234 248705
   Email: orders.uk@movianto.com
   Denosumab will be delivered direct to the Practice within 24 hours via refrigerated vehicles free of charge.

2. Alternatively the patient can collect their prescription from a local pharmacy via the GP writing an FP10.

Contraindications & precautions for use
https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations

Hypocalcaemia is an identified risk in patients treated with denosumab, which increases with the degree of renal impairment; patients with severe renal impairment (creatinine clearance less than 30mL/min; eGFR 15 – 29 mL/min/1.73m^2) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in all patients. As with all anti-resorptive agents, hypocalcaemia is a specific contraindication and must be corrected with adequate intake of calcium and vitamin D prior to initiation of therapy.
Patients with rare hereditary problems of fructose intolerance should not use denosumab.

Adverse effects

- The most common reported side effects in trials were constipation, urinary tract infection, upper respiratory tract infection, pain in extremity and sciatica.

- **Hypocalcaemia** has been reported rarely**.** Monitoring of calcium levels should be conducted:
  - Prior to each dose
  - Within two weeks after the initial dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment eGFR less than 30mL/min/1.73m^2
  - If suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient.

  Tell all patients to report symptoms of hypocalcaemia to the prescriber e.g. muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth.
  'Management of hypocalcaemia in adult inpatients' Worcestershire Acute Hospitals NHS Trust December 2011

- **Osteonecrosis of the jaw (ONJ)** has been reported rarely in osteoporosis studies and to the MHRA. Known risk factors for the development of ONJ should be taken into consideration before prescribing. Risk factors for ONJ include:
  - Smoking
  - Old age (increased risk over 65 years)

- Poor oral hygiene
- Invasive dental procedures e.g. tooth extractions, dental implants, oral surgery
- Co-morbidity e.g. dental disease, anaemia, coagulopathy, infection
- Advanced cancer
- Previous treatment with bisphosphonates
- Concomitant treatments e.g. chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy.

Before starting denosumab treatment, a dental examination and appropriate preventative dentistry are recommended in patients with concomitant risk factors prior to starting denosumab. During treatment patients should avoid invasive dental procedures if possible, maintain good oral hygiene practices and report any oral symptoms.

Patient reminder cards should be provided to inform patients of the risk of ONJ and precautions to take before and during treatment.

- **Atypical femoral fractures with long term use**

Two cases of atypical femoral fracture have been confirmed in patients receiving denosumab 60 mg for 2.5 or more years participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events occurred rarely (in ≥ 1/10 000 to < 10/10 000 patients), based on 8 928 subjects being exposed to denosumab 60 mg in bone loss studies.

Healthcare professionals are advised:

- 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
- atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur
- the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture, as atypical femoral fractures are often bilateral (as noted from the bisphosphonates assessment)
- discontinuation of denosumab treatment should be considered if an atypical femur fracture is suspected, while the patient is evaluated; an individual assessment of the benefits and risks should be performed

- 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.
- The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex) which may cause allergic reactions.

Drug interactions

No interaction studies have been performed with denosumab. There are no clinical data on the co-administration of denosumab and hormone replacement therapy (HRT), however the potential for pharmacodynamic interactions is considered low. Pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronic acid therapy. There is low potential for drug–drug interactions.

References:

- Denosumab Summary of Product Characteristics, available at: http://www.medicines.org.uk/emc/medicine/23127
- NICE Technology Appraisal 204 (October 2010): 'Denosumab for the prevention of osteoporotic fractures in postmenopausal women'.
- National Osteoporosis Society: Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. April 2013
- MHRA Drug Safety Update. 'Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia – updated recommendations'. September 2014; Volume 8, issue 2, A2.
- 'Management of hypocalcaemia in adult inpatients' Worcestershire Acute Hospitals NHS Trust December 2011
- MHRA Drug Safety Update. ' Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw – further measures to minimize risk'. July 2015; Volume 8, issue 12:1.
- MHRA Drug Safety update 'Denosumab: Rare cases of atypical femoral fracture with long-term use'. February 2013; Volume 6, issue 7:A1.

Appendix A - Loading dose of Vitamin D

Please also see Guidelines for the Treatment of Vitamin D Deficiency and Inadequacy in Adults

The National Osteoporosis Society 2013 guideline includes the following:

- *"Where rapid correction of vitamin D deficiency is required, such as in patients with symptomatic disease or about to start treatment with a potent antiresorptive agent (zoledronate or denosumab), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy:*
  - ***a loading regimen to provide a total of approximately 300,000 IU vitamin D, given either as separate weekly or daily doses over 6 to 10 weeks***
  - *maintenance therapy comprising vitamin D in doses equivalent to 800–2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at higher doses.*
- *Where correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses."*

Patients at risk of vitamin D deficiency include:
- Elderly patients in residential care or housebound.
- Black and ethnic minority patients with darker skin.
- Intestinal malabsorption e.g. coeliac disease, Crohn's disease, gastrectomy.
- Lack of sunlight exposure due to routine covering of face or body, habitual sunscreen use, atmospheric pollution.
- Vegan or vegetarian diet (or other non-fish eating diet)
- Liver or renal disease.

Patients should have a bone profile prior to starting Vitamin D loading and any patient who is hypercalcaemic should have vitamin D levels checked. Clinicians should contact secondary care for advice before proceeding with treatment. In others at risk of vitamin D deficiency, levels need not be checked but a loading dose of Vitamin D is recommended prior to the first administration of subcutaneous denosumab.
Oral supplements of calcium and vitamin D should be suspended while the patient is being loaded with Vitamin D.

Preferred preparations for use in Worcestershire

Colecalciferol 20,000unit capsules, 40,000unit capsules and 800 unit capsules and tablets are available as licensed products and included in the Drug Tariff Part VIIIA . Using the high dose capsules for loading regimens reduces the tablet burden for patients and is more affordable. Invita D3® oral ampoules are an alternative for patients who require a high dose **liquid** preparation. *N.B. A licensed injection of ergocalciferol 300,000 units is also available, however it is not recommended by NOS due to its unpredictable bioavailability, slower onset of repletion and the additional administrative burden in comparison to oral preparations.*[1]

	Dose	Suggested preparations / regimes
Loading	Colecalciferol up to a total of approximately 300,000 units given as weekly or daily split doses	Colecalciferol: • 40,000 unit capsules, one weekly for 7 weeks • 20,000 unit capsules, two weekly for 7 weeks • 800 unit capsules/tablets, five a day for 10 weeks • 25,000 units/ 1ml oral solution (*Invita D3®) 2 oral ampoules (2ml) weekly for 6 weeks

***Please refer to manufacturer's information for detailed prescribing information for each product INCLUDING ADVICE ABOUT PATIENTS WITH RENAL IMPAIRMENT, available via* http://www.medicines.org.uk/emc/**

For information about which products are suitable for a vegetarians and vegans see: **Which vitamin D preparations are suitable for a vegetarian or vegan diet?**

*Invita D3 Administration - The full contents of the ampoule should be either emptied into the mouth and swallowed orally, or emptied onto a spoon and taken orally. InVita D3 can also be taken by mixing with a small amount of cold or lukewarm food immediately prior to use.

Maintenance Prescribing

A maintenance dose of calcium 1,000mgs and vitamin D 800units is required afterwards in a suitable formulation for the patient. The Adcal-D3® range, which also contains calcium, may be used for maintenance therapy.
See 'Guidelines for the use of calcium and vitamin D in falls prevention in adults', Worcestershire Area Prescribing Committee January 2012; and monitor U&E's in patients at risk of renal impairment.

Appendix B

Checklist to Support Request for Administration of Maintenance Denosumab (Prolia®) Injection

Patient name, NHS number and address	
GP name and Practice	

Date prescription issued:	
Date injection due:	
Date of the previous injection:	

	Yes / No / Not applicable	Comments
Blood tests checked (calcium, phosphate and creatinine) and results acceptable.		
If administered previously; patient **did not** experience any severe adverse effects.		
Patient **is not** allergic to latex.		
Patient is taking Calcium/Vitamin D supplementation.		
Patient has had a dental check in the last 6 months.		
Patient **is not** awaiting or undergoing dental extraction / root canal treatment / dental implant or undergoing any other oral surgery.		
Patient **does not have** an infection such as LRTI, UTI, or Cellulitis.		
Patient **has not reported** a new onset of pain in the groin(s) or thigh(s) which is worse on weight bearing?		

IF THE ANSWER TO ANY OF THESE QUESTIONS IS NO THEN Denosumab (Prolia®) should not be administered and PRESCRIBER TO REVIEW APPROPRIATENESS OF PRESCRIBING for this patient at this time.

PRESCRIBER SIGNATURE:……

PRESCRIBER NAME: ……

DATE:……