401FM.3.2 DENOSUMAB FOR PRIMARY AND SECONDARY FRACTURE PREVENTION IN WOMEN AND MEN OVER THE AGE OF 50
Amber Recommendation Guideline

This guideline provides prescribing and monitoring guidance for denosumab therapy. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

BACKGROUND FOR USE

Denosumab is a monoclonal antibody that binds to RANK ligands and inhibits osteoclast formation, function and survival, thereby decreasing bone resorption. It is indicated for treatment of:

1. Osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.[2-4]
2. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

This Amber Recommendation guideline covers the use of denosumab in indications 1 and 2.

When used for fracture prevention in patients >50 years at high risk of fracture:

- with estimated glomerular filtration rate (eGFR) >30 ml/min or not on dialysis, patients are discharged by the specialist after recommending the use of denosumab.
- with eGFR <30 ml/min or on dialysis, patients are not discharged by the specialist. Denosumab is prescribed, administered and monitored in primary care but the patients are followed up by the specialist in secondary care.

PLACE IN THERAPY

Denosumab is recommended as a third line antiresorptive agent in patients >50 years at high risk of fractures who are unsuitable for at least two oral bisphosphonates (alendronic acid, risedronate or ibandronate) due to inability to comply with administration instructions, adverse effects or contraindications. If a patient has not responded to one oral bisphosphonate despite good adherence, a second oral bisphosphonate is not indicated. Instead, a treatment with on alternative mode of action will be chosen. (See Guideline 567FM Fracture Prevention for Adults >50 Years Old.)

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to the active substance or to any of its excipients, e.g. fructose	Do not use.
Allergy to latex	Not recommended.
Hypocalcaemia	Denosumab should not be used in patients with hypocalcaemia, regardless of severity.[6] Calcium and 25(OH) vitamin D should be checked before starting the treatment. **Vitamin D deficiency and hypocalcaemia must be corrected by ensuring adequate intake of calcium and vitamin D before initiating therapy**. See Guideline 785FM Vitamin D Testing and Treatment in Adults. All patients should be advised to report symptoms of hypocalcaemia to their doctor (e.g. muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth).
Renal failure (eGFR <30 ml/min)	No dose adjustment required in patients with eGFR >30 ml/min. Denosumab has no direct nephrotoxic effect. Patients with severe renal impairment (eGFR <30 ml/min) or receiving dialysis are at greater risk of developing **hypocalcaemia** and in these patients clinical monitoring of calcium levels two weeks after injection is recommended. These patients should be followed up by the specialist in secondary care. There is very limited data on denosumab use in patients with eGFR <15 ml/min.
Liver impairment	No dose adjustment required.
Cellulitis	Although uncommon, patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. The risk of cellulitis and other infections does not increase with the duration of treatment.
Prevention of jaw osteonecrosis	Dental examination with appropriate preventative dentistry is recommended in patients with risk factors (corticosteroids, radiotherapy to head and neck, chemotherapy, pre-existing dental disease, periodontal infections). Treatment should not be delayed in patients who are at high risk of fragility fractures. Patients should be advised to maintain good oral hygiene while on treatment and undergo regular dental checks
Osteonecrosis of the external auditory canal	Patients should be advised to report persistent ear pain, discharge from the ear or ear infection during denosumab treatment.
Pregnancy and lactation	Not recommended.

DOSAGE

- Patients must be calcium and vitamin D replete (serum 25-OH-Vit D >50 nmol/l) before and during treatment with denosumab.
- The recommended dose is denosumab Prolia® 60 mg, administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of the arm. Administration should be performed by an individual adequately trained in injection techniques.
- It is important that patients receive their 6 monthly injection in a timely manner, preferably within 2 weeks of the due date (either side). 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 secondary care specialist.
- Administration of densosumab 60 mg Prolia® is funded via the Near Patient Testing locally enhanced service.

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.[7] 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.[8,11] Bone loss following denosumab cessation can be attenuated (but not stopped) by changing to another treatment such as another bisphosphonate.[9] 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.[10,11]

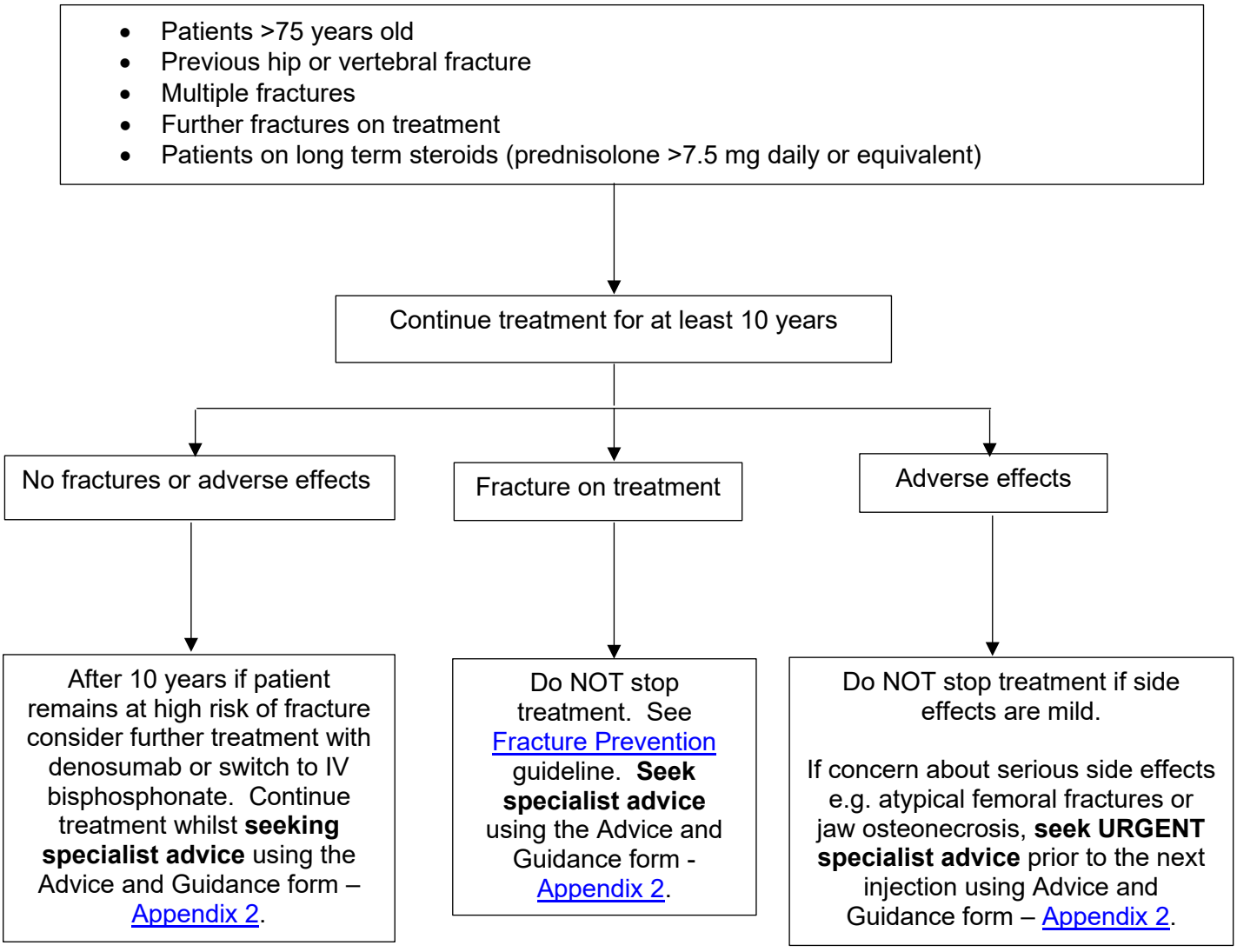
Do NOT stop or delay denosumab without prior specialist advice. Use 'Advice and Guidance' via ERS:

- In patients who are due for review of their treatment.
- if there are concerns about serious side effects prior to giving the next injection.

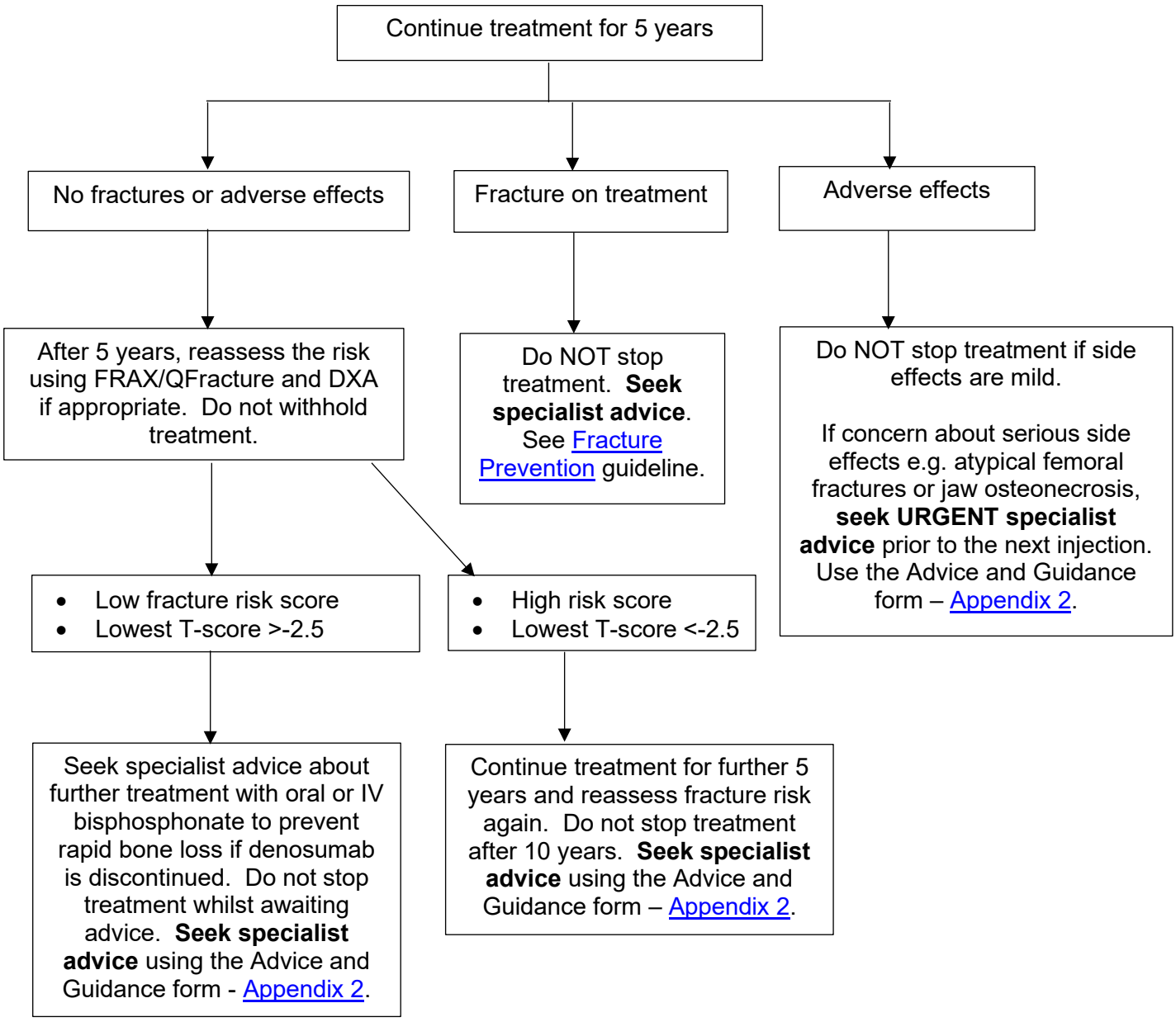
Treatment duration is determined by the patient's risk of facture and in many patients will be life-long.

High risk patients

- Patients >75 years old
- Previous hip or vertebral fracture
- Multiple fractures
- Further fractures on treatment
- Patients on long term steroids (prednisolone >7.5 mg daily or equivalent)



Non-high risk patients



TIME TO RESPONSE

- Suppression of bone turnover markers usually occurs 2 weeks post injection.
- Clinical trials demonstrated fracture risk reduction after the first year of treatment.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

Creatinine/eGFR, calcium, phosphate, 25(OH) vitamin D.

ONGOING MONITORING SCHEDULE

Calcium and urea and electrolytes (U&Es)	• Within 4 weeks prior to each injection., serum calcium level must be normal and renal function tests normal or unchanged. • In patients with eGFR <30 ml/min, check serum calcium 2 weeks after each injection.

RESPONSIBILITIES

(See patient information leaflet available on the Trust website: Denosumab (Prolia®) for Treatment of Osteoporosis (to follow).)

Responsibilities of the Specialist

Before recommending that treatment can be started the specialist will:

- Review prior treatments for osteoporosis, concomitant medical problems and allergies (including latex).
- Arrange DXA scan if appropriate.
- Organise baseline blood tests.
- Check calcium intake.
- Confirm that the patient is vitamin D replete (serum 25-OH-Vit D >50 nmol/l). If below normal, treat with e.g. colecalciferol 40,000 Units daily x 7 days, re-test to confirm normal vitamin D level.
- Advise GP and patient regarding calcium and vitamin D supplementation – see guideline 785FM Vitamin D Testing and Treatment in Adults. If calcium intake is insufficient, it is recommended that calcium 1200 mg to 1800 mg PO daily and colecalciferol 800 Units daily are prescribed as supplements, e.g. calcium carbonate 1.5 g/colecalciferol 400 Unit tablets one tablet PO twice daily. See Buckinghamshire Formulary for preparations.
- Discuss benefits and possible side effects of treatment, as listed in the patient information leaflet, including cellulitis, eczema, osteonecrosis of the jaw and ear canal and atypical femoral fractures.
- Explain about the importance of good oral hygiene and regular dental checks.
- Provide patient information leaflet and encourage patient to enrol in the PROLONG Patient Support Programme online, to access further support and to ensure that they are reminded when their next injection is due. See www.prolia.co.uk.
- Advise patient and GP on duration of treatment and the importance of not stopping treatment without specialist review.
- Provide advice to the GP if any concerns about adverse effects arise during the treatment.

Responsibilities of the GP

- On the recommendation of the specialist, initiate denosumab with the support of the practice nurse.
- Ensure that the date of each subsequent injection is clearly recorded and that the patient is informed.
- If advised by the specialist, ensure that the patient continues calcium and vitamin D supplementation throughout treatment with denosumab.
- Check calcium and U&Es approximately 4 weeks prior to each injection. A satisfactory result should be confirmed before giving the next denosumab injection.
- If there is concern that the patient is not taking calcium and vitamin D supplements, test Vitamin D level approximately 4 weeks prior to each injection. A satisfactory result should be confirmed before giving the next denosumab injection. If the result is below normal, treat with e.g. colecalciferol 40,000 Units daily x 7 days, re-test to confirm normal vitamin D level. See guideline 785FM Vitamin D Testing and Treatment in Adults.
- Refer the patient back to the specialist if the eGFR falls below 30 ml/min or if the patient starts on dialysis. Patients with eGFR <30 ml/min are followed up by the specialist. The GP prescribes, monitors and administers the denosumab.
- Review the treatment as recommended by the specialist after 5 or 10 years without stopping denosumab.
- Seek specialist advice without stopping or delaying treatment using the 'Advice and Guidance' form via ERS:
    - at the end of a recommended treatment.
    - if there are concerns about serious side effects e.g. atypical femoral fractures or jaw osteonecrosis, prior to giving the next injection.
    - If the patient sustains a fragility fracture whilst on denosumab,
- Inform the specialist of any adverse effects or treatment discontinuation.

Responsibilities of Nurse Administering Injection

- Ensure that the treatment is safe to administer by completing the checklist in Appendix 1.
- Save the completed checklist (Appendix 1) in the patient's medical notes.
- Check bloods have been done and reviewed by the GP within 4 weeks prior to injection, before giving injection
- Inform the GP urgently of any identified side effects.
- Remind the patient to continue taking calcium and vitamin D supplements as recommended If there is concern that the patient is not taking the supplements, inform the GP (see Appendix 1 for details).
- Remind the patient of the date when the next appointment should be booked. If the patient is approaching 5 or 10 years of treatment book an appointment with the GP to reassess fracture risk but do not stop the treatment.
- Inform the patient of the date to attend for a blood test four weeks before the next denosumab injection.

Responsibilities of the Patient

- Take calcium and vitamin D tablets regularly if recommended, before and during denosumab treatment.
- Organise a dental check-up and undergo any corrective dentistry ideally before starting denosumab, however the treatment should not be delayed in high risk patients particularly in patients who had a fracture in the last 24 months.
- Inform the GP/nurse if there is groin or thigh pain or rash after starting treatment.
- Do NOT stop treatment unless advised to stop by a doctor.
- Attend for a blood test four weeks prior to each injection.
- Attend for each injection on the date requested. If there is a two-week delay in receiving a dose, the treatment may be less effective.

SIDE EFFECTS

Common (1/100 to <1/10):	*Action to be taken*
Dysuria, haematuria, frequency, urinary tract infection (UTI)	Treat UTI appropriately. If patient is due for the injection - defer until treatment completed.
Upper respiratory tract infection	Treat appropriately. If patient is due for the injection - defer until treatment completed.
Sciatica	Treat symptomatically.
Cataracts	If patient presents with accelerated cataracts and no other cause found, discuss with the specialist.
Constipation	Treat appropriately. Continue treatment.
Rash	In case of a new rash following denosumab injection, discuss with the specialist before the next dose is given.
Pain in extremity	Treat symptomatically.
Uncommon (1/1,000 to <1/100):	
Cellulitis	Treat appropriately - defer until treatment completed.
Diverticulitis	Treat appropriately. If patient is due for the injection - defer until symptoms resolved.
Ear infection	Treat appropriately. If patient is due for the injection - defer until treatment completed.
Eczema	Consider benefits versus risks. If eczema is mild it is reasonable to continue to treat with denosumab, if more severe then seek specialist advice.

SIDE EFFECTS continued

Rare (1/10,000 to <1/1,000):	
Osteonecrosis of the jaw	Seek specialist advice.
Hypocalcaemia. Severe symptomatic hypocalcaemia has been reported in patients receiving denosumab 60 mg. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment.[6]	Do not give denosumab to patients with hypocalcaemia as this will make it worse. Check if patient is taking adequate calcium and vitamin D supplementation. Seek specialist advice.
Hypersensitivity to denosumab	This is a contraindication according to the manufacturer's literature. Do not give.
Atypical subtrochanteric fracture	Should be suspected in a patient complaining of a new thigh or groin pain, especially if it is bilateral and worse on weight bearing. Request an urgent AP and lateral X-ray of the whole femur (femora if bilateral symptoms). If the radiograph reports insufficiency fracture or localised periosteal reaction, the patient should be made non-weight bearing and referred urgently to the local trauma team. Inform osteoporosis specialist urgently and do not give further denosumab. If the radiograph is normal but the patient has persistent groin or thigh pain discuss with the specialist in osteoporosis.

NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC)

No interaction studies have been performed. There is no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen). However, the potential for a pharmacodynamic interaction is considered to be 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).

BACK-UP INFORMATION AND ADVICE

Contact Details	**Wycombe and Amersham**	**Stoke Mandeville**
Rheumatology	01494 734119 (specialist nurse helpline) Consultant secretary: Dr R Stevens: 01494 734079 or via switchboard Email: bht.rheumatology@nhs.net	01296 315960 (specialist nurse helpline) Consultant secretary: Dr M Magliano: 01296 316664 or via switchboard In an emergency contact Rheumatologist of the week (ROW) on 01296 316664 Email: bht.rheumatology@nhs.net
Endocrinology	Medical Day Unit (MuDAS) Suzanne Busby 01494 426318 Dr Henrietta Brain 01494 425349 (sec) or via switchboard	
Fracture liaison Service	Dr. Ana Phelps Jane Sutherington	
Medicines Resource Centre	01494 425355 Email: bucks.medicinesresourcecentre@nhs.net	
Switchboard	Amersham 01494 434411 Wycombe 01494 526161	01296 315000

REFERENCES

1. Denosumab for the prevention of osteoporotic fractures in post menopausal women, (October 2010), National Institute for Health and Care Excellence (Technology Appraisal 204).
2. Summary of Product Characteristics for Prolia® (Denosumab). last updated 8th June 2018. Available on 222.medicines.org.uk/emc [Accessed 20/02/2019].
3. Papapoulos S, Chapurlat R, Libanati C et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. J Bone Miner Res. 2012 Mar;27(3):694-701.
4. Cummings SR, San Martin J, McClung MR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756-65.
5. Watts NB, Roux C, Modlin JF, et al. Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association? Osteoporos Int. 2012 Jan;23(1):327-37.
6. MHRA Drug safety update. October 2012. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560
7. Bone HG, Wagman RB, Brandi ML et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017 Jul;5(7):513-523.
8. Cummings S et al, Vertebral Fractures after discontinuation of Denosumab. A post hoc analysis of the randomized placebo-controlled FRREDOM trial and its extension. JBMR 2017, 33 (2) 190-198.
9. McClung MR, Wagman RB, Miller PD et al. Observations following discontinuation of long-term denosumab therapy. Osteoporos Int. 2017 May;28(5):1723-1732
10. Tsourdi E, Langdahl B, Cohen-Solal M et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone. 2017 Dec;105:11-17
11. MHRA/CHM advice August 2020: Denosumab 60 mg (Prolia®): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment. 2020 https://www.gov.uk/drug-safety-update/denosumab-60mg-prolia-increased-risk-of-multiple-vertebral-fractures-after-stopping-or-delaying-ongoing-treatment
12. MHRA advice June 2017 Denosumab Prolia® osteonecrosis of the external auditory canal. https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal
13. Royal Osteoporosis Society Denosumab Patient Information: https://theros.org.uk/information-and-support/osteoporosis/treatment/denosumab/ and fact sheet: https://strwebstgmedia.blob.core.windows.net/media/sxif4dxc/denosumab-prolia-fact-sheet-octobe-2017.pdf

See also:

Guideline 222 Adult and Paediatrics Injectables Guide (BHT users only)
Guideline 567FM Fracture Prevention for Adults >50 Years Old
Guideline 785FM Vitamin D Testing and Treatment in Adults

Patient information leaflet: Denosumab (Prolia®) for Treatment of Osteoporosis (to follow)

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Author/s	Dr M Magliano, Consultant Rheumatologist Dr Shona Lockie, Clinical Director for Medicine, Bucks CCG Maire Stapleton, Formulary Manager, MRC
SDU(s)/Department(s) responsible for updating the guideline	Rheumatology Endocrinology
Uploaded to Intranet	24th February, 15th June and 21st June 2021
Buckinghamshire Healthcare NHS Trust/Buckinghamshire Clinical Commissioning Group	

Appendix 1: Checklist for nurse practitioners before denosumab injection.

Appointment date

Injection number …..
Date of the previous injection .....

Were there any adverse effects since previous injection? YES NO
If **YES,** please discuss with the doctor.

Allergy to latex (before the first injection) YES NO

Is patient taking calcium and vitamin D supplementation YES NO

State the name of the product and dose .....
If concern that the patient is not taking calcium and vitamin D supplements, test vitamin D level. If result is below normal, please discuss with the doctor.

Has the patient had a dental check in the last 6 months? YES NO

Is the patient awaiting or undergoing dental extraction/root canal treatment/dental implant or undergoing any other oral surgery? YES NO
If **YES,** please discuss with the doctor as treatment with denosumab may need to be delayed.

Does the patient have active infection such as LRTI, UTI, ear infection or cellulitis YES NO
If **YES,** please delay the injection until recovered.

Does patient report a new onset of pain in the groin or thighs which is worse on weight bearing?
YES NO
If **YES,** please discuss with the doctor.

Blood test results:		Date :
Calcium (corrected)		If low do not give denosumab and discuss with the doctor
Creatinine		if eGFR stable, continue treatment. If abnormal or rising please discuss with the doctor.
Vitamin D (if concern that supplements not taken)		If below normal, do not give denosumab. Discuss with the doctor so that a one week treatment course of vitamin D is prescribed and a further vitamin D test is arranged.

Does the patient have an eGFR <30 ml/min? YES NO
If YES, the patient should be followed up by the specialist. Denosumab is prescribed, monitored and administered by the GP. Please remember to:

- Check calcium level 2 weeks after each injection
- Ensure that the patient is being followed up by the specialist. If not, ask the GP to refer patient back to the specialist

NAME: .....
SIGNATURE: .....

Appendix 2: Advice and Guidance form to be completed when seeking specialist Rheumatology/Endocrinology advice regarding continuation of fracture prevention medication.

1. FRAX based 10 year risk of major OP fracture …….%

   NOGG recommendation Above / Below treatment threshold (circle)

2. FRAX based 10 year risk of hip fracture ……%

   NOGG recommendation Above / Below treatment threshold (circle)

3. Last DXA (in patients <80 years old) – date …….

T-score spine
T-score femoral neck
T-score total hip

4. What are the patients current renal function tests

EGFR …….ml/min. Creat Date

5. Has the patient had a new low trauma fracture since starting treatment

Site Date

6. Is the patient currently taking systemic steroids?

Daily dose

7. Does the patient have any adverse effects from denosumab? Yes/No

If yes please list

8. Is the patient able to take/tolerate oral bisphosphonate Yes/No

9. Is the patient able to attend hospital day unit for intravenous treatment. Yes/No

Any other information you feel may be relevant