**DENOSUMAB FOR PRIMARY AND SECONDARY FRACTURE PREVENTION IN WOMEN AND MEN OVER THE AGE OF 50**

**Green + 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](http://www.medicines.org.uk/emc) and the [BNF](https://bnf.nice.org.uk/).

**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 Green + Recommendation guideline covers the use of denosumab in indication 1,

# when the consultant rheumatologist has approved its use by Advice & Guidance

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

* with creatinine clearance (CrCl) >30 ml/min or not on dialysis, patients are discharged by the specialist after recommending the use of denosumab.
* with CrCl <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. Advice is sought from the consultant rheumatologist; the first injection is given in secondary care and the follow up 2 weeks later for calcium levels is 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.

Palliative care patients will need to be assessed on an individual patient basis.

# 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 Vitamin D Quick reference guide v3.0 <http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2020/05/Vitamin-D-Quick-reference-guide-v3.0.pdf>  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 (CrCl <30 ml/min) | No dose adjustment required in patients with CrCl >30 ml/min. Denosumab has no direct nephrotoxic effect.  Patients with severe renal impairment (CrCl <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 CrCl <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). No later than 1 month after their due date. 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.

# TREATMENT DURATION

Trial evidence from 10 years of denosumab treatment demonstrated ongoing improvement in bone density, low fracture rates and low rates 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’

* + 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 fracture 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)

Continue treatment for at least 10 years

Adverse effects

No fractures or adverse effects

After 10 years if patient remains at high risk of fracture consider further treatment with denosumab or switch to IV bisphosphonate. Continue treatment whilst **seeking specialist advice** using the Advice and Guidance form – [Appendix 2](#App2).

Do NOT stop treatment. **Seek specialist advice** using the Advice and Guidance form - [Appendix 2](#App2).

Do NOT stop treatment if side effects are mild.

If concern about serious side effects

e.g., atypical femoral fractures or jaw osteonecrosis, **seek URGENT specialist advice** prior to the next

injection using Advice and Guidance form – [Appendix 2](#App2).

Fracture on treatment

**Non high risk patients**

Fracture on treatment

No fractures or adverse effects

Adverse effects

Continue treatment for 5 years

Do NOT stop treatment. **Seek specialist advice**.

* High risk score
* Lowest T-score <-2.5
* Low fracture risk score
* Lowest T-score >-2.5

After 5 years, reassess the risk using FRAX/QFracture and DXA if appropriate. Do not withhold treatment.

Do NOT stop treatment if side effects are mild.

If concern about serious side effects e.g. atypical femoral fractures or jaw osteonecrosis, **seek URGENT specialist advice** prior to the next injection.

Use the Advice and Guidance form – [Appendix 2](#App2).

Seek specialist advice about further treatment with oral or IV bisphosphonate to prevent rapid bone loss if denosumab is discontinued. Do not stop treatment whilst awaiting advice. **Seek specialist advice** using the Advice and Guidance form - [Appendix 2](#App2).

Continue treatment for further 5 years and reassess fracture risk again. Do not stop treatment after 10 years. **Seek specialist advice** using the Advice and Guidance form – [Appendix 2](#App2).

**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 GP PRACTICE

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

# ONGOING MONITORING SCHEDULE

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| 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 CrCl <30 ml/min, check serum calcium 2 weeks after each injection. |

**RESPONSIBILITIES**

(See patient information leaflet available on the Royal Osteoporosis Society website ([Appendix 3](#app3)).

**Responsibilities of the specialist**

To provide authorisation for denosumab therapy if appropriate.

# Responsibilities of GP Practice- send an Advice & Guidance request to rheumatology using A&G form [Appendix 2](#App2) for authorisation of denosumab use, duration of treatment and review date

Before recommending that treatment can be started the specialist will need the following information

* Prior treatments for osteoporosis & rationale for denosumab treatment, concomitant medical problems and allergies (including latex)
* Arrange DXA scan if appropriate, copy of previous DXA scan
* Copy of FRAX assessment and score
* Baseline blood tests (FBC, renal, bone & liver profiles, 25(OH) D, PTH, SEP & urine for monoclonal bands)
* Calcium intake
* Confirm that the patient is vitamin D replete (serum 25-OH-Vit D >50 nmol/l). If below normal treat as follows:- Colecalciferol 20,000units/capsule: 2 capsules weekly for 7 weeks or colecalciferol 25,000units/ml: 2mls weekly for 6 weeks. Re-test to confirm normal vitamin D level after 8-12 weeks. NB Ensure denosumab treatment is clearly documented in the clinical details on the ICE form.

**If treatment is recommended by the specialist the GP practice will need to complete the following before starting treatment**

* Advise patient regarding calcium and vitamin D supplementation – see guideline <http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2020/05/Vitamin-D-Quick-reference-guide-v3.0.pdf>. 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.
* 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](http://www.prolia.co.uk/). Give the patient a patient reminder card (<https://www.medicines.org.uk/emc/rmm/236/Document>)
* Advise patient on duration of treatment and the importance of not stopping treatment without specialist review.
* Ensure that the date of each subsequent injection is clearly recorded and that the patient is informed.
* Ensure that the patient continues calcium (if dietary calcium is insufficient) and vitamin D supplementation throughout treatment with denosumab. If dietary calcium is sufficient only Vitamin D supplement will be required (<https://theros.org.uk/information-and-support/bone-health/nutrition-for-bones/calcium/calcium-rich-food-chooser>, <https://webapps.igmm.ed.ac.uk/world/research/rheumatological/calcium-calculator>).
* Check calcium and U&Es within 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 as above. Re-test to confirm normal vitamin D level. When requesting the repeat blood test indicate the patient is on denosumab therapy. See guideline <http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2020/05/Vitamin-D-Quick-reference-guide-v3.0.pdf>
* Refer the patient back to the specialist if the CrCl falls below 30 ml/min or if the patient starts on dialysis. Patients with CrCl <30 ml/min are followed up by the specialist. The clinician, 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’](#_bookmark1) form

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](#App1).
* Save the completed checklist ([Appendix 1](#App1)) in the patient’s medical notes.
* Check bloods have been done and reviewed by the clinician within 4 weeks prior to injection, before giving injection.
* Inform the clinician 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](#App1) 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 clinician 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 clinician/nurse if there is groin or thigh pain or rash after starting treatment.
* Do NOT stop treatment unless advised to stop by a clinician.
* 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

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| --- | --- |
| **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. |
| **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**](https://bnf.nice.org.uk/) **AND** [**SPC**](http://www.medicines.org.uk/emc)**)**

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).

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| Appointment date: | | |
| Injection number: | | |
| Date of previous injection: | | |
|  | **YES** | **NO** |
| **Were there any adverse effects since the previous injection?**  *If* ***YES*** *please discuss with doctor* |  |  |
| **Allergy to latex (before the first injection)?** |  |  |
| **Is patient taking calcium and vitamin D supplementation?**  **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.* |  |  |
| **Is the patient awaiting or undergoing dental extraction/root canal treatment/dental implant or undergoing any other oral surgery?**  *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**  *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?**  *If* ***YES****, please discuss with the doctor* |  |  |
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| |  |  |  | | --- | --- | --- | | **Blood test results:** | | **Date:** | | Calcium (corrected) |  | If low do not give denosumab and discuss with the doctor | | Creatinine |  | If CrCl 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. | | | |
|  | | |
|  | **YES** | **NO** |
| **Does the patient have a CrCl <30 ml/min?**  *If* ***YES,*** *the patient should be followed up by the specialist. The denosumab is prescribed, monitored and administered by the clinician.*  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 clinician to refer patient back to the specialist |  |  |
| **NAME:** | | |
| **SIGNATURE:** | | |

|  |  |
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| **Advice and Guidance form to be completed when seeking specialist rheumatology advice regarding initiation/continuation of denosumab** | |
|  | FRAX based 10 year risk of major OP fracture %  NOGG recommendation very high risk/high risk/lifestyle only |
|  | FRAX based 10 year risk of hip fracture %  NOGG recommendation very high risk/high risk/lifestyle only |
|  | Please enclose previous DXAs and latest DXA  Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  T-score spine  T-score femoral neck  T-score total hip |
|  | What are the patients current renal function tests?  CrCl ml/min  Creatinine umol/l  Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
|  | Is the patient currently taking systemic steroids?  Daily dose: |
|  | Is the patient able to take/tolerate oral bisphosphonate Yes/No |
|  | Is the patient able to attend hospital day unit for intravenous treatment Yes/No |
| **For initiation of treatment** | |
|  | Prior treatments for osteoporosis – reason for cessation |
|  | Confirm no latex allergies |
|  | Previous fractures |
|  | Any other information you feel may be relevant e.g., co-morbidities, risk factors (hip fracture, smoking, rheumatoid arthritis, diabetes, secondary osteoporosis, alcohol? |
| **For continuation of denosumab treatment** | |
|  | Has the patient had a new low trauma fracture since starting treatment?  Site:  Date: |
|  | Does the patient have any adverse effects from denosumab? Yes/No  If Yes, please list: |

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