Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Surrey Downs, Guildford & Waverley, North-West Surrey, and East Surrey Places & associated partner organisations.

Denosumab for the treatment of osteoporosis - prescribing information

This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

Link to the relevant SPC website: Prolia - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Licence: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures

Criteria for Use: Denosumab has been approved by NICE TA204 (2012)) for the prevention of osteoporotic fractures in *postmenopausal women*.

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 table within the NICE TA. (For the purposes of the NICE denosumab 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.)
  It should be noted that this differs from NICE CG 146 Osteoporosis: assessing the risk of fragility fracture which gives alcohol intake >14 units/week as a risk factor

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

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

[a] Treatment with denosumab is not recommended.

Secondary Prevention

Denosumab is recommended as a treatment option for the secondary 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.

Men

There is no current NICE TA for the use of denosumab in men. Men with osteoporosis are usually referred to specialist centres for management.
Alendronate and risedronate are first line treatments in men. Where these are contraindicated or not tolerated, denosumab provides an appropriate alternative and is licensed for treatment in men at increased risk of fractures.

NOGG Clinical Guideline for the Prevention and Treatment Of Osteoporosis Sept 2021

Considerations before starting treatment

- Before starting denosumab, ensure a long-term personalised osteoporosis management plan is in place and that both the patient and the practitioner are aware that denosumab treatment should not be stopped or delayed without discussion with a healthcare professional.
- Avoid unplanned cessation of denosumab because it can lead to increased vertebral fracture risk, hence it must not be stopped without considering an alternative therapy

Dose

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of the arm. Patients must have adequate intake of calcium and vitamin D. Most adults need 700mg of calcium a day, but if taking an taking an osteoporosis medication, they may benefit from increasing daily calcium intake to around 1,000mg. This may be obtained from food without taking a supplement and intake may be checked using an online calcium calculator or BDA Calcium: Food Fact Sheet

Surrey Osteoporosis pathway (http://pad.res360.net/PAD/Search/DrugCondition/256)
Denosumab is recommended as a treatment option where oral bisphosphonates are contraindicated or not tolerated.

Cautions (see BNF or SPC)

- Correct hypocalcaemia and vitamin D deficiency before starting therapy. Monitor plasma-calcium concentration during therapy.
- Patients receiving denosumab may develop skin infections (predominantly cellulitis). Patients must seek prompt medical attention if they develop signs of cellulitis.
- Osteonecrosis of the jaw (ONJ) has been reported (rare).
- A dental examination with appropriate preventive dentistry should be considered prior to starting denosumab in all patients with concomitant risk factors. Risk factors include smoking, old age, poor oral hygiene, invasive dental procedures (including tooth extractions, dental implants, oral surgery), co-morbid disorders (pre-existing dental disease, anaemia, coagulopathy, infection} advanced cancer, previous treatment with bisphosphonates, and concomitant treatments (chemotherapy, corticosteroids, anti-angiogenic biologics, corticosteroids and radiotherapy to head and neck).
- While on denosumab treatment patients should receive routine dental check-ups and maintain good oral hygiene.
- Patients should immediately report any oral symptoms such as dental mobility, pain, swelling, non-healing sores or discharge to a doctor and dentist.

Produced by: Linda Honey, Head of Medicines Management, NW Surrey CCG with input from Dr Sian Griffiths, Surrey & Sussex healthcare NHS Trust
Agreed by: Surrey Rheumatology Network April 2014 & Prescribing Clinical Network May 2014
Updated: Nov 2017, Sept 2018, May 2023 by Lis Stanford

- All patients should be given a patient reminder card and informed of the risk of ONJ.
- Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. 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.
- Atypical femoral fractures have been reported rarely in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g., bisphosphonates, glucocorticoids, proton pump inhibitors). Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. 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.
- Long-term antiresorptive treatment may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling
- An increased risk of multiple vertebral fractures has been reported in patients within 18 months of stopping or delaying ongoing denosumab 60mg treatment for osteoporosis. Patients with a previous vertebral fracture may be at highest risk. Evaluate a patient's individual factors for benefits and risks before initiating treatment with denosumab, particularly in patients at increased risk of vertebral fractures for example those with previous vertebral fracture. Patients should not stop denosumab without specialist review. The optimal duration of denosumab treatment for osteoporosis has not been established; re-evaluate the need for continued treatment periodically based on the expected benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use
- The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- Patients with rare hereditary problems of fructose intolerance should not use denosumab.

Contraindications (see BNF or SPC)

- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients
- Its use is not recommended in pregnancy or in those age under 18 years

Side effects (see BNF or SPC)

- Skin infections predominantly cellulitis - please monitor carefully if patients are on immunosuppressants particularly anti-TNFs
- In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab.
- The most common side effects with denosumab (seen in more than one patient in ten) are

Produced by: Linda Honey, Head of Medicines Management, NW Surrey CCG with input from Dr Sian Griffiths, Surrey & Sussex healthcare NHS Trust
Agreed by: Surrey Rheumatology Network April 2014 & Prescribing Clinical Network May 2014
Updated: Nov 2017, Sept 2018, May 2023 by Lis Stanford

musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis, rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have been observed in patients taking denosumab. Other common undesirable effects (incidence of 1-10%) were urinary tract infection, upper respiratory tract infection, constipation, abdominal discomfort, sciatica, rash, eczema and alopecia.

Interactions (see BNF or SPC)

- No interaction studies have been performed.

Check list for initiation of denosumab:

- Before starting denosumab, ensure a long-term personalised osteoporosis management plan is in place.
- Make patient aware that denosumab treatment must not be delayed or stopped without a plan for subsequent anti-resorptive therapy, where renal function permits
- It may be useful to use the Royal Osteoporosis Society Denosumab Factsheet to support your conversation
- Assess the suitability of the patient for denosumab including does the patient meets the NICE criteria/ Surrey osteoporosis pathway guidelines
- Denosumab treatment for renal patients with a CKD of 4 & 5 **OR** patients with a T- score of ≤ -4.5 should remain under specialist care and a GP should **not** initiate treatment or be approached to enter into a shared care agreement
- Check for ONJ risk factors before starting treatment. A dental examination and appropriate preventative dentistry are now recommended for patients with risk factors.
- Ensure that the patient does not have a latex allergy, the needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- Clinical monitoring of calcium levels is recommended before each dose and, in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance <30ml/min) within two weeks after the initial dose (there are no other specific monitoring requirements for denosumab).
- When requesting vitamin D tests please add as the first clinical detail "test prior to initiation of denosumab **or** patient on denosumab treatment"
- Vitamin D deficiency or insufficiency must be corrected **before** starting denosumab treatment, in line with Surrey Heartlands "Prevention, Investigation and Treatment of Vitamin D Deficiency and Insufficiency in Adults" Guidelines
    - Treat using a rapid correction regimen with a loading dose of 50,000units (1,250 micrograms) capsule colecalciferol once weekly for 6 weeks, total 300,000units should be prescribed
    - Prescribe full course of 6 capsules as an acute prescription to prevent accidental re-issue
    - Maintenance treatment should begin one month after completion of loading regime - 1000 IU (25 micrograms) tablet daily and this should be continued whilst patient is on treatment for osteoporosis
    - **Alternatively,** where calcium intake is inadequate, continue to prescribe a calcium and vitamin D supplement in line with local guidance
    - Check adjusted serum calcium level within 1 month after last loading dose, or after starting on lower dose maintenance therapy to detect calcium deficiency or unmasked primary hyperparathyroidism
    - Routine monitoring of serum 25-hydroxyvitamin D (25[OH]D) levels is not needed, including post loading regimes.

Produced by: Linda Honey, Head of Medicines Management, NW Surrey CCG with input from Dr Sian Griffiths, Surrey & Sussex healthcare NHS Trust
Agreed by: Surrey Rheumatology Network April 2014 & Prescribing Clinical Network May 2014
Updated: Nov 2017, Sept 2018, May 2023 by Lis Stanford

    - However, consider checking the serum 25(OH)D level 3–6 months after starting vitamin D treatment in people prescribed denosumab who have extremely low levels of vitamin D at baseline assessment or where poor concordance is suspected. Please note that vitamin D levels may not be requested until at least 3 months after the previous test
    - Discuss the importance of concordance with supplementation at each visit
- Ensure that other osteoporosis treatments (e.g. alendronate, risedronate) are stopped and removed from the patient's repeat prescription.
- Discuss the benefits and side effects of treatment with the patient, explaining to the patient that the treatment is 6 monthly injections and likely to be lifelong
- Contact a specialist if patient wishes to stop denosumab to discuss alternative options

Advise patients to:

- Seek prompt medical attention if they develop signs or symptoms of cellulitis.
- Avoid invasive dental procedures if possible (extractions, implants) and maintain good oral hygiene whilst on denosumab treatment. If treatments are considered necessary then patients are advised to seek advice from the prescribing consultant.
- Report any oral symptoms such as dental mobility, pain, swelling, non-healing sores or discharge to a doctor and dentist
- Report symptoms of hypocalcaemia to the doctor (e.g., muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes or around the mouth).
- Report any ear pain, discharge from the ear, or an ear infection during treatment
- Continue the vitamin D/calcium and vitamin D supplement throughout treatment emphasising the importance of good concordance. Ask patients to report promptly any issues they have with side effects so these may be addressed
- Attend the GP surgery every 6 months for the denosumab injection
- Explain to patent that if they miss a prescribed dose of denosumab, the missed injection should be administered as soon as possible. After this, their next injection should be scheduled 6 months from the date of their last injection

The optimal duration of denosumab treatment for osteoporosis has not been established; re-evaluate the need for continued treatment periodically based on the expected benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use

Patients should not stop denosumab without specialist review as an alternative therapy needs to be initiated since patients who discontinue denosumab have an increased risk of sustaining multiple vertebral fractures

- Report any adverse events to the doctor who administered the injection.
- Read the patient reminder card supplied as it includes important safety information about osteonecrosis of the jaw and precautions to take

Produced by: Linda Honey, Head of Medicines Management, NW Surrey CCG with input from Dr Sian Griffiths, Surrey & Sussex healthcare NHS Trust
Agreed by: Surrey Rheumatology Network April 2014 & Prescribing Clinical Network May 2014
Updated: Nov 2017, Sept 2018, May 2023 by Lis Stanford

Practice Responsibilities

- Ensure an account is set up to order denosumab and determine if it will come direct to the practice (more straightforward scenario for the patient). Denosumab can be delivered direct to the practice within 24 hours (Movianto; 01234 248631 - product code 900320). NB. The denosumab prefilled syringe must be kept in its outer carton, in order to protect from light, and stored in a refrigerator. Alternatively, if the patient will need to collect their prescription from the pharmacy ensure an FP10 is written.
- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded
- Report any adverse events to the MHRA and discuss with a specialist if action is uncertain.

MHRA Alerts

1. May 2022 Denosumab 60mg (Prolia): should not be used in patients under 18 years due to the risk of serious hypercalcaemia
2. August 2020 Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment
3. June 2017 Densoumab:reports of osteonecrosis of the external auditory canal
4. July 2015 Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk
5. December 2014 Rare cases of atypical femoral fracture with long-term use
6. September 2014 Denosumab: updated recommendations

References

1. NOGG Clinical guideline for the prevention and treatment of osteoporosis 2021
2. SPC Prolia
3. Royal Osteoporosis Society Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management 2020
4. Royal Osteoporosis Society Denosumab Fact Sheet Drug treatments for osteoporosis: Denosumab (Prolia) | Royal Osteoporosis Society (windows.net)

Produced by: Linda Honey, Head of Medicines Management, NW Surrey CCG with input from Dr Sian Griffiths, Surrey & Sussex healthcare NHS Trust
Agreed by: Surrey Rheumatology Network April 2014 & Prescribing Clinical Network May 2014
Updated: Nov 2017, Sept 2018, May 2023 by Lis Stanford