NHS
Frimley
Clinical Commissioning Group

Denosumab 60mg (Prolia®) 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:
https://www.medicines.org.uk/emc/product/568/smpc#gref

Licence: Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.
Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

Criteria for Use: Denosumab has been approved by NICE 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 (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 for men and women as a risk factor.

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
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 Guideline 2017 July 2019 Final Update 290719.pdf (sheffield.ac.uk)

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 be adequately supplemented with calcium and vitamin D.

Frimley Osteoporosis pathway

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Denosumab is recommended as per the NICE TA 204 as one of the treatment options where oral bisphosphonates are contraindicated or not tolerated, with zoledronic acid 5mg annual infusion as an alternative. Patient factors such as age and convenience should be considered when making a choice between treatments, noting that denosumab should not be stopped without considering an alternative treatment due to the increased risk of vertebral fractures. Denosumab 60mg is GREEN (These are drugs that can be initiated and continued in primary) on the formulary.

Cautions (see BNF or SPC)

- Correct hypocalcaemia and vitamin D deficiency before starting therapy.
- Monitor plasma-calcium concentration during therapy by checking levels prior to each 6 monthly dose. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.
- 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.
- 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. (Contact a specialist if patient wishes to stop denosumab to discuss alternative options)

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- 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
- 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

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 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, sciatica, rash, eczema and abdominal discomfort.

Interactions (see BNF or SPC)

- No interaction studies have been performed.

Check list for initiation of denosumab:

- Assess the suitability of the patient for denosumab.
- Following MHRA Safety Alert: Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment (August) 2020 it is important to
    - 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.
    - Counsel patients that they should not stop denosumab treatment without talking to their doctor to discuss their individual risk factors.
    - Contact a specialist if patient wishes to stop denosumab to discuss alternative options.
    - Explain to patient 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.

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  - Give patient the reminder card which includes important safety information about osteonecrosis of the jaw and precautions to take.

- 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.
- Adequate intake of calcium and vitamin D is important in all patients. Check calcium and vitamin D levels prior to initiation. Co-prescribe supplements if appropriate, depending upon dietary intake.
- 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).
- 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 for up to 5 years

- **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 calcium and vitamin D supplement.
  - Attend the GP surgery every 6 months for the denosumab injection
  - Report any adverse events to the doctor who administered the injection.
  - Read the patient reminder card supplied

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On-going monitoring

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.
However, there have been reports of increased risk of multiple fractures in the spine after stopping or delaying ongoing treatment with denosumab 60mg (Prolia) treatment. It is recommended that denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

Practice Responsibilities

- Denosumab (product code PRO2653L) can be ordered via AAH Pharmaceuticals Ltd (AAH Customer Care telephone number: 0344561 8899 or on-line www.AAH.co.uk).
- Alternatively, a FP10 may be written for the patient or surgery to collect the injection from a pharmacy. Please note fridge storage is required and less suitable method or ordering.
- NB. The denosumab prefilled syringe must be kept in its outer carton, in order to protect from light, and stored in a refrigerator
- Report any adverse events to the MHRA and discuss with a specialist if action is uncertain.

Local Commissioned Service (LCS) Drug Monitoring/ Near patient testing

- Denosumab is included in this service. Practices signed up to the LCS should refer to the latest specification for details of payments and service requirements.
- The recommended monitoring will need to be carried out for payment to be achieved:
    - 6 monthly calcium levels.

MHRA Alerts

August 2020 Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment
June 2017 Densoumab:reports of osteonecrosis of the external auditory canal
July 2015 Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk
September 2014 Denosumab: updated recommendations

Ardens Resources- for information

- Ardens has a Clinical Safety Warning, which will flag when denosumab is issued and the patient has not had the recommended blood test within the previous 4 weeks.

- To ensure doses are not missed use the Ardens Diary Recall System, find out more here.

- Ardens Denosumab Diary Searches may be accessed in the population reporting. See screenshot below,

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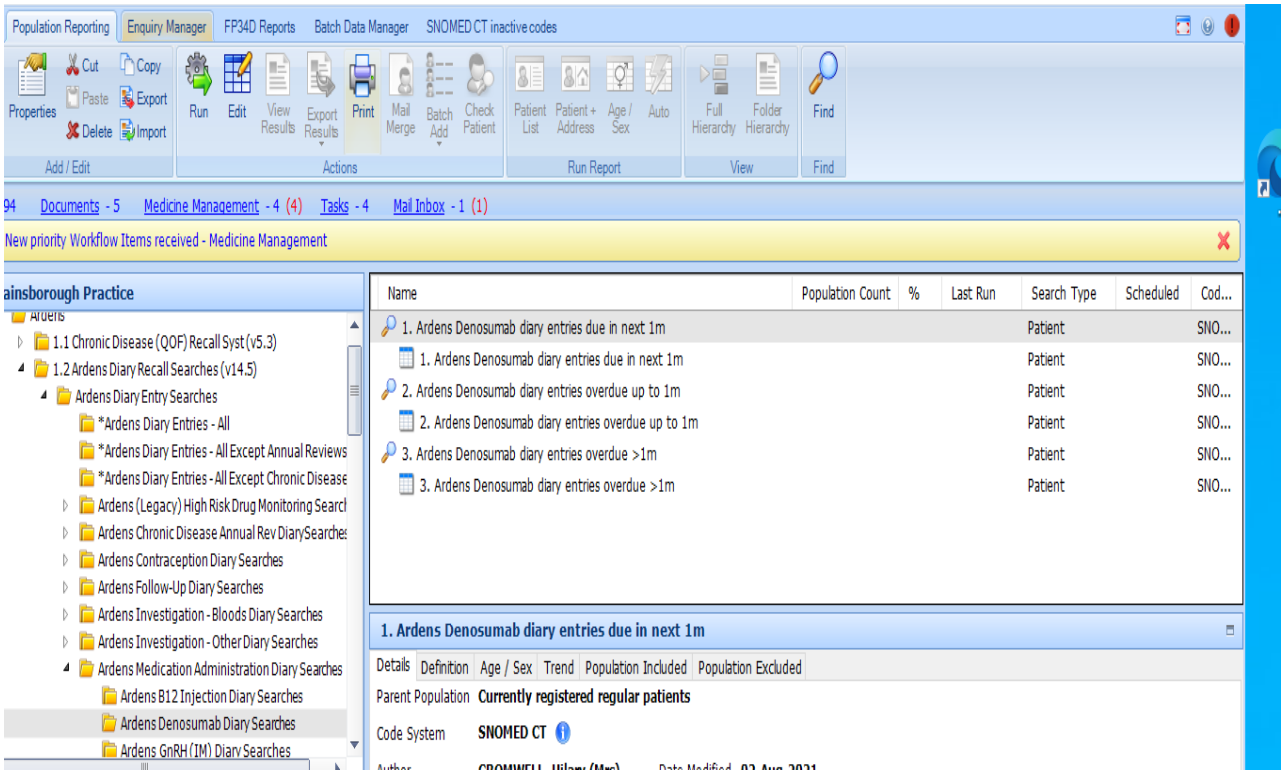

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