North of Tyne and Gateshead Area Prescribing Committee
Medicines Guidelines and Use Group

DENOSUMAB (Prolia®) 60mg sc twice yearly for osteoporosis Information for Treatment of Adults in Primary Care

Dec 2021 (expires Dec 2024)

Denosumab is licensed for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, bone loss associated with long-term systemic glucocorticoid therapy in patients at increased risk of fracture, and for bone loss associated with hormone ablation in men with prostate cancer. This information sheet applies to the use of denosumab in osteoporosis for both men and women.

Formulary Approved Indication

Denosumab is included in the North of Tyne & Gateshead Formulary for second and third line use in post menopausal osteoporosis in line with NICE and in men at increased risk of fractures, who fail to respond to, or have contraindications against, the use of oral bisphosphonates or strontium ranelate. It is classified Green PLUS in the formulary traffic light system.

Use in Osteoporosis

Denosumab (Prolia®) is a monoclonal antibody that inhibits osteoclast differentiation and survival, thereby decreasing bone resorption. NICE has approved it as cost-effective for use in postmenopausal women on the basis that initiation (first dose) will be in an outpatient environment in secondary care and subsequent doses will be given by a nurse in primary care (NICE TA204[1]). Within the North of Tyne & Gateshead Osteoporosis guidelines denosumab is placed as a second/ third line agent for patients where oral bisphosphonates are ineffective or not tolerated (NoT&G APC,2020[2]).

Denosumab (Prolia®) is also licensed for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and for bone loss associated with long-term systemic glucocorticoid therapy in patients at increased risk of fracture.
Denosumab in higher dosage (as XVEGA®▼, 120mg sc monthly) is licensed for use in patients with metastatic bone cancer from solid tumours. Such usage is outside the scope of this guidance.

Dose

60mg by subcutaneous injection every six months. No dosage adjustment is required in older people or in patients with renal impairment. Administration to the thigh, abdomen or back of arm should be performed by an individual who has been trained and is competent in subcutaneous injection. Care should be taken to adhere strictly to the six-month dosage regime (see “Stopping or Delaying Denosumab – risk of rebound vertebral fractures”, below).

Cautions

Adequate intake of calcium and vitamin D is important during treatment. Patients who are vitamin D deficient are at risk of severe hypocalcaemia after dosing. The risk of hypocalcaemia is increased further in patients with severe renal failure (CKD stage 4 or 5, eGFR <30 mL/minute) or on dialysis, as these patients may not adequately activate 25(OH) vitamin D. Use in patients in severe renal failure should be with the close involvement of a secondary care physician with experience in metabolic bone disorders.

Contra-indications

Hypocalcaemia or untreated vitamin D deficiency. Hypersensitivity to the active substance or any of the product excipients. Avoid use in pregnant or breastfeeding patients, or in children under 18 years of age.

Side-effects

- Mild, transient *hypocalcaemia* is common after therapy. Hypocalcaemia is most common in the first few weeks after dosing but can occur at any time. Rarely, denosumab can cause severe, life-threatening hypocalcaemia in patients, particularly if they are vitamin D deficient or in renal failure. Risk in patients receiving oncological doses (Xvega®▼) is higher, and fatal cases have occurred at these doses.

- Increased incidence of eczema (1.7% placebo, 3% denosumab), flatulence (1.4% placebo, 2.2% denosumab), skin infections / cellulitis (<0.1% placebo, 0.4% denosumab), urinary infections (0.5% placebo, 0.7% denosumab), and ear infections (0.1% denosumab, 0% placebo) were also observed in phase III trials.[3]

- The needle cover contains a derivative of latex which may potentially cause allergic reactions.

- Cases of *osteonecrosis of the jaw (ONJ)* have been reported but, as with bisphosphonates, the vast majority were in patients receiving the drug at higher doses (120mg monthly). Although extremely rare at the dosage used in the treatment of osteoporosis, to minimise the risk of this adverse effect, good oral hygiene should be maintained and patients should avoid invasive dental procedures if possible. *Osteonecrosis of the auditory canal* has been reported very rarely: consider in patients on denosumab presenting with chronic ear infections or suspected cholesteatoma[4].

- *Atypical femoral fractures (AFF)* have been reported rarely (incidence ≥1/10,000 to <1/1,000 per year of treatment) in patients with postmenopausal osteoporosis receiving long-term (≥ 2.5 years) treatment with denosumab 60 mg in clinical trials[5]. Although typically subtrochanteric they can occur anywhere along the femoral shaft. During denosumab treatment, patients presenting with new or unusual thigh, knee, hip or groin pain should be evaluated with bilateral full length femur XRs.

- The risk of both ONJ and AFFs appears to be increased in patients with rheumatoid arthritis, or who are on corticosteroid therapy. Denosumab is not a viable alternative anti-osteoporosis therapy for patients who experience either ONJ or AFF whilst on bisphosphonate therapy.

All serious adverse drug reactions with denosumab (Prolia®) should be reported using the yellow card system at https://yellowcard.mhra.gov.uk/

Before starting treatment with denosumab[6]

- Measure eGFR, calcium and vitamin D levels at baseline. Recheck eGFR and calcium prior to each dose of denosumab. Monitor vitamin D levels at least annually, but can be done prior to each dose if deemed clinically necessary.
- If 25(OH) vitamin D <50 nmol/l prior to commencing denosumab rapidly load the patient using colecalciferol 20,000 units TWICE a DAY for 10 days.
- Ask about risk factors for ONJ (corticosteroid use, smoking, poor oral hygiene, planned invasive dental surgery e.g., tooth extraction, dental infection).
- A dental assessment should be considered prior to treatment in patients with risk factors. The principle should be to get the patient as dentally fit as possible before initiating therapy. The Scottish NHS has issued useful guidance on avoidance of medication induced ONJ[7].

- Initiation of denosumab therapy should be delayed in patients with planned dental surgery. For patients currently receiving denosumab for osteoporosis who require dental surgery, the dental surgery should be delayed until 3 months post-denosumab dose as the risk of rebound vertebral fracture outweighs the risk of ONJ (see "Stopping or Delaying Denosumab", below).
- Whilst on denosumab therapy patients should be encouraged to maintain good dental hygiene, receive routine dental check-ups and report any oral symptoms.
- Patients should also be advised to report symptoms of hypocalcaemia (paraesthesiae, cramps, muscle twitching, spasms); of atypical femoral fracture (new, unusual hip or groin pain); or of ear pain, discharge or recurrent infection during treatment.
- Adequate intake of calcium and vitamin D during treatment should be maintained through supplementation or diet. Assessment of intake should be documented if supplementation not felt to be necessary.

Monitoring of denosumab (Prolia®)

The MHRA recommend monitoring of calcium levels

- prior to each dose of denosumab
- within two weeks of the initial dose in patients with renal impairment (eGFR<30ml/min) and hence predisposed to hypocalcaemia.
- If symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient
- A more stringent monitoring regime is recommended for patients on oncological doses of denosumab (Xvega▼) but is outside the scope of this document. See MHRA website for details[6].

Stopping or delaying Denosumab – risk of rebound vertebral fractures

Unlike potent bisphosphonates, denosumab does not exert a prolonged anti-osteoporotic effect. When used to treat osteoporosis, each dose is only effective for around six months. If an interval much over six to eight months is allowed to elapse between doses, then patients may experience rapid rebound loss of bone mineral density gained whilst on therapy. Under these circumstances patients may sustain so-called *rebound vertebral fractures* (RVFs), which can be multiple[8]. New MHRA data shows the increased risk of multiple rebound vertebral fractures continues for at least 18 months after stopping or delaying denosumab treatment[9] It is therefore recommended that the six-monthly dosing regime is strictly adhered to. Where dental surgery is required for a patient on denosumab therapy, then surgery should be delayed until 3 months after injection as the risk of rebound vertebral fracture outweighs the risk of ONJ. Previous advice to delay the denosumab injection and proceed with surgery is now felt unsafe.

It is unclear how this risk can be mitigated in patients where withdrawal of treatment is being considered. Because of this risk it may be preferable to continue denosumab therapy indefinitely; the extension to the FREEDOM trial showed continued improvement in BMD for up to ten years without plateau[10]. As such Denosumab must not be discontinued unless instructed by a secondary care bone specialist.

Denosumab therapy during Covid-19 (NICE rapid guideline NG167[11])

Denosumab must be administered at 6 monthly intervals and not delayed for any reason including Covid-19. To reduce contact with healthcare personnel and premises, the pre-treatment calcium check may be omitted during the pandemic in low risk individuals, e.g. those who:

1. Have previously received treatment with denosumab on 2 or more occasions without clinical or biochemical evidence of hypocalcaemia pre- or post-treatment
2. Are taking adequate calcium and vitamin D supplementation daily or almost daily providing ~1000mg calcium and ~800 units vitamin D per day
3. Have adequate and stable renal function - defined as CKD G1-3a

4. Have no new comorbidities/medications since previous injection likely to affect renal function or calcium handling

Precautions to reduce risk of hypocalcaemia if pre-treatment blood test is omitted

1. Ensure dietary and supplemental calcium equates to at least 1000mg per day
2. Ensure patient takes at least 800 units colecalciferol per day (a higher dose may be needed in obese patients)
3. Administration of an additional bolus of oral vitamin D a week or two prior to injection is advised, e.g. oral colecalciferol 20,000 units
4. Where feasible, a blood sample to check calcium and creatinine may be obtained at the time of injection

Drug Interactions

None known

How to order

Primary Care
Denosumab can be delivered directly to the practice within 24 hours (to order, contact Movianto on 01234 248631 – Product code 9002794). Alternatively, it can be provided to patients through a retail pharmacy by writing an FP10.

Secondary Care
Denosumab can be ordered directly from Amgen Ltd via e-mail to cs-uk@amgen.com (they cannot accept phone orders) quoting item to be supplied, quantity and hospital address. If registered with their system this will be sent within 24 hours.

Cost

NHS cost of each 1ml prefilled 60mg syringe is £183 (ie £366 for two injections per year).

How to store

Denosumab should be stored in a refrigerator (2° - 8°). Do not freeze. Keep the pre- filled syringe in the outer carton to protect from the light.

References

[1] NICE TA204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010). Available from https://www.nice.org.uk/guidance/ta204

[2] NoT&G APC Guideline for the management of osteoporosis in primary care. Available from: http://www.northoftyneapc.nhs.uk/wp-content/uploads/sites/6/2018/01/Osteoporosis-guidelines-including-bisphosphonate-review-Dec-17.pdf - Reference will need updating once guideline updated

[3] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009; 361: 756-765.

[4] Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal. MHRA 21/6/2017. Available from https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal

[5] Denosumab 60 mg (Prolia®): rare cases of atypical femoral fracture with long-term use : MHRA Feb 2013 Drug Safety update volume 6 Issue 7. Available from https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia

[6] Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia. MHRA 25/9/2014, accessible from https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations

[7]Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw; NHS Education for Scotland. Available from: http://www.sdcep.org.uk/wp-content/uploads/2017/04/SDCEP-Oral-Health-Management-of-Patients-at-Risk-of-MRONJ-Guidance-full.pdf

[8] Vertebral fractures after discontinuation of Denosumab: a Post Hoc analysis of the FREEDOM trial and it's extension. Cummings *et al* J Bone Min Res (2018). Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jbmr.3337

[9] Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment, MHRA Aug 2020 Drug Safety Update Volume 14 Issue 1. Available from: https://www.gov.uk/drug-safety-update/denosumab-60mg-prolia-increased-risk-of-multiple-vertebral-fractures-after-stopping-or-delaying-ongoing-treatment

[10] 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open label extension. Bone *et al* Lancet (2017). Available from: https://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587(17)30138-9.pdf

[11] "COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders" NICE guideline [NG167]Published date: 03 April 2020 Last updated: 02 July 2020. Available from: https://www.nice.org.uk/guidance/ng167/chapter/4-Treatment-considerations