Summary of ONZ & FLNNZ Denosumab Recommendations

Osteoporosis New Zealand (ONZ) and the Fracture Liaison Network New Zealand (FLNNZ) have jointly developed recommendations for the use of denosumab (Prolia®) following the expansion of Pharmac-funded access from March 2025.

Denosumab, a monoclonal antibody targeting RANKL, significantly reduces bone resorption, increases bone mineral density, and lowers fracture risk. It is recommended for high-risk osteoporosis patients who cannot take oral or IV bisphosphonates due to adverse effects, contraindications (e.g., renal impairment), or ongoing fractures despite prior bisphosphonate therapy.

Key considerations for prescribing denosumab (Prolia®)

- Lifelong treatment commitment: Patients must understand and commit to ongoing injections every six months to avoid rapid bone loss and 'rebound' vertebral fractures.
- Pre-treatment assessments: Renal function and serum calcium levels must be evaluated to mitigate the risk of hypocalcaemia, particularly in CKD patients.
- Vitamin D and calcium supplementation: Patients should be vitamin D replete and take calcium supplements if at risk for deficiency.

Use in Chronic Kidney Disease (CKD)

- CKD 1-2: Denosumab can be prescribed as in the general population.
- CKD 3: Can probably be used if CKD-mineral and bone disorder (CKD-MBD) is ruled out.
- CKD 4-5: Not recommended unless in consultation with an osteoporosis or renal specialist due to a high risk of severe hypocalcaemia.

Post-prescription monitoring and potential side effects

- Monitoring: Patients at risk of hypocalcaemia should have serum calcium checked 7-14 days post-injection.
- Side effects: These include hypocalcaemia, atypical femoral fractures (AFF), osteonecrosis of the jaw (ONJ), and skin reactions.

Discontinuation guidelines

- Denosumab should not be stopped abruptly due to the risk of rebound fractures. If discontinuation is necessary, a bisphosphonate (e.g., IV zoledronate) should be initiated six months after the last dose to prevent rapid bone loss.

Recommendations for use of Denosumab (Prolia®) in New Zealand

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This recommendations document was developed independently from Amgen, the manufacturer of Prolia®. Task force members have no declaration of interest in relation to developing this document.

Why?

- From the 1st of March 2025, Pharmac has broadened the funded access to denosumab (Prolia®) in patients with osteoporosis.

What is denosumab?

- Denosumab is a monoclonal antibody against RANKL.
- RANKL binds to osteoclasts and its precursors to proliferate and activate them, leading to increased bone resorption and turn-over.
- Denosumab use results in drastic reduction in bone resorption, increased bone mineral density, and reduced fracture risk.

This document refers specifically to the **Prolia® brand** of denosumab (60mg subcutaneous injection delivered every 6 months), and our recommendations are relevant to patients who meet the new Pharmac funding criteria below.

Denosumab

Initial application — Osteoporosis
Applications from any relevant practitioner. Approvals valid without further renewal unless notified.
Prerequisites(tick boxes where appropriate)

- ☐ The patient has established osteoporosis

and

- ☐ History of one significant osteoporotic fracture demonstrated radiologically, with a documented T-Score less than or equal to -2.5, that incorporates BMD measured using dual-energy x-ray absorptiometry (DEXA)

or

- ☐ History of one significant osteoporotic fracture, demonstrated radiologically, and either the patient is elderly, or densitometry scanning cannot be performed because of logistical, technical or pathophysiological reasons

or

- ☐ History of two significant osteoporotic fractures demonstrated radiologically

or

- ☐ Documented T-Score less than or equal to -3.0

or

- ☐ A 10-year risk of hip fracture greater than or equal to 3%, calculated using a published risk assessment algorithm that incorporates BMD measured using DEXA

and

- ☐ Bisphosphonates are contraindicated because the patient's creatinine clearance or eGFR is less than 35 mL/min

or

- ☐ The patient has experienced at least two symptomatic new fractures or a BMD loss greater than 2% per year, after at least 12 months' continuous therapy with a funded antiresorptive agent

or

- ☐ Bisphosphonates result in intolerable side effects

or

- ☐ Intravenous bisphosphonates cannot be administered due to logistical or technical reasons

Which patients to prescribe denosumab (Prolia®)

- It is intended for use in patients with established osteoporosis who are at high risk of future fractures, who are not suitable for oral or intravenous bisphosphonate.
- These include patients with significant adverse drug reactions to bisphosphonates, those with renal function not suitable for bisphosphonate use, and those experiencing further fragility fractures despite adequate bisphosphonate use.

Before prescribing denosumab

Denosumab (Prolia®) is generally considered a life-long treatment

- Denosumab **must not be delayed or stopped,** otherwise patients are at risk of a rapid loss of bone mineral density, often leading to **'rebound' vertebral fractures.**
    - It should, therefore, only be used in patients who understand and agree to the life-long nature of this treatment and who will be able to be reliably followed up.
- At the moment, there is no large-scale long-term data beyond 10 years of denosumab use, therefore prescribers should carefully consider all other options before using it in younger patients.

Hypocalcaemia is a common, rarely life-threatening, side-effect

- All patients should have their renal function (ideally creatinine clearance (CrCl) especially in >80 years of age and weight <45kg) and albumin-adjusted serum calcium checked prior to being prescribed denosumab. This is because of the risk of hypocalcaemia, particularly in chronic kidney disease (CKD). If hypocalcaemia is detected, denosumab should not be prescribed until calcium has been replaced (e.g. with 500mg BD of elemental calcium for a few weeks) and is in the normal range.
- Patients with risk factors for post-treatment hypocalcaemia should be on calcium supplementation of 500-1000mg/day (in addition to recommendations about dietary calcium intake of 1000-1300mg/day) for at least 2-3 months after the denosumab dose.
  Main risk factors for hypocalcaemia are:
    - CKD 4-5 (eGFR/CrCl <30) [use CrCl in elderly >80 and in those with very low body weight <45kg]
    - Pre-treatment hypocalcaemia
    - Malabsorptive conditions
    - Low vitamin D level/ *high risk for vitamin D deficiency (e.g. frail/ institutionalised elderly, veiled women and those with dark skin living at higher latitudes)
- All patients must be vitamin D replete. In CKD 3-5 and those at high risk for vitamin D deficiency (**see above*) not on adequate replacement, 25(OH) vitamin D level should ideally be checked. If this is not possible, or vitamin D insufficiency (<50 nmol/L) is confirmed, then patient should be loaded with vitamin D (e.g. 2 x 1.25mg cholecalciferol capsules followed by another 2 x 1.25mg dose after a week, then 1 x 1.25mg monthly thereafter). Denosumab treatment should be delayed for at least 3 weeks after the second loading dose of cholecalciferol.

- Patients should also be counselled to seek medical attention if they experience symptoms of hypocalcaemia (muscle spasms, twitches, or cramps, numbness or tingling in fingers, toes, or around the mouth.)
- Denosumab should not be administered within a few weeks of iron infusion – there is a risk of an interaction resulting in hypocalcaemia and/or hypophosphataemia.
- Consider a dental review in patients with planned extractive dental procedures. This is because of the very small risk of osteonecrosis of the jaw (ONJ) (**see below).

Denosumab (Prolia®) use in chronic kidney disease (CKD)

- The risks of complication (primarily hypocalcaemia) are significantly higher in patients with CKD, and as such great care must be taken before using denosumab in this group.
- CKD 1-2 (eGFR/CrCl >60): Denosumab can be prescribed as in the general population.
- CKD 3 (eGFR/CrCl 30-59): Denosumab can probably be prescribed safely in this group if they have no evidence of CKD-mineral and bone disorder (CKD-MBD), i.e. a normal PTH, serum calcium, phosphate, and are vitamin D replete.
- CKD 4 (eGFR/CrCl 15-29): We recommend not initiating unless you have discussed with an osteoporosis specialist or a renal physician.
- CKD 5 (eGFR/CrCl <15): We recommend not initiating. Denosumab in this group should be initiated by a renal physician or osteoporosis specialist in discussion with a renal physician. The risk of hypocalcaemia, including severe life-threatening hypocalcaemia, is highest in this group. A renal physician will make the decision about the use of calcitriol and calcium supplementation according to the clinical need of the individual patient.

After prescribing denosumab (Prolia®):

- In any patients with *risk factors* for hypocalcaemia, we recommend checking (albumin adjusted) serum calcium between 7-14 days post injection.
- *Risk factors* include:
    - CKD 3-5 (eGFR/CrCl <60)
    - Pre-treatment hypocalcaemia
    - Malabsorptive conditions
    - Low vitamin D levels/ high risk for vitamin D deficiency (e.g. frail/institutionalised elderly, veiled women and those with dark skin living at higher latitudes)
- Denosumab **MUST be given every 6 months**, and so it is very important to establish a recall process. At the absolute latest, it should be given 1 month late. The use of standard primary care Practice Management System recall and reminder processes are considered the bare minimum.

Side effects to be aware of:

- Rebound rapid loss of bone mineral density (BMD) if treatment ceased/ delayed (as discussed above)
- Hypocalcaemia (as discussed above)
- Atypical femoral fracture (AFF, 0.8 per 10,000 patient years)
- **Osteonecrosis of the jaw (ONJ, 5.2 per 10,000 patient years)
    - Risk factors include poor oral hygiene, invasive dental procedures such as tooth extractions, dental implants, active cancer with bone lesions, immunosuppression and uncontrolled diabetes.
- Skin reactions (either cellulitis or allergic)
- Mild aches and pains in the days afterwards

Bone density (DXA) monitoring:

- DXA monitoring can be considered after several years of denosumab treatment. However, as management strategy is highly unlikely to be altered by the DXA result, the merit of a repeat DXA is diminished.

Fractures while on denosumab (Prolia®):

- Fractures will occur in some denosumab treated patients as anti-osteoporosis medications significantly reduce, but do not eliminate, fragility fractures. Therefore, even if fracture occurs while on denosumab therapy, treatment should be continued.

Discontinuing denosumab (Prolia®):

- Denosumab is considered an indefinite treatment, but discontinuation may occur in response to significant adverse events, as a consequence of patient preference or non-adherence.
- If discontinuation is necessary, the case should be promptly discussed with a local bone clinic/ osteoporosis specialist.
- When denosumab is stopped, BMD decreases in all skeletal sites with most of the loss occurring in the first 6 months. Risk of 'rebound' vertebral fractures is particularly high in patients who have received more than 2 years of denosumab treatment.
- Denosumab should not be stopped without appropriate replacement antiresorptive therapy except in specific circumstances (such as end of life care).
- Denosumab should not be transitioned to teriparatide, because of evidence linking this to a reduction in BMD.
- If discontinuing denosumab, your local bone clinic/ osteoporosis specialist will likely recommend:
    - Commencing bisphosphonate therapy (IV zoledronate or oral bisphosphonate) 6 months after the last denosumab injection – renal function allowing, especially for IV zoledronate.
    - Closely monitoring procollagen type 1 N-terminal propeptide (P1NP) for confirmation maintenance of adequate suppression of bone turnover, with values of P1NP of >35ug/L guiding further dosage if IV zoledronate was used or medication change (to IV zoledronate) if oral bisphosphonate was used.
    - Bisphosphonate treatment to be continued for at least 1-2 years.

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