Greater Manchester Interface Prescribing Group Shared Care Template

Shared Care Guideline the use of Denosumab for the prevention of osteoporotic fractures in postmenopausal women.	**Reference Number**
Author(s)/Originator(s): (please state author name and department) *Dr Neil Snowden, Consultant Rheumatologist, Pennine MSK (with acknowledgement to Dr Sophia Naz, Consultant Rheumatologist, PAHT who developed the SCG).*	**To be read in conjunction with the following documents:** Current Summary of Product characteristics (http://www.medicines.org.uk) BNF
Date approved by Commissioners:	**Review Date:**

Please complete all sections

1. Licensed Indications	Treatment of osteoporosis in postmenopausal women at increased risk of fractures.
2. Therapeutic use & background	Denosumab (Prolia, Amgen) is a monoclonal antibody that reduces osteoclast activity, and so reduces bone breakdown. Denosumab is indicated for use in patients with an intolerance of, or a contraindication to oral bisphosphonates. It would be expected that Denosumab would not be used for intolerance until the patient has tried both Alendronic Acid and Risedronate: a. For primary prevention only for those with severe osteoporosis (essentially only when T score<-4) b. For secondary prevention in those at high risk of further fracture.
3. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	Hypocalcaemia and vitamin D deficiency must be corrected before initiating therapy. Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia such as patients with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe

	renal impairment/dialysis. Patients receiving Denosumab (Prolia) may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. Osteonecrosis of the jaw (ONJ) has been reported in patients treated with Denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis. ONJ has been reported rarely in clinical studies in patients receiving Denosumab at a dose of 60 mg every 6 months for osteoporosis. There have been reports of ONJ in clinical studies in patients with advanced cancer treated with Denosumab at the studied dose of 120 mg administered monthly. Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (e.g., pre-existing dental disease, anaemia, coagulopathy, infection) and previous treatment with bisphosphonates. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Denosumab (Prolia) in patients with concomitant risk factors. While on treatment, these patients should avoid invasive dental procedures if possible. Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on Prolia therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with Prolia, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation. 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 or in those with suspected cholesteatoma. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. Patients being treated with Prolia should not be treated concomitantly with other Denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours). <u>Warnings for Excipients</u> Patients with rare hereditary problems of fructose intolerance should not use Prolia.

<table>
<tr><td>4. Prescribing in pregnancy and lactation</td><td colspan="3">This drug cannot be prescribed in the pregnant or breastfeeding patient. Under these circumstances prescribing should be the responsibility of the Consultant Rheumatologist</td></tr>
<tr><td rowspan="9">5. Dosage regimen for continuing care</td><td>Route of administration</td><td colspan="2">Subcutaneous Injection</td></tr>
<tr><td colspan="3">Preparations available:

Pre-filled syringe contains 60 mg of Denosumab in 1 ml of solution (60 mg/ml).</td></tr>
<tr><td colspan="3">The recommended dose of Denosumab is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.</td></tr>
<tr><td>Is titration required</td><td></td><td>No</td></tr>
<tr><td colspan="3">The first year of therapy (i.e. first 2 Denosumab injections) will usually take place in the community specialist service with the drug being administered in clinic by the rheumatology specialist nurses at Pennine MSK</td></tr>
<tr><td colspan="3">Conditions requiring dose reduction
e.g. impaired renal/ liver function
No dose adjustment is required in patients with renal impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.</td></tr>
<tr><td colspan="3">Usual response time
12 months</td></tr>
<tr><td colspan="3">Duration of treatment
There are no data on the ideal duration of Denosumab therapy, although it is important to note that markers of bone turnover increase within three to six months after discontinuation of Denosumab consideration should be given to alternative agents 6 months after the last injection as its effects are short lived.</td></tr>
<tr><td colspan="3">Treatment to be terminated by
As per advice of individual clinician on case by case basis</td></tr>
<tr><td colspan="3">NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.</td></tr>
<tr><td>6.Drug Interactions

For a comprehensive list consult the BNF or Summary of Product</td><td colspan="3">The following drugs must <u>not</u> be prescribed without consultation with the specialist:

No interaction studies have been performed. 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)</td></tr>
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<tr><td>Characteristics</td><td colspan="3">The following drugs may be prescribed with caution:

Denosumab may enhance adverse/toxic effect of immunosuppressant’s, specifically the risk for serious infections may be increased</td></tr>
<tr><td rowspan="8">7. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF</td><td colspan="3">Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.</td></tr>
<tr><td>Adverse event
System – symptom/sign</td><td>Action to be taken
Include whether drug should be stopped prior to contacting secondary care specialist</td><td>By whom</td></tr>
<tr><td>Hypocalcemia: Denosumab may cause or exacerbate hypocalcemia; severe symptomatic cases (including fatalities) have been reported. Monitor calcium levels; correct pre-existing hypocalcemia prior to therapy.</td><td>Stop or do not commence drug if hypocalcaemic and ensure adequate calcium and vitamin D intake. Check renal function and bone profile before administration</td><td>To be done by secondary care physician for first 12 months and GPs subsequently for those patients with creatinine clearance<30ml/min)</td></tr>
<tr><td>Infection: UTIs and URTIs are common. Cellulitis, diverticulitis and ear infection are uncommon</td><td>Patients should be advised to contact healthcare provider if signs or symptoms of severe infection or cellulitis develop.</td><td>Evaluate the need for continued treatment with serious infection (secondary care physician in first 12 months and GP thereafter)</td></tr>
<tr><td>ONJ (may manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth/periodontal infection, toothache, gingival ulceration/erosion.)</td><td>Patients developing ONJ while on Denosumab therapy should receive care by a dentist or oral surgeon. Further treatment should be based on individual benefit/risk evaluation.</td><td>To be done by secondary care physician for first 12 months and GPs subsequently</td></tr>
<tr><td>Dermatologic reactions</td><td>Dermatitis, eczema, and rash (which are not necessarily specific to the injection site) have been reported. Consider discontinuing if severe symptoms occur</td><td>To be done by secondary care physician for first 12 months and GPs subsequently</td></tr>
<tr><td colspan="3">The patient should be advised to report any of the following signs or symptoms to their GP without delay:

Patients should be advised to contact their healthcare provider if signs or symptoms of severe infection or cellulitis develop.</td></tr>
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<tr><td></td><td colspan="5">Other important co morbidities (e.g.Chickenpox exposure). Include advice on management and prevention and who will be responsible for this in each case:
As above</td></tr>
<tr><td></td><td colspan="5">Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the “Yellow Card” scheme.</td></tr>
<tr><td>8.Baseline investigations</td><td colspan="5">List of investigations / monitoring undertaken by secondary care

Renal function and bone profile should be done prior to treatment.
Patients with chronic kidney disease (creatinine clearance <30 mL/min, including patients receiving dialysis) are at higher risk for hypocalcemia following Denosumab administration than patients with normal renal function. Calcium should be measured in such patients approximately 10 days after Denosumab administration. Monitoring of serum calcium is not required in patients with normal renal function
If hypocalcaemia risk also check magnesium and phosphate</td></tr>
<tr><td>9. Ongoing monitoring requirements to be undertaken by GP</td><td colspan="3">Is monitoring required?</td><td colspan="2">Yes or No (if yes complete following section) Yes, but only for patients with creatinine clearance < 30ml/min</td></tr>
<tr><td></td><td>Monitoring</td><td>Frequency</td><td>Results</td><td>Action</td><td>By whom</td></tr>
<tr><td></td><td>Bone profile and Renal function for patients with Creatinine clearance <30ml/min</td><td>Every 6 months</td><td>Treat any hypocalcaemia prior to Denosumab administration</td><td>Treat any hypocalcaemia prior to Denosumab administration</td><td>To be done by secondary care physician for first 12 months and GPs subsequently</td></tr>
<tr><td></td><td>Bone profile and Renal function for patients with Creatinine clearance <30ml/min</td><td>10 days after Denosumab</td><td>Treat any hypocalcaemia</td><td>Treat any hypocalcaemia</td><td>To be done by secondary care physician for first 12 months and GPs subsequently</td></tr>
<tr><td>10. Pharmaceutical aspects</td><td colspan="5">e.g. special storage requirements, washout periods Or where there are “no special considerations”

Determine stocking process for the injection –ideally it will be stored in the practice refrigerator; where this is not possible, work with local pharmacy/pharmacies to agree process for collection.</td></tr>
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	1. Ensure patient is taking calcium and vitamin 2. Before administration, inspect the solution. Do not inject the solution if it contains particles, or is cloudy or discoloured. Do not shake excessively. 3. To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting and inject slowly (company leaflet is available with specific instructions for administration). 4. Inject the entire contents of the pre-filled syringe and dispose of any medicinal product remaining in the pre-filled syringe 5. Any unused product or waste material should be disposed of in accordance with local requirements 6. Record batch number and site of injection on patient's notes 7. Instruct patient to report any adverse events to the practice so these can in turn be reported to the MHRA
11. Secondary care contact information	**If stopping medication or needing advice please contact:**
	Rheumatology team
	Contact number: 0161 621 3838
	Hospital: Pennine MSK Partnership
12. Criteria for shared care	Prescribing responsibility will only be transferred when . Treatment is for a specified indication and duration. . Treatment has been initiated and established by the secondary care specialist. . The patient's initial reaction to and progress on the drug is satisfactory. . The GP has agreed in writing in each individual case that shared care is appropriate. . The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements
13. Responsibilities of initiating specialist	Initiate treatment for the first 12 months. Undertake baseline monitoring. Monitor patient's initial reaction to and progress on the drug. Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan. Provide patient with relevant drug information to enable informed consent to therapy Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action Provide patient with relevant drug information to enable understanding of the role of monitoring. --- Repeat prescribe and administer the Denosumab injection at 6 monthly intervals as specified by the initiating specialist.
14. Responsibilities of the GP	Ensure no drug interactions with concomitant medicines

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<tr><td>15. Responsibilities of the patient</td><td colspan="4">To monitor and prescribe in collaboration with the specialist according to this protocol

To ensure that the monitoring and dosage record is kept up to date

Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary.

After 3 years of treatment, review therapy

To take medication as directed by the prescriber, or to contact the GP if not taking medication

To attend hospital and GP clinic appointments

To report adverse effects to their Specialist or GP.</td></tr>
<tr><td rowspan="3">16.Additional Responsibilities</td><td>List any special considerations</td><td>Action required</td><td>By whom</td><td>Date</td></tr>
<tr><td>[insert]</td><td>[insert]</td><td>[insert]</td><td>[insert]</td></tr>
<tr><td>[insert]</td><td>[insert]</td><td>[insert]</td><td>[insert]</td></tr>
<tr><td>17. Supporting documentation</td><td colspan="4">The SCG must be accompanied by a patient information leaflet.</td></tr>
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