Denosumab *(Prolia®)* (TLS Amber)

Shared Care Guidelines: For the treatment of postmenopausal osteoporosis.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of Denosumab for postmenopausal osteoporosis is shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with postmenopausal osteoporosis are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for Denosumab and the consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Initiate treatment and administer the first dose.
2	Discuss the benefits and side effects of treatment with the patient. Advise patients that they should seek prompt medical attention if they develop signs or symptoms of cellulitis. Advise the patient to promptly report any signs or symptoms of hypocalcaemia to their doctor. Patients should also maintain good oral hygiene, receive routine dental check-ups during treatment and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist. Advise all patients with concomitant risk factors that a dental examination with appropriate preventative dentistry will be necessary prior to treatment. Such patients should also be warned to avoid invasive dental procedures whilst on this treatment if possible. Ensure that the patient understands that dosing is via subcutaneous injection every 6 months, administered at their GP surgery.
3	Ask the GP whether he or she is willing to participate in shared care, and discuss the shared care arrangement with the patient & obtain their consent.
4	Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.
5	Baseline calcium levels will be taken initially and any hypocalcaemia will be corrected by adequate intake of calcium & vitamin D before initiating therapy.
6	Baseline vitamin D levels will be taken initially and any deficiency will be corrected by adequate intake of vitamin D before initiating therapy UNLESS the patient is seen in the GWH Orthogeriatric Clinic following confirmed osteoporotic hip fracture, where baseline vitamin D levels will not be taken but all patients will be pre-loaded with vitamin D before initiation of denosumab.
7	Identify all patients with risk factors for hypocalcaemia and check their calcium levels 2 weeks after initial dose.
8	Check calcium levels before any subsequent dose of denosumab administered at Great Western Hospital.
9	Review the patient's condition and monitor response to treatment regularly where indicated.
10	Give advice to the GP on when to stop treatment.
11	Report adverse events to the MHRA & GP.
12	Ensure that clear backup arrangements exist for GPs to obtain advice and support.

	General Practitioner responsibilities
1	Reply to the request for shared care as soon as practicable.
2	Prescribe medicine at the dose recommended and also calcium & vitamin D supplements.
3	Ensure that the patient understands dosing is via subcutaneous injection every 6 months, and will be administered at their GP surgery.
4	Ensure compatibility with other concomitant medication.
5	Check calcium levels before each dose of denosumab and if suspected symptoms of hypocalcaemia occur.
6	Regular monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.
7	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
8	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment.
9	Stop treatment on the advice of the specialist.
10	Report adverse events to the specialist and MHRA.

Patient's role	
1	Attend all appointments with GP and specialist.
2	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
3	Share any concerns in relation to treatment with medicine.
4	Inform specialist or GP of any other medication being taken, including over-the-counter products.
5	Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Dr David Collins Consultant Rheumatologist	01793 604317	n/a	01793 605387	David.Collins@gwh.nhs.uk
Dr Nicola Watson Consultant Orthogeriatrician	01793 605108	n/a	01793 605157	Nicola.Watson@gwh.nhs.uk
Dr Sarah Woods Associate Specialist in Orthogeriatrics	01793 605106	n/a	01793 605157	sarah.woods@gwh.nhs.uk
Hospital Pharmacy Dept:	01793 605029/605024	n/a	01793 605028/605021	medinfo@gwh.nhs.uk

Points for the GP to pass on to the patient.

SUPPORTING INFORMATION
Summary of condition and licensed indications.

Postmenopausal osteoporosis is a condition that mainly affects older women and is characterized by a decrease in bone mass.
Denosumab is indicated for:

- Treatment of osteoporosis in postmenopausal women at increased risk of fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (but indication is not covered by this Shared Care Agreement).

Treatment Aims (Therapeutic plan)
Denosumab is the first in a new class of drugs to treat osteoporosis. It is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to receptor activator of nuclear factor-K B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

As this drug is the first in a new class of drugs for the treatment of postmenopausal osteoporosis it was deemed to be appropriate to provide a shared care agreement for GPs.

- Evidence to support efficacy is from one double-blind, randomised, placebo-controlled study of the effect of denosumab on fracture prevention in postmenopausal women, 60 to 90 years with bone mineral density (BMD) T-score (total hip or lumbar spine) < -2.5 but ≥ -4.0.
- The incidence of new radiographic vertebral fractures at 3 years was 2.3% (86/3,702) and 7.2% (264/3,691) for patients receiving denosumab and placebo, respectively. This represents a relative reduction in risk of 68% for denosumab, risk ratio (RR) 0.32 (95% confidence interval [CI] 0.26 to 0.41).
- Denosumab reduced the risk of hip fracture relative to placebo, cumulative incidence 0.7% versus 1.2% for denosumab and placebo, respectively, HR 0.60 (95% CI 0.37 to 0.97), a 40% relative risk reduction.
- Denosumab reduced new clinical vertebral fractures relative to placebo, 0.8% versus 2.6% RR 0.31 (95% CI 0.20 to 0.47) (cumulative Kaplan-Meier estimate).
- Denosumab produced a relative increase in bone mineral density of 9.2% (95% CI 8.2 to 10.1) in lumbar spine and 6.0% (95% CI 5.2 to 6.7) in total hip relative to placebo. Denosumab also reduced bone turnover markers serum C-telopeptide and serum procollagen type 1 N-terminal propeptide by 72% and 76%, respectively relative to placebo at 36 months.

NICE TA204 (October 2010) sets out how this drug should be used in primary & secondary prevention in postmenopausal women. Further information about the appropriate use of this drug in the treatment pathway for postmenopausal osteoporosis can be found at NHS Wiltshire, BANES & Swindon's joint formulary websites.

Treatment Schedule (including dosage and administration)
The recommended dose of Denosumab in postmenopausal women is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.

Patients that continue on Densoumab at 5 years need to be referred back to a specialist in order to decide whether the medication should be continued or not.

Contra-indications and precautions for use

- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients.
- Patients with rare hereditary problems of fructose intolerance should not use Prolia.

N.B. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

Adequate calcium & vitamin D intake is important for all patients. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D 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.

Patients receiving 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.

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 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.

Side-effects

Common (≥ 1/100 to <1/10): Urinary tract infection, Upper respiratory tract infection, sciatica, cataracts*, constipation, rash, pain in extremity.
Uncommon (≥ 1/1,000 to <1/100): Diverticulitis*, cellulitis, ear infection, eczema.
Very rare (<1/10,000): Hypocalcaemia.

**There was no evidence of increased incidence of cataracts or diverticulitis in postmenopausal women with osteoporosis; these conditions occurred only in patients with prostate cancer.*

Refer patient back to the specialist if any of these side-effects cause concern. Refer to the SPC for a full list of adverse effects & further information http://www.medicines.org.uk.

Denosumab was launched in May 2010 and has black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Monitoring

Parameter	Frequency of monitoring	Action (adjustment and referral back to hospital)
Calcium levels	Check 4 weeks after initial dose, then before each subsequent dose of denosumab or if symptoms of hypocalcaemia occur.	If level is low, check compliance with calcium/vitamin D supplement and re-check in 4 wks providing patient is asymptomatic. If patient is symptomatic seek specialist advice.

Drug Interactions
No interaction studies have been performed.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

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).

Ensure you ask the patient about concomitant medications including over-the-counter medications.

Cost
At current prices, one year's treatment with medicine at the dose is £366.

References

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009 Aug 20; 361(8):756-65.
Electronic Medicines Compendium. Summary of Product Characterisitics. Prolia (denosumab). Amgen Ltd. http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/
NICE TA 204 October 2010. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. http://www.nice.org.uk/nicemedia/live/13251/51293/51293.pdf

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