Denosumab *(Prolia®)* (*TLS Amber with shared care*)

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 are 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.

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. Patients should also maintain good dental hygiene during treatment Advise that for patients with concomitant risk factors, a dental examination with appropriate preventative dentistry may 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 the 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. Refer to the shared care arrangements and provide copy/link to the shared care guidelines.
5	Baseline calcium & vitamin D levels will be taken initially and any hypocalcaemia will be corrected by adequate intake of calcium & vitamin D before initiating therapy.
6	Review the patient's condition and monitor response to treatment regularly where indicated.
7	Check for ONJ risk factors before starting Denosumab. A dental examination and any appropriate preventive dentistry work are now recommended for patients with risk factors. Tell patients to maintain good oral hygiene and report any oral symptoms. (MHRA advice September 2014)
8	Give advice to the GP on when to stop treatment.
9	Report adverse events to the MHRA & GP.
10	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 that the dosing is via subcutaneous injection every 6 months, administered at their GP surgery.
4	Ensure compatibility with other concomitant medication.
5	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. new incident fracture, decline in BMD) or intolerance to therapy occurs.
6	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.
7	Stop treatment on the advice of the specialist.
8	Report adverse events to the specialist and MHRA.
9	Patients should have their calcium monitored prior to administering each dose of denosumab. and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured.
10	Patients that continue on denosumab at 5 years need to be discussed with a specialist in order to decide whether denosumab should be continued or not.

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.
6	Maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to their doctor or dentist.
7	Report symptoms of hypocalcaemia to their doctor (eg, muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).

BACK-UP ADVICE AND SUPPORT

Contact details	Telephone No.	Bleep:	Email address:
Specialist: Dr Zoe Cole	01722 336262 ext 4791		Zoe.cole@salisbury.nhs.uk
Other: Cathy Gulliver, Sister Rheumatology	01722 336262 Ext 4136		Cathy.gulliver@salisbury.nhs.uk

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.

NICE TA204 (October 2010) sets out how this drug should be used in primary & secondary prevention in postmenopausal women.

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 denosumab at 5 years need to be referred back to a specialist in order to decide whether denosumab 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 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 denosumab 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 denosumab 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 denosumab therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with denosumab, 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. New MHRA guidance Drug Safety Update in Oct 2014 http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452540

Denosumab Monitoring
Updated September 2014 as per MHRA guidance: Denosumab is also associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment. Consider monitoring calcium levels more frequently in patients with risk factors for hypocalcaemia (e.g. severe renal impairment, creatinine clearance <30 ml/min).

Monitoring parameters	**Frequency of monitoring**	**Action (adjustment and referral back to hospital)**
For patients with a Creatinine Clearance of ≤ 35ml/min or those receiving dialysis. *This is calculated using the Cockcroft-Gault Equation which requires the patients height weight and creatinine level.*	**Check serum calcium weekly for at least one month and until calcium normalised post each injection.** Check creatinine clearance and serum calcium before each dose.	Seek specialist advice if calcium level low and /or patient is symptomatic. Ensure compliance with calcium and vitamin D supplementation.

For patients with a Creatinine clearance of > 35ml/min or those receiving dialysis. *This is calculated using the Cockcroft-Gault Equation which requires the patients height weight and creatinine level (see next page)*	**Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose.**	If serum calcium level is low, check compliance with calcium/vitamin D supplement and re-check serum calcium in 2 weeks providing patient is asymptomatic. If patient is symptomatic seek specialist advice. Should the **Creatinine Clearance** fall to ≤35ml/min, please contact specialist for advice before going ahead with the injection.

NB. On TPP Primary Care prescribing systems Creatinine Clearance is calculated automatically using equation below.

Cockcroft-Gault Equation (see BNF) *http://www.evidence.nhs.uk/formulary/bnf/current/guidance-on-prescribing/prescribing-in-renal-impairment/principles-of-dose-adjustment-in-renal-impairment*

Cockcroft and Gault formula:

$$\text{Estimated Creatinine Clearance in mL/minute} = \frac{(140 - \text{Age (yrs)}) \times \text{Weight(kg)} \times \text{Constant}}{\text{Serum creatinine (mcmol/l)}}$$

Constant = 1.23 for men; 1.04 for women

Use ideal body-weight in the calculation *(http://www.nhs.uk/Tools/Pages/Healthyweightcalculator.aspx)*
(NB IBW (kg) = (no of inches over 5ft x 2.3) + 50 (male) or 45.5 (female))

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. (£183.00 per injection excluding VAT)

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 Characteristics. 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
- MHRA Drug Safety Update 25/9/14. Denosumab: Updated recommendations. https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations