Guidance for the administration of Denosumab (Prolia®) in Primary Care	
GENERAL INFORMATION	• Denosumab is suitable for patients with established osteoporosis for both primary and secondary fracture prevention who either cannot tolerate oral medication such as bisphosphonates or strontium ranelate (i.e. GI side-effects or rash), have renal impairment precluding the use of other drugs (eGFR < 35ml/min) or are non-compliant (usually impaired mentation) or unable to travel to hospital because of poor mobility. See also NICE guidance on Denosumab. • Although denosumab is ideally suited for use in primary care it is a second line drug after oral medication (bisphosphonates and/or strontium). • Its use **should be recommended** by a secondary care physician experienced in the use of this drug, and should include guidance on the duration of use.. The **treatment can then be started in primary care**. (see below re general monitoring requirements) • The primary care physician should inform the secondary care physician if there are any problems with the use of denosumab (i.e. side effects precluding further use, further fractures after 2-3 years) so that further appropriate treatment can be recommended. The full summary of product characteristics (SPC) should be read before prescribing.
PHARMACOLOGICAL SUMMARY	Denosumab is the first in a new class of drug to treat osteoporosis. It is a human monoclonal antibody (IgG2) BUT it does not act as an immunosuppressive agent. It inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.
INDICATIONS FOR THERAPY	**Licensed indication** Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures. [It is also important to note that Denosumab is licensed for bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.]
CONTRA-INDICATIONS	• Hypocalcaemia (see section 4.4 of SPC). • Low Vitamin D - ensure patient is vitamin D replete. Even insufficient patients may require a stat dose of high dose vitamin D3 (100,000units) to ensure vitamin D >50 • Hypersensitivity to the active substance or to any of the excipients. • **The needle sheath contains latex so denosumab is contra-indicated in latex allergy**

CAUTIONS	Osteonecrosis of the jaw (ONJ) has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for 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 Denosumab. 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.
POTENTIAL DRUG INTERACTIONS	Nil known
INITIAL SCREENING	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. <u>These patients may require alfacalcidol; liaise with endocrinology or renal team re dose of calcitriol</u>
STORAGE AND PRESCRIBING	Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Do not shake excessively. Shelf life is 30 months. Denosumab may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, it must be used within this 30 day period. 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. Patients must be adequately supplemented with calcium and vitamin D (see section 4.4 of SPC).
MONITORING	***There are no specific monitoring requirements for denosumab***. It is recommended that you follow the same practice in monitoring patients on denosumab as you would for other anti-resorptive therapy (such as bisphosphonates). Suggest annual checks of vitamin D to ensure compliance and check calcium levels prior to each injection.

ADVERSE EVENTS

Patients receiving Denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8 of SPC). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Common undesirable effects observed with an incidence of 1-10% were: urinary tract infection, upper respiratory tract infection, cataract, constipation, sciatica, rash, pain in extremity. In prostate cancer patients receiving androgen deprivation therapy, cataracts and diverticulitis were reported more frequently in the Denosumab patients compared to placebo. No imbalances of either adverse event were observed in postmenopausal women with osteoporosis.

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

Please refer to section 4.8 of the SPC for more information.

RESPONSIBILITY OF PRESCRIBERS

Summary

- As with bisphosphonates, assess to ensure the patient has good oral hygiene and use clinical judgement to determine if a dental examination is required prior to initiating therapy (see section 4.4 of product SPC if needed)
- Ensure practice system is set-up to recall patient after six month interval.
- Ensure account is set up to order denosumab and determine if it will come direct to the practice (preferred scenario, as this is more straightforward for the patient) or if the patient will need to collect their prescription from the pharmacy. If it is the latter, ensure a reminder letter is set up to be sent to patient with the relevant instructions.
- Prescribe and administer denosumab at six-monthly intervals. It is important that **where re-treatment is recommended this is commenced within +/- 10 days of the six month date** to prevent elevated bone turnover.
- **Note: a protocol on how to administer the injection is available from the pharmaceutical companies if required and is appended to the end of this guidance.**
- If there are any problems with the use of denosumab (i.e. side effects precluding further use, further fractures after 2-3 years) alternative treatments should be considered promptly. Effects of denosumab wear off quickly so alternatives need to be considered without delay.
- Report any adverse events to the Committee on Safety of Medicines (CSM) at the Medicines and Health Care Regulatory Agency (MHRA).

CONTACTS

A patient information leaflet also attached. If any problems occur please contact relevant specialist:

Consultant Rheumatologists:

Consultant Rheumatologists secretary:	01274 365227 01274 365399
E consult via SystmOne	

Appendix 1 Denosumab Patient Information Leaflet for treatment of post-menopausal osteoporosis

Information on Prolia® (denosumab) - a treatment for post menopausal osteoporosis

What is osteoporosis?

Osteoporosis is a long-term condition that usually requires treatment. Many women with osteoporosis have no symptoms but they are at higher risk of breaking bones, particularly those in the spine, hip and wrists. With a 'silent' condition like osteoporosis, it might be easy to forget you have the illness.

Why are my bones weaker?

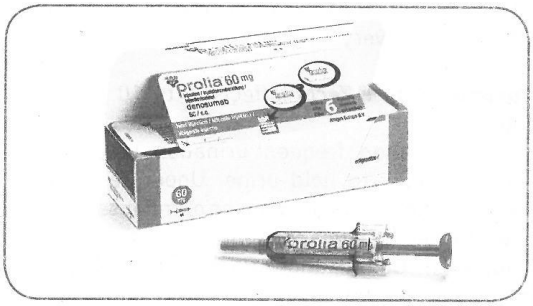
Your bones are continuously being renewed. Normally there is a balance of old bone being removed (bone resorption) and new bone being created (bone formation). In osteoporotic patients this balance is disrupted because bone is broken down faster than it can be rebuilt.

Can fractures be prevented?

As we get older, we have a higher risk of breaking a bone. Osteoporosis causes your bones to become less strong and more fragile and falling is more common. Lifestyle changes and keeping active can help to prevent falling. Food supplements, such as calcium and vitamin D, and drug treatments can strengthen bones which can reduce your risk of having a fracture.

If left untreated, osteoporosis can progress painlessly and your bones may be at risk of breaking.

About your treatment with Prolia®



How am I given Prolia®?

Prolia® is a quick and simple under-the-skin (subcutaneous) injection given every six months by someone trained in injection techniques.

Why have I been given Prolia®?

Your doctor has prescribed Prolia® to help reduce your risk of fractures. Prolia® is a new treatment option mimicking the way the body works to prevent bone loss, helping to make your bones stronger and less likely to break. You may not see any changes or feel any different in yourself when you are taking it, but Prolia® can reduce your risk of fractures.

What if I miss an injection?

If you miss your injection, you should contact your doctor to book a new appointment so that you continue to receive Prolia® and help reduce your risk of fractures.

Possible side effects

Like all medicines, Prolia® can cause side effects, although not everybody gets them.

Common side effects (affects 1 to 10 users in 100):
Painful urination, frequent urination, blood in the urine, inability to hold urine. Upper respiratory tract infection. Pain, tingling or numbness moving down the leg (sciatica). Cloudy area in the eye lens (cataracts). Constipation. Rash. Arm or leg pain (pain in extremity).

Uncommon side effects (affects 1 to 10 users in 1,000):
Swollen, red area of skin, most commonly in the lower leg, that feels hot and tender (cellulitis), and possibly with fever symptoms. Fever, vomiting and abdominal pain and discomfort (diverticulitis). Ear infection. Skin condition with itching, redness and/or dryness (eczema).

Rare side effects (affects 1 to 10 users in 10,000):
Persistent pain and/or non-healing sores of the mouth or jaw.

Very rare side effects (affects less than 1 user in 10,000):
Low calcium levels in the blood (hypocalcaemia).

If you notice any side effects or you want more information, tell your doctor or pharmacist or see the Package Insert Leaflet that comes with your drug.

Further information

Support programme

Prolia® patient support programme (prolong)

Ask your doctor or pharmacist for more details

Osteoporosis societies

National osteoporosis society (NOS)
www.nos.org.uk

International osteoporosis federation
www.iofbonehealth.org

Osteoporosis helpline

NOS helpline 0845 450 0230

Other relevant disease area organizations

Age concern
www.ageuk.org.uk

Arthritis care
www.arthritisresearchuk.org

AMGEN
Amgen Ltd,
240 Cambridge Science Park,
Milton Road, Cambridge, CB4 0WD.

GlaxoSmithKline
GlaxoSmithKline Ltd,
980 Great West Road, Brentford, Middlesex, TW8 9GS, UK.

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Appendix 2: Support Documents for Healthcare Professionals (Available from Amgen & GlaxoSmithKline)

Protocol for primary care management of patients prescribed PROLIA® ▼ (denosumab) for prevention of fractures

Step 1: before the patient is administered denosumab

- 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
- Ensure Movianto account is set-up for ordering (refer to company leaflet) / ensure pharmacy has stock
- Ensure the practice system is set-up to recall patients on a six-monthly interval. Determine if you would like to use the PROLONG patient support programme from the pharmaceutical companies to support recall and patient education (more information available from company representative)
- Ensure you are familiar with the product SPC – including the shelf life and storage instructions (sections 6.3 & 6.4)

Step 2: initiating denosumab

- Discuss benefits and side effects with patients and provide patient information leaflet
- Ensure patient is taking calcium and vitamin D and, as with other anti-resorptive medications, has been assessed for risk of osteonecrosis of the jaw (ONJ)
- Before administration, inspect the solution. Do not inject the solution if it contains particles, or is cloudy or discoloured. Do not shake excessively
- 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) .
- Inject the entire contents of the pre-filled syringe and dispose of any medicinal product remaining in the pre-filled syringe
- Any unused product or waste material should be disposed of in accordance with local requirements
- Record batch number and site of injection on patient's notes
- Instruct patient to report any adverse events to the practice so these can in turn be reported to the MHRA

Step 3: follow-up care and administration

- Patient should have been recalled six months after last administration of Prolia
- Check that patient was satisfied that there were no AEs following the last administration of denosumab

Useful Contact Information

Amgen UK medical information: 01223 436441 or gbinfoline@amgen.com

UK Adverse Event Reporting: 01223 436712

Movianto: 01234 248631 or customercare.uk@movianto.com

THIS TEMPLATE PROTOCOL HAS BEEN DEVELOPED BY AMGEN & GLAXOSMITHKLINE TO SUPPORT PRIMARY CARE PROFESSIONALS IN THE APPROPRIATE USE OF DENOSUMAB. IT IS EXPECTED THAT THE TEMPLATE WILL BE ADAPTED ACCORDING TO THE NEEDS OF THE PRACTICE AND SHOULD BE FULLY REVIEWED BY PROFESSIONALS WHO WILL BE INVOLVED IN THE MANAGEMENT OF PATIENTS ON DENOSUMAB