SHARED CARED GUIDELINE FOR DENOSUMAB (PROLIA®)

INDICATION

This shared care guideline has been prepared to support healthcare professionals in the implementation of shared care management of patients who have been prescribed denosumab (Prolia®) for the prevention of fragility fractures.

Denosumab is licensed for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women denosumab significantly reduces the risk of vertebral, non-vertebral and hip fractures.

This document should be used alongside guidance published by the National Institute for Health and Care Excellence (Technology Appraisal 204 "Denosumab for the prevention of osteoporotic fractures in post menopausal women", October 20101).

Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures in postmenopausal women at increased risk of fractures:

- Who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate or have an intolerance of or a contraindication to those treatments and
- Who have a combination of T-score, age and number of independent clinical risk factors for fracture as indicated in the following table.

Table 1: T-scores at (or below) which denosumab is recommended when oral bisphosphonates are unsuitable

	Number of independent clinical risk factors for fracture		
Age (years)	**0**	**1**	**2**
65–69	– [a]	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

[a] Treatment with denosumab is not recommended.

For the purposes of the NICE guidance, independent clinical risk factors for fracture are parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis.

Denosumab is also recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures only in postmenopausal women at increased risk of fractures who are unable to comply with the special instructions for administering alendronate and either risedronate or etidronate or have an intolerance of or a contraindication to those treatments.

Please be aware some patients may not meet all of the NICE criteria however, there may be no other option but to initiate treatment if they are presenting with fractures.

AREA OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of denosumab can be 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 the specialist asks the GP to prescribe this drug, the GP must reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Shared Care is only appropriate if it provides the optimum solution for the patient.

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

CONSULTANT RESPONSIBILITIES	
1	To assess the patient and establish/confirm the diagnosis
2	To determine a management strategy and ensure follow-up in conjunction with the GP
3	To initiate denosumab treatment including: • Ensuring the suitability of the patient for denosumab treatment in accordance with NICE TA 204 • Ensuring the patient does not have hypocalcaemia and that their renal function and vitamin D is satisfactory. • Discussing and agreeing the management strategy with the patient including: ➢ Informing them of possible side-effects to the treatment and ensuring they are aware of who to contact in this instance. Provide a patient reminder card on steps to minimise the risk of developing osteonecrosis of the jaw. • Giving the initial injection of denosumab) • In patients with severe renal failure (creatinine clearance < 30 ml/min) serum calcium should be measured two weeks after the denosumab injection • Ensuring the patient understands the proposed plan for follow-up • Writing to the patient's GP advising them of the treatment commenced, including appropriate prescribing information, assuming confirmation of their agreement to 'share care' and administer further denosumab injections • Advising the patient's GP of duration of therapy before a review by a specialist is required (normally within 5 years), to assess continuation of therapy or a drug holiday. This review is on an individual patient basis. • Advise if serum calcium should be rechecked post injection (necessary for those at increased risk of hypocalcaemia i.e. CKD patients)
4	To be available for advice if the patient's condition changes and to arrange for the patient to be followed up in the out-patient clinic as necessary

GENERAL PRACTITIONER RESPONSIBILITIES	
1	Where shared care is agreed, to prescribe and administer denosumab at six-monthly intervals after the initial administration by the specialist. [Note: a protocol on how to administer the injection is available from the pharmaceutical company if required]
2	In patients with severe renal failure (creatinine clearance < 30 ml/min) serum calcium should be measured two weeks after denosumab injection
3	To ensure practice system is set up to recall patient at six monthly intervals for monitoring of vitamin D, eGFR and serum Ca and for administration of repeat injections.
4	To monitor side effects of treatment and seek advice from the specialist if necessary
5	Report any adverse events via the Yellow Card Scheme of the Medicines and Health Care Regulatory Agency (MHRA) at www.yellowcard.mhra.gov.uk
6	To liaise with the specialist regarding any complications of treatment, continued fractures or the discontinuation of treatment. A follow up appointment with the specialist within 5 years is required to determine future treatment or a drug holiday on an individual patient basis. The specialist review date needs to be documented in the patient record from the start.
7	To deal with general health issues of the patient
8	To check for possible drug interactions when newly prescribing concurrent medication

Patient's role (or that of carer)	
1	Report to the specialist or GP if he/she does not have a clear understanding of the treatment (including the need for calcium and vitamin D unless replete) and to report any concerns.
2	Attend appropriate specialist and GP appointments. Ensure good oral hygiene and attend dental checks regularly. Report any ear pain or discharge from the ear to the consultant or GP.
3	To have any required monitoring/tests carried out at regular intervals, as appropriate
4	Report any adverse events to the healthcare professional who last administered their injection.

SUPPORTING INFORMATION

Dosage and administration

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm. Administration should be performed by an individual who has been adequately trained in injection techniques.

Patients must be calcium and vitamin D replete during treatment with denosumab.

Dosage adjustments in specific patient populations

Patients with liver impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment.

Patients with kidney impairment
No dose adjustment is required in patients with renal impairment.
Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients.

Elderly patients
No dose adjustment is required in elderly patients.

Contraindications

Denosumab is contraindicated in:

- Hypersensitivity to the active substance or to any of the excipients.
- Hypocalcaemia

Cautions / Special Warnings

Vitamin D deficiency (please refer to local guidance)

Hypocalcaemia (see MHRA/CHM advice)
It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose 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. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia.

Osteonecrosis of the jaw (see MHRA/CHM advice)

ONJ has been reported rarely in patients receiving denosumab for osteoporosis. The start of treatment / new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.
The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
• Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
• Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
• Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
• Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.
All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.
The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal (see MHRA advice)

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.

Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Patients should be advised to report any ear pain, discharge from the ear or an ear infection during denosumab treatment.

Atypical femoral fractures (see MHRA/CHM advice)

Atypical femoral fractures have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the sub trochanteric and diaphyseal regions of the femur. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit risk assessment. During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

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

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.

Patients with rare hereditary problems of fructose intolerance should not take denosumab.

Pregnancy and breastfeeding

Denosumab is not recommended for use in pregnant women. It is unknown whether denosumab is excreted in human milk. A decision on whether to abstain from breast-feeding or to abstain from treatment with denosumab should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of denospumab therapy to the woman.

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).

Side Effects

The BNF lists: diarrhoea, constipation, abdominal discomfort, dyspnoea, urinary tract infection, upper respiratory tract infection, pain in extremity, sciatica, hypocalcaemia (fatal cases reported, see also Cautions), hypophosphataemia, musculoskeletal pain, osteonecrosis of the jaw (see also Cautions), cataracts, rash, eczema, sweating; *less commonly* diverticulitis, skin infections including cellulitis (seek prompt medical attention), ear infection; *rarely* atypical femoral fractures (see MHRA/CHM advice

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Storage

Denosumab has a shelf life of 30 months. 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. 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.

Drug Cost:

Denosumab (Prolia®) 60mg/ml solution for injection pre-filled syringes x 1 £183.00

Annual treatment cost at 60mg every 6 months: £366

Prices correct as of: Drug Tariff March 2018, accessed April 2018.

References

1. Denosumab for the prevention of osteoporotic fractures in post menopausal women (October 2010), National Institute for Health and Clinical Excellence (Technology Appraisal 204)
2. Summary of product characteristics for Prolia® (Denosumab). Amgen. Last updated September 2017, accessed April 2018
3. BNF.NICE.online Accessed April 2018
4. Drug Tariff March 2018 accessed April 2018

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