**Denosumab** DRAFT

RICaD: For the treatment of osteoporosis

Specialist details:

Name:

Tel:

Hospital Pharmacy Dept:

Other:

Patient details:

This RICaD supports the transfer of the responsibilities for managing the prescribing of subcutaneous denosumab in people with osteoporosis from secondary to primary care. 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 and administer this drug, the GP should reply to this request as soon as practicable.**

It is intended that the specialist complete this document in order to give Primary Care prescribers a clear indication of the reason for recommending the medication, together with suggested criteria for its subsequent continuation or discontinuation.

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

Rationale for Choice

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| Relevant diagnosis | Osteoporosis |
| Reason for choice | * Prevention of osteoporotic fragility fractures in postmenopausal women and men at increased risk of fragility fractures , where alendronate or risedronate are contraindicated or not tolerated\* 🞎   *\*persistent upper gastrointestinal disturbance of sufficient severity to warrant discontinuation, and despite instructions for administration being correctly followed1* |
| Patient counselling points | * Discuss the benefits and risk of treatment with the patient * Advise of the need to adhere to any calcium and vitamin D treatment prescribed * Report any other adverse effects or warning symptoms to the specialist or GP whilst receiving denosumab. Especially, any signs or symptoms of cellulitis, any unusual groin, hip or thigh pain, or chronic ear infections * Maintain good oral hygiene, with regular dental review if appropriate. Inform dentist that denosumab treatment has been received |
| Special precautions | Denosumab is contraindicated in patients with hypersensitivity to denosumab or to any of the excipients. Caution is advised in patients with known hypersensitivity to other bisphosphonates.  *Hypocalcaemia (MHRA guidance available; see references):* must be corrected by an adequate intake of calcium and vitamin D before initiating therapy with denosumab. 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. According to the Summary of Product Characteristics,2 concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.  *Skin Infections (cellulitis leading to hospitalisation):* Signs and symptoms include: red, painful, hot, swollen and tender skin that spreads rapidly, that may be accompanied or preceded by fever, malaise, nausea, shivering, and rigors.  *Osteonecrosis of the Jaw (ONJ)3*: has been reported with denosumab and bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered before treatment with denosumab.  *Atypical fractures of the femur4:* Discontinuation of denosumab therapy should be considered if patient reports any new or unusual thigh, hip, or groin pain, pending evaluation of the patient for an atypical femoral fracture, based on an individual benefit risk assessment. |
| Drug interactions | There is low potential for drug-drug interactions (see SPC). |
| Pre-treatment test results | Vitamin D level > 50 nmol/l 🞎  eGFR > 30 ml/min 🞎  Normal serum calcium? 🞎 |

Guidance on initiation (to be completed by the specialist)

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| Initiation dose | 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of the arm. No dose adjustment is indicated in renal impairment and the elderly |
| Specific safety concerns | **Adequate intake of calcium and vitamin D is important in all patients**.  MHRA safety alerts (Oct 2012 and Sept 2014) caution about the risks of hypocalcaemia with denosumab5. Patients with severe renal impairment (eGFR < 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 (see monitoring, below). Patients should be asked to report symptoms of hypocalcaemia e.g. muscle spasms, cramps or tingling of fingers, toes or around mouth. |
| Monitoring | Blood test one month before next injection |
| Frequency | Ensure that the practice system is set to book any pre-treatment tests i.e. calcium/vitamin D levels for the patient after five months, and an appointment for the next denosumab injection after six months |
| Follow up of first dose | Agree with the GP who will be responsible for a) following up the patients response to treatment and b) administering the second dose |
| Specialist recommendations, any additional information |  |

Suggested criteria for Continuation or Discontinuation after 5 years’ treatment

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| Location | Secondary care |
| Continuation criteria | Continued high risk of a fracture |
| Review | After five years of treatment; continue denosumab if patient still at high risk of fractures (BMD T-score <2, or <2.5 with multiple vertebral fractures, or high fracture risk score)6. There is no evidence to guide decisions beyond 10 years of treatment, and management options in such patients should be considered on an individual basis7. |
| Discontinuation criteria | Based on current data**6,**7, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk7. |
| Follow up action |  |

**Therapeutic Use**

Refer to the MTRAC Commissioning Support guidance on denosumab.

**Side Effects**

Infections of the urinary tract and upper respiratory tract are listed as common in the SPC; along with sciatica, cataracts, constipation, rash, and pain in the extremities. For adverse effects other than those described under contraindications, please see the SPC.2

*Denosumab was launched in 2010 and no longer has black triangle* (▼) *status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA..*

**References**

1. Hope S, Copus H, MKassim J. Using Denosumab in Primary Care 2014. <https://www.ouh.nhs.uk/osteoporosis/documents/InitiatingDenosumabinprimarycare.pdf>.

2. Amgen. Prolia 2019. <http://www.medicines.org.uk/emc/medicine/23127/SPC/Prolia/>.

3. MHRA. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk 2015. <https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk>.

4. MHRA. Denosumab 60 mg (Prolia): rare cases of atypical femoral fracture with long-term use 2013. <https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia>.

5. MHRA. Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment - monitoring recommended 2012. <https://www.gov.uk/drug-safety-update/denosumab-monitoring-recommended>.

6. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone* 2017;105:11-17. doi: <https://doi.org/10.1016/j.bone.2017.08.003>

7. NOGG 2017: Clinical guideline for the prevention and treatment of osteoporosis. <https://www.sheffield.ac.uk/NOGG/NOGG%20Guideline%202017.pdf>.