Rationale for Initiation, Continuation and Discontinuation (RICaD)

Denosumab (Prolia®)

Denosumab (Prolia®) is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures.

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 within 4 to 6 weeks.**

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.

Patient details		GP details		Specialist details	
Name		**GP Name**	**Dr**	**Specialist Name**	
PID		**GP address**		**I confirm that this patient has been initiated on Desonumab for the reasons shown below**	
DOB				**Signature**	
Patient address				**Date**	
				Contact details	

Rationale for Choice and Guidance on initiation

Relevant Diagnosis:	Osteoporosis	
Therapeutic use	Refer to the MTRAC Commissioning Support guidance on denosumab.	
Reason why Denosumab has been chosen	Prevention of osteoporotic fragility fractures in postmenopausal women and men at increased risk of fragility fractures, where alendronate, risedronate or etidronate are contraindicated or not tolerated* **persistent upper gastrointestinal disturbance of sufficient severity to warrant discontinuation, and despite instructions for administration being correctly followed*[1]	
Pre-treatment test results and specialist responsibilities	• Benefit and side effects of the treatment with patient (or carer) are discussed (see patient counselling below) • **The responsibilities of patient/carer are discussed which should particularly include discussion around not stopping treatment unplanned without medical advice, booking relevant appointments every 6 months at their surgery, and the importance to attend for tests and review of treatment as indicated** • Vitamin D level > 50 nmol/l ☐ • eGFR > 30 ml/min ☐ • Normal serum calcium ☐ • Administer first dose of Denosumab and follow-up patient prior to transfer to GP ☐ • Initiate calcium and/or vitamin D where appropriate ☐ • Confirm patient is suitable for transfer to primary care • Inform GP on next DEXA scan and review date (under continuation criteria) ☐	
Initiation dose	**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. First dose is administered by the specialist. Subsequent doses administered by GP 6 monthly.

		Date of first dose administration: ___/___/___
	Maximum dose	**60mg via subcutaneous injection every 6 months**
	Renal impairment	No dose adjustment is needed in patients with impaired renal function. There is an increased risk of hypocalcaemia if creatinine clearance is less than 30ml/minute.
	Hepatic impairment	No dose adjustment is needed in patients with impaired hepatic function.
Follow up of first dose	Specialist will be responsible for following up the patient's response to treatment and counselling patient if required.	
Monitoring	• Blood test within 1 month prior to next injection (renal function and adjusted calcium levels) • The patient should book pre-treatment blood tests with their GP five months after their last injection. At this point the patient should also book an appointment for the next denosumab injection (six months after their last one).	
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. These patients should also be informed to report any symptoms of hypocalcaemia (see additional information). According to the Summary of Product Characteristics,[2] concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia. *Skin Infections (cellulitis leading to hospitalisation):* Patient receiving denosumab may develop skin infections (predominantly cellulitis). 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 femur[4]:* 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. **Check the current BNF and SPC for detailed precautions, contraindications and drug interactions**.	
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.*	

Additional information	**Patient counselling points** • 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 (atypical femur fracture), or chronic ear infections (osteonecrosis of auditory canal). In addition tell all patients to report symptoms of hypocalcaemia to their doctor (e.g. muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth). • Maintain good oral hygiene, with regular dental review if appropriate. Remind patients to inform their dentist of treatment with denosumab and immediately report any oral symptoms such as dental mobility, pain, or swelling (osteonecrosis of the jaw) to a doctor and dentist. • to prevent small risk of rebound vertebral fractures. The dosing frequency should not be delayed for more than 4 weeks. • If their GP surgery is changed then they must notify their new GP asap of this treatment to ensure they can provide the service, and that the next injection is not delayed. **Drug interactions** There is low potential for drug-drug interactions (see SPC). **Additional information from specialist:**

Suggested Criteria for 6-monthly review (up to 5 years of Treatment)

Assessment of Efficacy	
Frequency of review	Every 6 months
Location	GP Surgery
Method (what tests are required)	Prior to each injection: • Check renal function ☐ • Check adjusted calcium levels ☐ • Review of side-effects – specifically signs or symptoms of cellulitis, dental problems, ear problems, swelling or non-healing of tissues and any unusual groin, hip or thigh pain ☐ *If patients develop symptoms suggestive of hypocalcaemia to check calcium level (at any time during treatment).*
Continuation Criteria	• No significant side-effects reported. • Calcium and/or vitamin D supplement is continued and no hypocalcaemia or vitamin D deficiency suspected. • eGFR >30mL/min. • Arrange a repeat DEXA in 5 years But continue Denosumab until reviewed by the specialist • To prevent small risk of rebound vertebral fractures. The dosing frequency should not be delayed for more than 4 weeks. • Date of next DEXA scan ___/___/____ to be arranged by GP
Criteria to withhold treatment and refer to specialist	• Denosumab should be withheld and patient referred back to the specialist in the event that the patient has hypocalcaemia (serum adjusted calcium <2.2mmol/L or below testing laboratory normal range) or if the eGFR is <30ml/min^2. Referral can be via advice and guidance. Hypocalcaemia should be managed as clinically indicated in the interim • Treatment should be withheld pending specialist review if the patient suffers an atypical fracture or significant side-effects whilst on treatment.

Follow up action	• Advise patient next denosumab dose due in 6 months. • Ensure recall procedure in place for next administration. • Advise patient to undergo regular dental checks and for the patient to advise their dentist they are receiving denosumab therapy. • Denosumab was launched in 2010. All suspected reactions (including those not to be serious and even where the causal link is uncertain) should be reported to the MHRA.

Suggested Criteria for Continuation or Discontinuation after intervals of 5 year treatment

Assessment of Efficacy	
Frequency of review	After 5 years of treatment GP to refer for review to specialist.
Location	Secondary Care
Method (what tests are required)	Continue denosumab if patient still at high risk of fractures on advise of the specialist. There is no evidence to guide decisions beyond 10 years of treatment, and management options in such patients should be considered on an individual basis[7]
Continuation Criteria	Continued high risk of a fracture
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 risk[7].
Follow up action	As per instructions from specialist. Where it is considered that treatment should be continued duration of treatment and review to be determined by specialist.

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.