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Guidance for the use of denosumab (Prolia®) 60mg injection in Primary Care for clinicians in North Cumbria

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Document Status

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1. Introduction

Denosumab (Prolia®) is a monoclonal antibody that inhibits osteoclast differentiation and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Denosumab has been approved by National Institute for Health and Care Excellence (NICE) for the prevention of osteoporotic fractures in postmenopausal women (NICE TA 204 www.nice.org.uk/TA204).

Prescribers should refer to the manufacturer's Summary of Product Characteristics (SPC) for detailed prescribing information (http://www.emc.medicines.org.uk).

2. Licensed indications and local arrangements

Denosumab 60mg injection is licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and is GREEN (suitable for prescribing in primary care) in North Cumbria traffic light system (http://medicines.necsu.nhs.uk/cumbria-traffic-light-classification/) for this indication ONLY when prescribed in line with NICE TA204.

It is also licensed for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures but is BLACK (no prescribing) for this indication in North Cumbria.

NICE TA 204 states that denosumab should only be used for primary and secondary prevention of fracture for post-menopausal women 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 in primary prevention they must also** have a combination of T-score, age and number of independent clinical risk factors (RF) for fracture (RFs: parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis) as indicated below.

Age	0 RFs	1 RF	2RF
65-69yrs	X	-4.5	-4.0
70-74yrs	-4.5	-4.0	-3.5
75+yrs	-4.0	-4.0	-3.0

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

NICE defines intolerance as: **'persistent upper gastrointestinal disturbance that is sufficiently severe to warrant discontinuation of treatment and that occurs even though the instructions for administration have been followed correctly.'**

The large negative T-score in the table above should not be interpreted that denosumab is more effective than a bisphosphonate for treating severe

osteoporosis. There is no evidence to directly compare the treatment options for osteoporosis, first line treatment should be a bisphosphonate irrespective of T-score.

Denosumab should not be considered if the T-score has failed to improve despite being prescribed a bisphosphonate, NICE recommend that compliance and secondary causes should be considered in this situation.

Denosumab is NOT an option if there are concerns about atypical fracture after bisphosphonate use, atypical femoral fractures have also been seen in patients prescribed denosumab.

2.1. Dosage, contraindications, cautions and administration

Denosumab (Prolia®) has been risk assessed for local use in postmenopausal osteoporosis and assigned an NPSA risk score of 1.

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

No dose adjustment is indicated in renal impairment and the elderly.

Patients should receive their 6 monthly injections in a timely manner, preferably within 2 weeks either side of the due date. There is a potential for rebound bone loss if the injection is delayed.

Administration should be performed by an individual who has been trained and is competent in subcutaneous injection. To avoid discomfort at the injection site, the pre-filled syringe should be allowed to reach room temperature before administration.

Clinicians administering denosumab should be familiar with and follow the 'Safe Management of healthcare waste' https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/167976/HTM_07-01_Final.pdf.

As medicinally-contaminated (non-cytotoxic or cytostatic) sharp, the used delivery device should be placed in a yellow-lidded sharps receptacle for disposal.

Patients must be adequately supplemented and/or replete with calcium and vitamin D before and during therapy.

2.2. Contraindications

Hypocalcaemia or untreated vitamin D deficiency	**Denosumab should NOT be used in patients with hypocalcaemia, regardless of severity.** Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy and maintained throughout. Patients with severe renal impairment (eGFR <30) or receiving dialysis are at greater risk of developing hypocalcaemia – in these patients clinical monitoring of calcium levels 2 weeks after injection is recommended.
Hypersensitivity to the active substance/ excipients	**Do not use**
Allergy to Latex	**Not recommended** – the needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

2.3. Precautions

Osteonecrosis of the jaw (ONJ) and external auditory canal	ONJ and external auditory canal has been reported rarely. Dental examination with appropriate preventative dentistry is recommended in those at risk (e.g. cancer diagnosis with bone lesions, chemotherapy, radiotherapy to head and neck, corticosteroids, pre-existing dental disease, periodontal infections and previous treatment with bisphosphonates). Patients should be advised to have regular dental check ups and maintain good oral hygiene while on treatment
Atypical femoral fractures	Patients presenting with new or unusual thigh, hip or groin pain (rare) should be evaluated for an incomplete femoral fracture. Denosumab should be discontinued if an atypical femur fracture is suspected.
Skin infections and cellulitis	Cellulitis may develop leading to hospitalisation (uncommon). Advise patients to seek prompt medical attention if they develop signs or symptoms of cellulitis.

2.4. Drug Interactions

The current SPC does not report any significant drug interactions. Please check the current British National Formulary (BNF) and SPC.

3. Initiating treatment with denosumab

Before initating treatment with denosumab, the clinician should consider the following aspects in line with MHRA recommendations and complete the "Initiating denosumab (Prolia®) prescribing checklist" (Appendix 3) to ensure treatment is appropriate. The completed checklist should be scanned into the patient notes. The Pathway for the Prescribing and Administration of denosumab (Prolia®) (Appendix 2) shows the steps necessary for initiation and continuation of therapy.

Perform baseline measures (and thereafter calcium levels prior to each dose – see section 4 Monitoring)	• Renal function • Bone profile (serum calcium, alkaline phosphatase, phosphate, albumin) • Vitamin D • Correct any calcium and/or vitamin D insufficiency or deficiency – this may require the use of high dose vitamin D preparations. • See the Cumbria guidance on the management of vitamin D deficiency and insufficiency (http://medicines.necsu.nhs.uk/download/cumbria-vitamin-d-guidelines-november-2016).
Ensure adequate calcium and vitamin D supplementation throughout treatment	• Recommend use of a calcium calculator tool (http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator) • Advise to buy/prescribe a combined calcium and vitamin D preparation OR if they have sufficient dietary calcium (700mg/day), advise 800 units vitamin D daily. • Document reason if supplementation of calcium is deemed unnecessary.
Assess for good oral hygiene and consider dental examination where appropriate	• Ask about risk factors for osteonecrosis of the jaw and external auditory canal (corticosteroid use, chemotherapy, smoking, poor oral hygiene, planned invasive dental surgery e.g. tooth extraction, dental infection). • Consider dental assessment prior to treatment in patients with risk factors • Withhold treatment until after any planned dental surgery. • Encourage routine dental check-ups and to report any oral symptoms.
Discuss benefits and side effects and provide all patients with the package leaflet and the **Patient safety information sheet (Appendix 5)**	• Advise patients to report symptoms of hypocalcaemia (paraesthesia, muscle spasms, cramps or twitching, tingling or numbness of fingers, toes or around the mouth); of atypical femoral fracture (new, unusual hip or groin pain); any skin infections/symptoms of cellulitis; ear symptoms • Ask about latex allergy (latex contained in needle cover) (https://assets.publishing.service.gov.uk/media/55a66d9eed915d151b000003/AMGEN_PROLIA_patient_card.pdf

4. Monitoring requirements in primary care

The MHRA (2012 and 2014) recommend the following monitoring, which should be recorded on the "Continuation of prescribing and administration of denosumab (Prolia®) checklist" (Appendix 4) before each repeat administration and scanned into the patient notes.

Calcium profile (serum calcium, adjusted calcium, albumin)	• Calcium levels should be monitored as follows:
	  ○ Before each dose
	  ○ Within two weeks after the initial dose in patients with risk factors for hypocalcaemia (renal impairment, eGFR <30ml/min)
	  ○ If suspected symptoms of hypocalcaemia occur in the event of impaired renal function
	• Patients should be asked to report symptoms of hypocalcaemia (paraesthesia, muscle spasms, cramps or twitching, tingling or numbness of fingers, toes or around the mouth)

Osteonecrosis of the jaw (ONJ) and external auditory canal	• Monitor for oral symptoms (loose teeth, pain, swelling, non-healing sores or discharge) • Monitor for any ear pain, discharge from ear or ear infection.
Infection	Assess for presence of active infection (LRTI, UTI or cellulitis)
General monitoring	Assess for adverse effects prior to each injection

5. Adverse effects

Common (≥1/100 to <1/10) adverse effects listed in the denosumab SPC include urinary tract infection, upper respiratory tract infection, sciatica, eczema, rash, constipation and cataracts.

The only very commonly (≥1/10) associated adverse effects reported in the SPC are musculoskeletal pain and pain in extremities.

Mild transient hypocalcaemia may occur after therapy but is rare according to the SPC. Hypocalcaemia is most common in the first 6 months but can occur at any time. Even more rarely, denosumab can cause severe, life-threatening hypocalcaemia in patients, particularly if they are vitamin D deficient or in renal failure.

Adverse Event	Frequency	Management
Cellulitis	Uncommon ≥1/1,000 to <1/100	Standard clinical management
Atypical femoral fractures (i.e. new or unusual thigh, hip, or groin pain)	Rare ≥1/10,000 to <1/1,000	Evaluate for an incomplete femoral fracture and if fracture confirmed consider stopping drug
Osteonecrosis of the jaw (ONJ)	Rare ≥1/10,000 to <1/1,000	If osteonecrosis occurs during treatment, use clinical judgment to guide the management plan of each patient based on individual benefit/risk evaluation. Note dental surgery may exacerbate the condition.
Osteonecrosis of the external auditory canal	Unknown	

All serious adverse reactions to denosumab should be reported using the yellow card system at https://yellowcard.mhra.gov.uk/

6. Duration of treatment

Patients who have completed three years of treatment (6 injections) should have a comprehensive review to reach a shared decision on the risk and benefits of continuing treatment. At this point clinicians should consider a DXA scan to assess response to treatment. (SIGN). A >4% fall in bone mineral density at this point suggests treatment failure and referral to specialist may be appropriate.

Patients can be offered the option of continung therapy for up to 5 years, when treatment should be stopped for all patients.

The optimal duration of treatment with denosumab has not been established. NICE TA204 does not specify duration, nor does NICE clinical guidelines and quality standards for osteoporosis. Current SIGN (2015) guidance states maximum treatment duration for denosumab as ?5 years and notes this is based on poor evidence.

There is currently no recommendation in any national guidance to consider a drug holiday for denosumab. Unlike the bisphosphonates whose effects can persist for months and years after treatment cessation, the effect of denosumab on bone remodeling processes stops very quickly when treatment is stopped.

This section will be reviewed as and when national guidance changes.

7. Pharmaceutical aspects

- Store denosumab (Prolia®) in a fridge between 2 and 8°C. Do not freeze.
- Keep the pre-filled syringe in the outer carton to protect from light.
- Inspect solution before use and do not use if there are any particles or discoloration or the solution is cloudy.
- Do not shake excessively.
- Denosumab (Prolia®) 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 (SPC).
- To avoid discomfort, allow the pre-filled syringe to reach room temperature before slowly injecting. Instructions for use can be found in the package insert.

8. Cost

The price of each 1ml prefilled syringe is £183 (Drug Tariff Sept 2017).

9. Procurement

There are two ways for denosumab to be sourced in primary care:

i) A GP practice can have an account with the distributors (Movianto UK) and orders can be made by telephone, fax or email

Telephone: 01234 248500
Fax: 01234 248705/01234 248575
Email: orders.uk@movianto.com
The product code is 900320

If a GP practice is a new customer an account can be started by phoning the above number. Denosumab will be delivered direct within 24 hours free of carriage charges. Orders must be placed by 16.30 Monday-Friday.

ii) Alternatively, the patient can collect their prescription from a community pharmacy via the usual route. Note that denosumab needs to be ordered by pharmacies direct from Movianto rather than their normal wholesalers, which means delivery can take up to 3 days.

10. References

1 Summary of Product Characteristics (SPC), Prolia. Date of last amendment October 2016. Prolia SPC. http://www.medicines.org.uk/emc/medicine/23127

2. NICE TA204: Denosumab for the prevention of osteoporotic fractures in postmenopausal women (October 2010). www.nice.org.uk/TA204

3 NICE NG56 Multimorbidity https://www.nice.org.uk/guidance/ng56

4 SIGN: Management of osteoporosis and the prevention of fragility fractures 2015. http://www.sign.ac.uk/sign-142-management-of-osteoporosis-and-the-prevention-of-fragility-fractures.html

5 NHS North Cumbria CCG traffic light system http://medicines.necsu.nhs.uk/cumbria-traffic-light-classification/

6 Before starting treatment with denosumab (MHRA 2014) https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations

7 Cumbria Guidance on the Management of Vitamin D Deficiency and Insufficiency States for treatment options.
http://medicines.necsu.nhs.uk/guidelines/cumbria-guidelines/

8 Calcium Calculator tool
http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator

9 MHRA Safety alert. Denosumab; intravenous bisphosphonates: osteonecrosis of the jaw, further measures to minimise the risk (July 2015). (MHRA 2015). https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk

10 MHRA safety alert. Denosumab. Fatal cases of severe symptomatic hypocalcaemia and risk of hypocalcaemia at any time during treatment. Monitoring recommended. (Oct 2012) MHRA 2012. https://www.gov.uk/drug-safety-update/denosumab-monitoring-recommended

11 MHRA safety alert. Denosumab 60mg (Prolia): Rare cases of atypical femoral fracture with long term use (Feb 2013) MHRA 2013. https://www.gov.uk/drug-safety-update/denosumab-60-mg-prolia

12 Patient information leaflet for Prolia®: patient information leaflet. http://www.medicines.org.uk/emc/medicine/23128/XPIL/Prolia/

13 Osteonecrosis of the jaw safety card
https://assets.publishing.service.gov.uk/media/55a66d9eed915d151b000003/AMGEN_PROLIA_patient_card.pdf

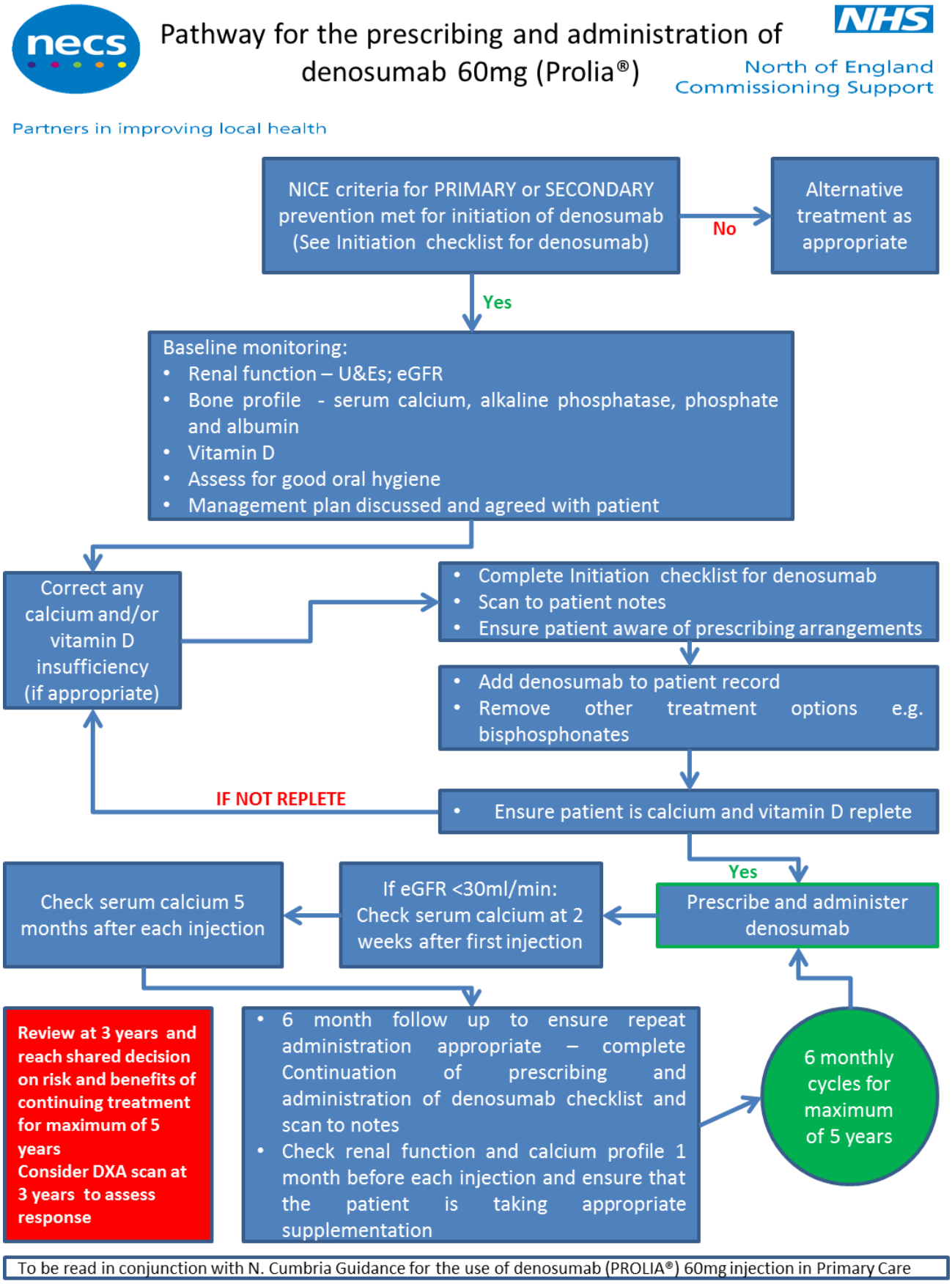
14 DoH: Environment and sustainability Health Technical Memorandum 07-01: Safe management of healthcare waste.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/167976/HTM_07-01_Final.pdf

15 NPSA alert NPSA/2007/20 Promoting safer use of injectable medicines
http://www.nrls.npsa.nhs.uk/resources/?entryid45=59812

Appendix One: Abbreviations

Abbreviation	Definitions
SPC	Summary of Product Characteristics
NICE	National Institute for Health and Care Excellence
RF	Risk Factors
ONJ	Osteonecrosis of the jaw
BNF	British National Formulary
DXA (formerly DEXA)	Dual-energy X-ray Absorbtiometry
SIGN	Scottish Intercollegiate Guidelines Network
NPSA	Former National Patient Safety Agency (now part of NHS Improvement)

Appendix Two: Denosumab prescribing pathway



Appendix Three: Initiating denosumab (Prolia®) prescribing checklist

This checklist should be completed by the clinician initiating prescribing and the completed form scaned into the patient's notes

Patient Name		**Appointment Date**	
Clinician name		**Clinician Signature**	

Denosumab 60mg injection is licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and is GREEN (suitable for prescribing in primary care) in North Cumbria traffic light system system (http://medicines.necsu.nhs.uk/cumbria-traffic-light-classification/) for this indication ONLY when prescribed in line with NICE TA204.

Dose: 60mg subcutaneous injection, every 6 months for 3-5 years

Age	Most recent T-Score	Independent clinical risk factors (RFs)	Tick all that apply	Total no. RFs
		Parental history of hip fracture		
		Alcohol intake of 4 or more units/day		
		Rheumatoid arthritis		

NICE criteria for PRIMARY PREVENTION of osteoporotic fractures – ALL CRITERIA MUST BE MET	Tick
Post-menopausal	
Increased risk of fractures	
Has an intolerance of, or a contraindication to alendronate **and** either residronate or etidronate, or is unable to comply with the special instructions for administering those treatments – specify details:	
Has a combination of T-score, age and number of independent clinical risk factors for fracture as indicated in the following table – *circle appropriate number*	

Age	0 RFs	1 RF	2RF
65-69yrs	X	-4.5	-4.0
70-74yrs	-4.5	-4.0	-3.5
75+yrs	-4.0	-4.0	-3.0

T-scores (SD) at (or below) which denosumab is recommended when alendronate and either risedronate or etidronate are unsuitable

NICE criteria for SECONDARY PREVENTION of osteoporotic fractures – ALL CRITERIA MUST BE MET	Tick
Post-menopausal	
Increased risk of fractures	
Has an intolerance of, or a contraindication to alendronate **and** either residronate or etidronate, or is unable to comply with the special instructions for administering those treatments – specify details:	

Before starting treatment with denosumab 60mg (Prolia®)		Tick
Perform baseline measures	• Renal function • Bone profile (serum calcium, alkaline phosphatase, phosphate, albumin) • Vitamin D • Correct any calcium and/or vitamin D insufficiency or deficiency – this may require the use of high dose vitamin D preparations. • See the Cumbria guidance on the management of vitamin D deficiency and insufficiency (http://medicines.necsu.nhs.uk/download/cumbria-vitamin-d-guidelines-november-2016).	
Ensure adequate calcium and vitamin D supplementation throughout treatment	• Recommend use of a calcium calculator tool (http://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator) • Advise to buy/prescribe a combined calcium and vitamin D preparation OR if they have sufficient dietary calcium (700mg/day), advise 800 units vitamin D daily. • Document if supplementation of calcium not felt to be necessary	
Latex allergy	• Ask about latex allergy (latex contained in needle cover).	
Discuss benefits, side effects and provide patients with the package leaflet and the **Patient safety information sheet** (https://www.gov.uk/drug-safety-update/denosumab-xgeva-prolia-intravenous-bisphosphonates-osteonecrosis-of-the-jaw-further-measures-to-minimise-risk)	• Advise patients to report symptoms of hypocalcaemia (paraesthesia, muscle spasms, cramps or twitching, tingling or numbness of fingers, toes or around the mouth); of atypical femoral fracture (new, unusual hip or groin pain); any skin infections/symptoms of cellulitis; ear symptoms	
Assess for good oral hygiene and consider dental examination where appropriate	• Ask about risk factors for osteonecrosis of the jaw (corticosteroid use, chemotherapy, smoking, poor oral hygiene, planned invasive dental surgery eg. tooth extraction, dental infection). • Consider dental assessment prior to treatment in patients with risk factors • Withhold treatment until after any planned dental surgery. • Encourage routine dental check-ups and to report any oral symptoms.	

Appendix Four: Continuation of prescribing and administration of denosumab (Prolia®)

(To be completed by nurse administering injection. Scan completed form into patient's notes)

Patient Name:		**Appointment Date:**	
Completed by:		**Signature**	

1.	Injection Number	☐2 ☐3 ☐4 ☐5 ☐6
2.	Date of the previous injection	
3.	Were there any adverse effects following previous injection?	☐Yes ☐No
	If YES – list and please discuss with doctor:	
4.	Is the patient taking calcium and vitamin D?	☐Yes ☐No
	If vitamin D alone, is the dietary calcium sufficient?	☐Yes ☐No
	List the name of the product(s) and dose(s):	
5.	When did patient last have a dental check?	00/00/0000
6.	Is patient awaiting or undergoing dental extraction/root canal treatment/dental implant or undergoing any other oral surgery or is it more than 12 months since last dental check?	☐Yes ☐No
	If YES – list and please discuss with doctor:	
7.	Does patient have active infection (such as LRTI, UTI or cellulitis)?	☐Yes ☐No
	If YES – list and please discuss with doctor:	
8.	Does patient report any ear symptoms such as pain, discharge or infection?	☐Yes ☐No
	If YES – list and please discuss with doctor:	

9.

Blood test	Reference range	Results:	Date:
Calcium	2.1-2.6 mmol/L		If out of reference range do not give denosumab; discuss with the doctor
Creatinine	49-90umol/L		
eGFR	90-120 mls/min/1.73m^2		

10.	Add code to clinical system: **Denosumab Therapy**	☐Yes ☐No
11.	Inform patient to next blood test due in 5 months followed by a subsequent injection 1 month later, at 6 months.	☐Yes ☐No
12.	AFTER the 6th injection, advise to book appointment for GP or specialist review	☐Yes ☐No

Appendix Five: Denosumab Patient safety info sheet

This sheet contains important safety information that you need to be aware of before and during treatment with denosumab (Prolia).

Your doctor has recommended that you receive denosumab (Prolia), which is used to treat osteoporosis and bone loss. These diseases involve thinning and weakening of the bones so they may break more easily.

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported rarely (may affect up to 1 in 1,000 people) in patients receiving Prolia for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try to prevent ONJ developing as it may be a painful condition that can be difficult to treat.

In order to reduce the risk of developing ONJ, there are some precautions you should take.

Before starting treatment:
Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.

Your doctor may ask you to undergo a dental examination if you:

- were previously treated with a bisphosphonate
- are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- are a smoker
- have cancer
- have not had a dental check up for a long time
- have problems with your mouth or teeth

While being treated:

- You should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures
- you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your
- doctor and tell your dentist that you are being treated with Prolia.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or
- teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be
- signs of osteonecrosis of the jaw

Please read the package leaflet that comes with your medicine for further information.

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

By reporting side effects, you can help provide more information on the safety of Prolia

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