Hull and East Yorkshire Hospitals NHS
NHS Trust

HERPC
Hull & East Riding Prescribing Committee

Prescribing Framework for Denosumab (Prolia®) in Osteoporosis

Patients Name:……..… NHS Number: ……

Patients Address:……..……(Use addressograph sticker)

Communication

We agree to treat this patient within this Prescribing Framework	
Specialist prescriber's name:	GMC No
……	……..
Specialist prescriber's signature:	Date:
……	……..
Consultant's name if prescriber is ***not*** a Consultant:	Consultant's GMC No
……	……..
Consultant's signature:	Date:
……	……...
General Practitioner's name:	GMC No
……	……..
General Practitioner's signature:	Date:
……	……..

The front page of this form should be completed by the specialist and the form sent to the patient's General Practitioner.

The patient's GP should sign and **send back to specialist**, to confirm agreement to enter into shared care arrangement. If the General Practitioner is **unwilling** to accept prescribing responsibility for the above patient the specialist should be informed within two weeks of receipt of this framework and specialist's letter.

Full copy of framework can also be found at : http://www.hey.nhs.uk/amber.htm

1. Background

Denosumab is a fully human monoclonal antibody that inhibits bone resorption by neutralising RANKL, a key mediator of osteoclast formation, function, and survival.

Denosumab is licensed for treatment of osteoporosis in both men and women. NICE TA204 covers primary and secondary prevention of osteoporotic fractures in postmenopausal women with increased risk of fractures.

This document aims to provide a framework for the prescribing of denosumab by GPs. It sets out the associated responsibilities of GPs and hospital specialists who enter into the shared care arrangements.

This document should be read in conjunction with the general guidance on prescribing matters given in EL (91) 127 "Responsibility for prescribing between hospitals and GPs".

Traffic Light Classification
Please note this Shared Care Framework refers to **Denosumab 60mg injection (*Prolia*)** which is approved as an **AMBER Drug** within Hull and East Riding.

Denosumab 120mg Injection (XGEVA), licensed for reduction of bone damage in patients with bone metastases from solid tumours, is classified as a RED drug and should not be prescribed by non-specialist team.

2. Initiation

a. Initiation of treatment will follow a formal face-to-face consultation between the secondary care specialist (a registrar or a consultant in metabolic bone disease, a consultant in orthogeriatrics or a consultant in community geriatrics) and the patient and, where appropriate, the patient's carer. This consultation may take place in a hospital clinic, an inpatient episode (for orthogeriatrics), or in a step-down facility or a community clinic (for community geriatrics).

b. It is the responsibility of the initiating specialist to prescribe and arrange administration of the first dose except where the patient is already a resident in a nursing or a residential home. In the latter case, the GP may be asked to prescribe the first dose after the community geriatrician has organised and reviewed relevant investigations.

c. Usually, the use of denosumab will be for treatment of osteoporosis in post-menopausal women with osteoporosis and increased risk of fractures as per NICE TA 204.

d. Where NICE TA 204 is not applicable, i.e. because the patient is a man or a pre-menopausal woman, the specialist should affirm that the estimated 10-year fracture risk, or lifetime risk where life expectancy may be shorter than 10 years, is at least equivalent to, if not greater than, that envisaged in NICE TA 204. [See clinic letter]

e. The specialist should always state the rationale for prescribing denosumab in preference to other alternative bone protection drugs. [See clinic letter]

f. For the purposes of this guidance, it is assumed that the specialist has determined either (a) that intravenous bisphosphonate therapy is not suitable and/or (b) that subcutaneous denosumab therapy is more suitable for the patient's needs.

Whenever possible, the secondary care physician should take into account the patient's informed choice. (See Appendix I)

3. Administration

Denosumab (Prolia®) 60 mg is 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 (at least 700 mg daily) and vitamin D (at least 800 units daily). Vitamin D supplementation alone may suffice if there is adequate dietary calcium intake. (See Appendix III)

Before administration, the denosumab solution should be inspected. 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 a single subcutaneous injection into the thigh, abdomen or back of arm. Inject slowly. Inject the entire contents of the pre-filled syringe. 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.

4. Duration of treatment

It is envisaged that this treatment is for long-term. Typically, the duration of therapy will be between 3 to 5 years. There is as yet no established data on the optimal duration of therapy with denosumab.

Unlike oral or systemic bisphosphonates, antiresorptive effect of denosumab does not last beyond 6 months after each injection. It is now recognised that there is a potential rebound 'off-effect', i.e. fracture risk may be increased after discontinuing denosumab.

It is essential that the dosing frequency of every six months plus or minus two weeks is maintained.

5. Contraindications and cautions

Serum adjusted calcium must be >2.2 mmol/L and vitamin D levels adequate (50-100 nmol/L) before each injection. Where either serum corrected calcium and/or vitamin D level is low, this requires correction prior to proceeding with the next injection of denosumab.

Denosumab should not be used in patients with known latex allergy, rare hereditary problems of fructose intolerance, in pregnancy or in lactating women.

WARNING

Cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120mg (*XGEVA*) or 60mg (*Prolia*).

Pre-existing hypocalcaemia must be corrected prior to initiating denosumab. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560

6. Adverse effects

The table below describes adverse reactions listed in the Summary of Product Characteristics (SPC).

The following convention has been used for the classification of the adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	**Common** **Common** Uncommon Uncommon Uncommon	**Urinary tract infection** **Upper respiratory tract infection** Diverticulitis Cellulitis Ear infection
Immune system disorders	Rare Rare	Drug hypersensitivity Anaphylactic reaction
Metabolism and nutrition disorders	Rare	Hypocalcaemia
Nervous system disorders	**Common**	**Sciatica**
Eye disorders	**Common**	**Cataracts**
Gastrointestinal disorders	**Common** **Common**	**Constipation** **Abdominal discomfort**
Skin and subcutaneous tissue disorders	**Common** **Common**	**Rash** **Eczema**
Musculoskeletal and connective tissue disorders	**Very common** **Very common** Rare Rare	**Pain in extremity** **Musculoskeletal pain** Osteonecrosis of the jaw Atypical femoral fractures

<u>Skin infection</u>
Patients receiving denosumab may develop skin infections (predominantly cellulitis), which may lead to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

<u>Hypocalcaemia</u>
Hypocalcaemia should be prevented by ensuring adequate intake of calcium and vitamin D before initiating therapy (Appendices II and III). Calcium and vitamin D levels should be checked within 8 weeks before to each injection of denosumab.

<u>Antiresorptive related osteonecrosis of the jaw (ARONJ)</u>
ARONJ 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 ARONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g. chemotherapy, anti-angiogenic 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).

7. Interactions

None reported

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or the Summary of Product Characteristics (SPC) (www.medicines.org.uk).

Denosumab is monitored intensively by the CHM and MHRA and all suspected adverse reactions (including those considered not serious) should be reported through the Yellow Card Scheme (www.yellowcard.gov.uk).

8. Monitoring

Timing (weeks)	Test/treatment	Notes
- 4	Biochemical profile (BCP) or calcium profile	All patients
0	Denosumab administration	All patients
+ 3	Biochemical profile	Patients with e-GFR <30 or on dialysis

Care should be individualised. Further diagnostic tests, e.g. DXA and/or bone turnover markers, may be appropriate in individual patients and may not be in the patient's best interests in others (e.g. very frail patients from care homes). It is the responsibility of the secondary care specialist to organise such tests where appropriate.

9. Information to patients

All patients (and/or carers where appropriate) should be given an information leaflet, outlining the benefits and risk of treatment.

The patients and/or carers should be given clear advice about the therapeutic window (6 months ± 2 weeks).

Where treatment is initiated by the Centre for Metabolic Bone Disease, patients are advised to enrol in the PROLONG Patient Support Programme online, by post or fax to access further support and to ensure that they are reminded when their next injection is due. The PROLONG service reminds the patients that their next injection is due 6 weeks before. As long as the GP's details are correctly entered in the registration, the GP should receive a similar reminder.

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 unless necessary. Good oral hygiene should be maintained during treatment with denosumab.

10. Responsibilities of clinicians involved

Stage of Treatment	Hospital Specialist	General Practitioner
Initiation	1. Select patients appropriate for treatment and baseline assessment 2. Inform patient of risks and benefits of treatment and supply arrangements. 3. Take responsibility for safety precautions: a. Exclude hypocalcaemia b. Establish baseline renal function c. Ensure vitamin D sufficiency (50-100 nmol/L) 4. Review baseline risk for ARONJ. Advise dental review or treatment prior to administration if appropriate. 5. Specify initial intended duration of treatment: ☐ 3 years, ☐ 5 years, or ☐ lifelong. 6. Prescribe and administer or arrange for administration of the first dose. 7. Contact the GP to invite shared care for the patient and provide information on treatment.	1. Return the Shared Care Protocol to the secondary care specialist within 2 weeks of receipt. If GP requires further clarification or does not wish to enter shared care guidance then to reply as soon as possible.
Maintenance	8. Advise patient to enrol in the PROLONG Patient Support Programme. 9. Organise DXA (if appropriate). 10. Organise clinic review (if appropriate). 11. Provide advice and support to the GP as needed. 12. To report any suspected adverse events to the MHRA. http://yellowcard.mhra.gov.uk/	2. Maintain system of recall for injections (every 6 months ± 2 weeks) and tests (4 weeks before due date for injection). This may be supplemented (but not substituted) by the PROLONG service. 3. Prescribe treatment and ensure administration at 6 monthly intervals (± 2 weeks either side of date due) 4. Check biochemical profile or calcium profile within 4-6 weeks prior to each injection. Ensure serum adjusted calcium ≥ 2.2 mmol/L. 5. Check vitamin D level within 4-6 weeks prior to each injection. Ensure level is within target range (50-100 nmol/L). Correct if low. (See Appendix II) 6. Check renal function within 4-6 week prior to each injection. If the e-GFR was > 30 ml/min at initiation but has now declined to <30 mL/min (i.e. progressed to CKD stage 4 since the time of initiation), please let the secondary care specialist know. This does not apply to patients who were already known to have CKD stage 4 or worse or who are known to be on dialysis at the time of initiation. 7. Monitor patient for adverse effects. 8. Refer back to specialist where appropriate (please see section 11 below). 9. To report any suspected adverse events to the MHRA. http://yellowcard.mhra.gov.uk/
Discontinuation	Provide advice on further bone protection treatment (if any) after initial specified period of treatment.	Inform secondary care specialist if the drug was discontinued, e.g. due to a severe adverse reaction.

11. When to refer back to the secondary care specialist

The GP should contact the specialist in the following situations:

1. *Development of a new fragility fracture after one year (2 doses) of therapy.* Most patients receiving denosumab will have high baseline risk of fractures. Development of a new fracture does not necessarily mean treatment failure. It may simply be a reflection of high fracture risk. Treatment failure may be suspected if a new fracture occurs after 1 year of treatment (i.e. 2 doses) and especially if the fractures are multiple, e.g. multi-level vertebral fractures or multiple rib fractures.

2. *Suspected atypical femoral fracture.* For the purposes of this guidance, an atypical fracture should be suspected if it occurred anywhere distal to the lesser condyle of the femur down to just above the supracondylar area (i.e. subtronchanteric or diaphysial femoral fracture) with no or minimal impact, often with a prodrome of pain.

3. Development of antiresorptive-related osteonecrosis of the jaw (ARONJ).

4. Development of significant adverse reactions: hypocalcaemia, severe or recurrent cellulitis, recurrent UTI, recurrent chest infections. Referral should also be made if there was any other suspected adverse reaction if it prompted the GP to report to the MHRA via the Yellow Card Scheme.

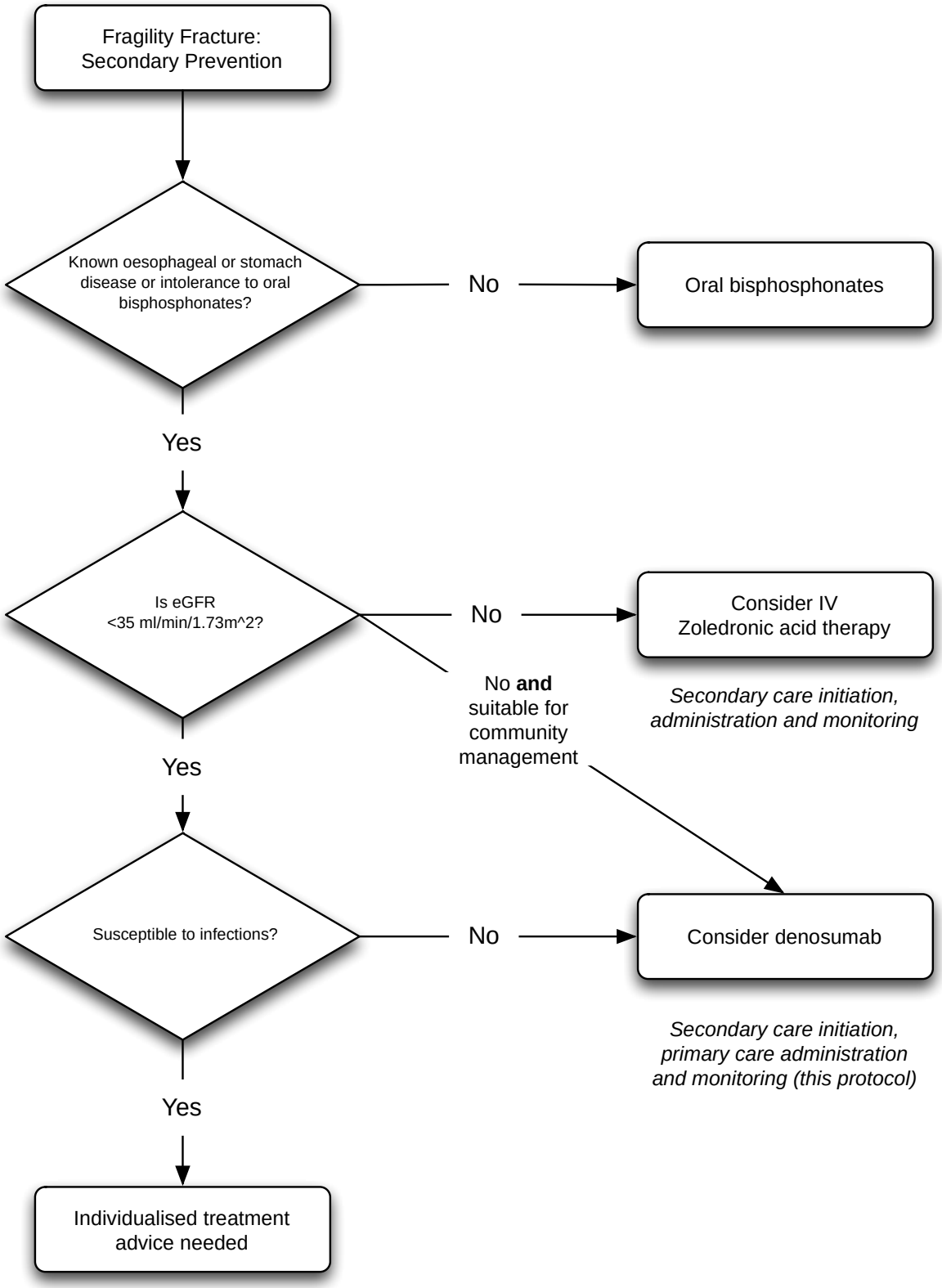
5. Deterioration in renal function to CKD stage 4 (eGFR <30 ml/min/1.73m^2 BSA) or worse if the patient is not known to have CKD 4 at the time of initiation.

6. The patient declines further treatment.

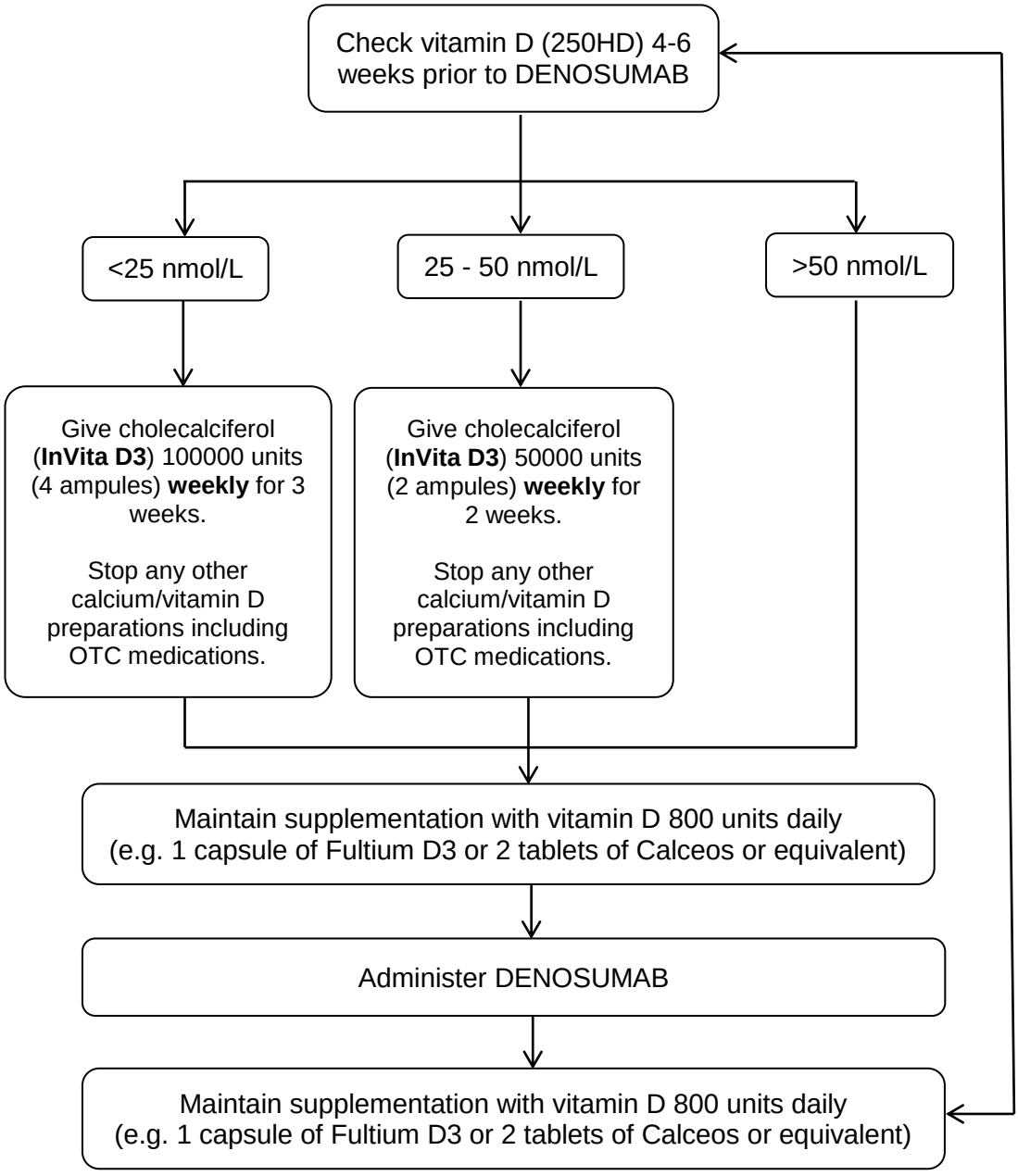
12. Contact Details

During office hours	Contact initiating Consultant as per clinic or hospital letter, via HEY Switchboard (01482 328541) **or** Dr Mo Aye Consultant Endocrinologist. Centre for Metabolic Bone Disease 01482 675369
Out of hours	Contact on-call Consultant Endocrinologist via HEY Switchboard (01482 328541)

Appendix I: Algorithm for choosing anti-resorptive therapies



Appendix II: Ensuring vitamin D repletion



Appendix III: Assessing dietary calcium intake

	0	100 mg	200 mg	300 mg	400 mg	600 mg	900 mg
Milk	None	<1/3 pint	1/3 pint	1/2 pint	2/3 pint	1 pint	1½ pint
Servings of dairy (per matchbox cheese or small pot or yoghurt)			1		2	3	4

APPROVAL PROCESS

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