NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT FRAMEWORK

Shared care guidelines - Denosumab for prevention of osteoporotic fractures in men and post-menopausal women

AMB 1 **Prescribe the drug and perform a higher level of monitoring, e.g. 6-monthly**

Generic and Proprietary/Brand Name	
Denosumab (generic and biosimilar - 60mg biosimilar preparation for local Trust use - Ponlimsi®)	
Indications for shared care	
Prevention of osteoporotic fractures in men and post-menopausal women	
Summary of Specialist Prescribing and Monitoring Responsibilities	**Summary of GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities**
• Check baseline calcium levels in patients being considered for treatment with denosumab, especially those with severe renal impairment (creatinine clearance < 30 mL/min) or who are receiving dialysis, who are therefore at greater risk of developing hypocalcaemia. • Initiate treatment with denosumab and recommend to the patient's GP that the treatment is provided from second injection onwards in primary care. • Patients initiated on treatment with denosumab will be counselled by the specialist regarding the potential effects of the treatment and encouraged to report symptoms indicative of hypocalcaemia, such as muscle stiffness, twitching, spasms and muscle cramps.	• Clinical monitoring of calcium levels is recommended before each dose is administered. • Calcium levels are checked if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient. • Patients at risk of developing hypocalcaemia have adequate intake of calcium and vitamin D. • Prescribe 6 monthly, checking blood calcium levels prior to each dose, and ensuring that the patient has adequate intake of calcium and vitamin D as appropriate.

Patient Information

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 during treatment with denosumab. While on treatment, patients should avoid invasive dental procedures if possible.

Patients are advised to report any symptoms indicating suspected hypocalcaemia, such as muscle stiffness, twitching, spasms and muscle cramps.

Specialist Contact Details

• Dr De Silva's secretary (NNUH)	(01603) 288623
• Dr Gaffney's secretary (NNUH)	(01603) 289670
• Professor MacGregor's secretary (NNUH)	(01603) 288677
• Dr Marshall's secretary (NNUH)	(01603) 288677
• Dr Merry's secretary (NNUH)	(01603) 287003
• Dr Mukhtyar's secretary (NNUH)	(01603) 287118
• Dr Turner's secretary (NNUH)	(01603) 288172
• Dr Lee's secretary (NNUH)	(01603) 288559
• Dr J Thomas's secretary (JPUH)	(01493) 452216
• Dr D Makkuni's secretary (JPUH)	(01493) 452216
• Dr Pradip Sarda's secretary (QEH)	(01553) 613526

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are 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 this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Denosumab is a monoclonal antibody that reduces osteoclast activity and reduces bone breakdown.

It is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to Receptor Activator of NF-kappaB Ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts.

Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Denosumab treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-terminal telopeptide cross links (CTX) (85% reduction) by 3 days, with reductions maintained over the dosing interval.

Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose.

Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Licenced use and agreed local off-label use

Denosumab has a UK marketing authorisation for:

- prevention of osteoporotic fractures in men and post-menopausal women
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (NB - not currently covered by this Shared Care Agreement and not recommended by NICE).

Criteria for Patient Selection

Clinical risk factors for fracture in this circumstance include:

- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

Primary prevention:

Denosumab in patients 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 (see above) as indicated in the following table.

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

Secondary prevention:
Denosumab is 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.

Avoidance of adverse events whilst on denosumab:
Osteonecrosis of the jaw (ONJ):
The doctor initiating treatment will evaluate patients for ONJ risk factors prior to starting treatment with denosumab.
Known risk factors for ONJ include -
Previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, concomitant therapies (e.g. chemotherapy, anti-angiogenic biologics, corticosteroids, radiotherapy to head and neck).
A dental examination with appropriate preventive dentistry is recommended **prior** to treatment with denosumab **in patients with concomitant risk factors**.
All patients will 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 during treatment with denosumab. Patients will also be advised to avoid invasive dental procedures while on treatment if possible.
Hypocalcaemia:
Consideration of risk factors for developing hypocalcaemia whilst on treatment with denosumab.

Form and strength of preparation

Each pre-filled syringe contains 60 mg of denosumab in 1 ml of solution (60 mg/ml). It is a clear, colourless to slightly yellow solution.

Side Effects

Please refer to the manufacturer's SPC for full details. List of preparations can be found here - Search Results - (emc)

Common undesirable effects include:
Pain in extremity and musculoskeletal pain (reported incidence ≥ 1/10)
Urinary tract infection, upper respiratory tract infection, constipation, sciatica, rash, eczema (reported incidence ≥ 1/100 to < 1/10).

Cellulitis - Patients receiving denosumab may *rarely* develop skin infections (predominantly cellulitis) requiring hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Atypical femoral fractures have been reported *rarely* in patients treated with denosumab. Atypical femoral fractures have also been reported in patients with certain co-morbid 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 anti-resorptive therapy. 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.

Osteonecrosis of the jaw (ONJ) has *rarely* been reported in patients treated with denosumab treated with six-monthly doses of 60mg subcutaneously for osteoporosis. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.
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 if possible.
For patients who develop ONJ while on denosumab therapy, dental surgery may exacerbate the condition. The management plan of the individual 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.

Hypocalcaemia
Cases of severe symptomatic hypocalcaemia have been predominantly reported in patients at increased risk of hypocalcaemia receiving denosumab, with most cases occurring in the first weeks of initiating therapy.
Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status. Symptoms of hypocalcaemia in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. 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.

Drug Interactions

See BNF for up-to-date list of interactions. Please also refer to the manufacturer's SPC for full details. List of preparations can be found here - Search Results - (emc)

Cautions and Contraindications

Please refer to the manufacturer's SPC for full details. List of preparations can be found here - Search Results - (emc)

- Denosumab should not be given to patients with **hypocalcaemia**. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D ***before initiating therapy***. Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.
- Monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia.
- Denosumab is not recommended in patients aged < 18 years.
- No dose adjustment is required in patients with renal impairment.
- No dose adjustment is required in elderly patients.
- The safety and efficacy of denosumab have not been studied in patients with hepatic impairment. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.
- Some denosumab preparations contain sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
- Long-term anti-resorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone re-modelling.

As per MHRA Drug Alert (August 2020), there may be an increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment. Patients should not miss doses or stop treatment without specialist review

Initiation of therapy

The first dose should be administered in a secondary care setting under the instructions of a consultant with routine experience of the treatment of osteoporosis.

The doctor initiating denosumab is responsible for evaluating the risk of the patient developing osteonecrosis of the jaw (ONJ) (as described under Criteria for Patient Selection) and, for patients with concomitant risk factors for ONJ, enquiring whether they have had any necessary preventative dental treatment prior to starting treatment.

The doctor initiating denosumab is responsible for evaluating whether the patient is hypocalcaemic and for ensuring that the patient's calcium levels are corrected and maintained prior to starting treatment. Special consideration of calcium levels is necessary in patients with renal impairment.

Initial dose and method of administration and supply

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

Maintenance Dose and Administration

Maintenance is 60mg every 6 months administered as a single subcutaneous injection into the thigh, abdomen or back of the arm.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

5 years and review. Consider risk/benefit of continuing therapy, with consultant input.

Further information about administration

Administration should be performed by an individual who has been adequately trained in injection techniques.

Denosumab should be stored in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton to protect from light. The product has a shelf life of 3 years under these conditions.

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, denosumab must be used within this 30 day period. 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 and inject slowly. Inject the entire contents of the pre-filled syringe.

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

Initial monitoring / baseline assessment – by Specialist

Check baseline calcium levels in patients being considered for treatment with denosumab, especially those with severe renal impairment (creatinine clearance < 30 mL/min) or who are receiving dialysis, who are therefore at greater risk of developing hypocalcaemia.
Severe symptomatic hypocalcaemia has been reported in patients treated with denosumab, with most cases occurring in the first weeks of initiating therapy, although it can occur later.

In patients predisposed to hypocalcaemia (i.e. patients with severe renal impairment, with creatinine clearance <30mL/min (or equivalent eGFR)) clinical monitoring of calcium levels is recommended within two weeks after the initial dose of denosumab.

The clinician initiating treatment should also provide such patients with an ICE form for them to have a second blood test to monitor calcium levels within two weeks after the initial dose of denosumab.

Specialist monitoring responsibilities regarding ongoing treatment

None required

GP / Community Team or other Primary Care monitoring responsibilities

Severe symptomatic hypocalcaemia has been reported in patients treated with denosumab, with most cases occurring in the first weeks of initiating therapy, although it can occur later.

It is therefore recommended that:

- Clinical monitoring of calcium levels is recommended before each dose is administered.
- Calcium levels are checked if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient.
- Patients at risk of developing hypocalcaemia have adequate intake of calcium and vitamin D.

Consultant / Specialist prescribing responsibilities

The specialist will initiate treatment with denosumab in secondary care and recommend to the patient's GP that the treatment is provided from second injection onwards in primary care.

Patients initiated on treatment with denosumab will be counselled by the specialist regarding the potential effects of the treatment and encouraged to report symptoms indicative of hypocalcaemia, such as muscle stiffness, twitching, spasms and muscle cramps.

GP prescribing responsibilities

To prescribe 6 monthly, checking blood calcium levels prior to each dose, and ensuring that the patient has adequate intake of calcium and vitamin D as appropriate.

Indications for referral back to Specialist

- Development of ONJ, hypocalcaemia, or any other intolerable side effects.
- Further fracture and deteriorating bone density indicating suitability for teriparatide.

Further information and supporting documents

NICE Guidance:
https://www.nice.org.uk/guidance/ta204 / https://pathways.nice.org.uk/pathways/osteoporosis
MHRA safety recommendations September 2014:
https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations
MHRA safety report June 2017:
Denosumab (Prolia, Xgeva▼): reports of osteonecrosis of the external auditory canal
https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal
MHRA Drug Alert – August 2020
Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment

Author(s) and Organisation	Dr Tarnya Marshall: Consultant Rheumatologist, Norfolk and Norwich University Hospitals NHS Foundation Trust Professor Jeremy Turner: Consultant Endocrinologist, Norfolk and Norwich University Hospitals NHS Foundation Trust Dr Susan Lee: Consultant Physician, Medicine for Elderly, Norfolk and Norwich University Hospitals NHS Foundation Trust

Date of initial approval	December 2011
Last review date	February 2026
Reviewed by	TAG and MOPB
Date of next review	February 2028

Document history:

Version	Date	Author / Editor	Status	Comment
1.	Dec 2011	Dr Tarnya Marshall: Consultant Rheumatologist, Dr Jeremy Turner: Consultant Endocrinologist, Dr Susan Lee: Consultant Physician, Medicine for Elderly, NNUH FT / Fiona Marshall TAG Lead Pharmacist	Superseded	Finalised by the NHS Norfolk & Waveney Drugs & Therapeutics Commissioning Group (D&TCG) – December 2011
2.	March 2014	As for v1	Superseded	Minor changes recommended by the authors. Duration of treatment confirmed as 5 years. Continued use of the agreement supported by the TAG, March 2014.
3.0	Oct - Nov 2014	As for v2	Draft for review following updated MHRA safety guidance on the risk of osteonecrosis of the jaw and of hypocalcaemia	SCA updated to reflect prescribing and monitoring responsibilities in line with revised safety recommendations from the MHRA and the manufacturer. Also updated in line with recent template for TAG SCAs. Draft version reviewed and supported by the authors ahead of the November 2014 TAG meeting. November 2014: The TAG recommended that the specialist should provide at-risk patients with an ICE blood test form for a follow-up calcium check within two weeks after the initial dose.

				Specialist contact numbers at the NNUH corrected.
3.1	Feb 2015	As for v3	Superseded	Additional information added regarding ordering arrangements for Prolia® in primary and secondary care.
4.0	Dec 2016	As for v3	Draft for review	NNUH contact numbers updated. Links to MHRA safety warnings and NICE guidance updated. Sent to authors for review
4.1	Jan 2017	As for v3.1	Superseded	No recommendations for review received from the authors. Supported for continued use by the TAG.
4.2	August 2017	As for 3.1	Current	Movianto telephone contact for ordering Prolia updated to 01234 248500. Customer care e-mail added for any queries.
5.0	Dec 2018	As for 3.1	Draft for review	Updated with current logos and checked against current SPC. Proposed changes highlighted in red text. Sent to authors for review.
5.1	Jan 2019	As for 3.1	Final	Dr John Pradeep contact removed. Recommended changes supported by the authors.
6.0	October 2020	Jennifer Carroll, TAG Lead Technician, AGEM CSU	Draft for review after discussion at TAG regarding addition of MHRA Drug Alert	Added MHRA Drug Alert (August 2020) regarding increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment. Updated 'contraindications and precautions', 'duration of treatment' and 'additional information'
6.1	November 2020	As for 6.0	Final	Recommendations supported by authors
7.0	May 2023	Jen Carroll, TAG Lead Technician, NWICB	Draft	Updated information regarding how to obtain supplies of prolia® in primary care

7.1	July 2023	Jen Carroll, TAG Lead Technician, NWICB	Final	Ratified by Planned Care and Medicines Management Working Group
8.0	Feb 2026	JC, Senior Interface and Formulary Technician	Draft	Review content. • Added 'use in men' with appropriate details to agreement. • References to 'prolia' brand removed • All links checked and working
8.1	March 2026	As above	Final	• Version 8.0 update supported by TAG. • SCA level amended to 1 as only requires 6-monthly monitoring • Ratified by Medicines Optimisation Programme Board