BSW APC: BaNES, Swindon & Wiltshire (BSW) CCG, Avon & Wiltshire Mental Health Partnership NHS Trust (AWP), Royal United Hospitals Bath NHS Foundation Trust, Great Western Hospitals NHS Foundation Trust, Salisbury NHS Foundation Trust, Virgin Care, Swindon Community Health Services, Wiltshire Health & Care

SHARED CARE AGREEMENT

Denosumab (Prolia®) for Osteoporosis – Adults

Amber TLS – 1 Month

Principles of Shared Care

Shared care agreements provide a framework for the seamless transfer of care from a hospital or specialist service setting to general practice, where this is appropriate and, in the patient's, best interest. When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP (or other primary care prescriber) concerned and the patient to share their care.

Patients and/or carers must be centrally involved in any decision-making process. They should be supported by good quality information that helps them to both come to an informed decision about engagement in a shared care arrangement and sets out the practical arrangements for ongoing supplies of medicines.

The existence of a shared care agreement does not necessarily mean that the GP has to agree to and accept clinical and legal responsibility for prescribing; they should only do so if they feel clinically confident in managing that condition. Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

Responsibilities of Secondary Care Specialist

- Initiate treatment and prescribe for the length of time agreed (1 month) – this should be enough time to allow optimisation of treatment and demonstrate that the patient's response is consistent.
- Discuss the benefits and side effects of treatment with the patient. Advise patients that they should seek prompt medical attention if they develop signs or symptoms of cellulitis. Patients should also maintain good dental hygiene during treatment. Check for osteonecrosis of the jaw (ONJ) risk factors before starting Denosumab. Advise that for patients with concomitant risk factors, a dental examination with appropriate preventative dentistry may be necessary prior to treatment. Such patients should also be warned to avoid invasive dental procedures whilst on this treatment if possible. Give patients a patient reminder card about the risk of osteonecrosis of the jaw (MHRA advice July 2015)
- Ensure that the patient understands that the dosing is via subcutaneous injection every 6 months, administered at their GP surgery.
- Review concurrent medications for potential interactions prior to initiation.
- Baseline calcium & vitamin D levels will be taken initially, and any hypocalcaemia will be corrected by adequate intake of calcium & vitamin D before initiating therapy.
- Undertake the clinical assessment and relevant monitoring at baseline and during the initiation period.
- Communicate details of treatment to GP (in writing or via secure email) within the first month of treatment and ask the GP whether he or she is willing to participate in shared care.
- Discuss shared care arrangements with the patient/carer, obtain their consent and explain their responsibilities.
- Review the patient's condition and monitor response to treatment regularly where indicated.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Supply GP with clinic letter or discharge summary within 14 days of an outpatient review or inpatient admission, and inform GP if patient does not attend scheduled clinic appointments.
- Ensure that clear arrangements exist for GPs to obtain advice and support.
- Report adverse events to the MHRA.
- Stop treatment where appropriate or provide GP with advice on when to stop.

Responsibilities of GP/Primary Care Prescriber

- Reply to the request as soon as practicable if they are **unable** to support shared care (in writing or via secure email).
- Prescribe medicine at the dose recommended after the initiation period and calcium & vitamin D supplements.
- Ensure that the patient understands that the dosing is via subcutaneous injection every 6 months, administered at their GP surgery.
- Undertake ongoing clinical assessment and relevant monitoring following initiation period.

- Review any new concurrent medications for potential interactions.
- Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
- Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
- Report adverse events to the specialist and MHRA.
- Stop treatment on the advice of the specialist.
- Patients should have their calcium monitored prior to administering each dose of denosumab. and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured.
- Patients that continue on denosumab at 5 years need to be discussed with a specialist in order to decide whether denosumab should be continued or not.

Responsibilities of Patient/Carer

- Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
- Share any concerns in relation to treatment with medicine.
- Report any adverse effects to the specialist or GP whilst taking the medicine.
- Attend appointments for clinical review and monitoring.
- Maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to their doctor or dentist. If patients wear dentures make sure the dentures fit properly before starting treatment.
- 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).
- Advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment.

1. Summary of condition and treatment aims Include links to relevant clinical guidelines e.g. NICE	Postmenopausal osteoporosis is a condition that mainly affects older women and is characterized by a decrease in bone mass. Denosumab is a licensed and NICE-approved option for women with this condition. Denosumab is also licensed for use in men at increased risk of fractures.	
2. Details of medicine and indication Please state whether licensed or unlicensed (off-label) use. Note that shared care is generally unsuitable for off-label prescribing unless it is a widely recognised use (e.g. included in BNF)	Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to receptor activator of nuclear factor-K B 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. NICE TA204 (October 2010) sets out how this drug should be used in primary & secondary prevention in postmenopausal women.	
3. Pharmaceutical aspects	Route of administration:	subcutaneous injection
	Formulation:	solution for injection in pre-filled syringe
	Administration details:	single subcutaneous injection once every 6 months
	Other important information:	Store in a refrigerator (2°C – 8°C).

4. Usual dose and frequency (including details of dose adjustments, e.g. in renal impairment) and duration of therapy

Transfer of monitoring and prescribing to Primary care is normally after the patient is on regular dose and with satisfactory investigation results.
All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.
The duration of treatment will be determined by the specialist, based on clinical response and tolerability.
Termination of treatment will be the responsibility of the specialist.

The recommended dose of denosumab is 60mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or back of arm.
The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use Therefore patients that continue denosumab at 5 years need to be referred to a specialist to decide whether denosumab should be continued or not.
Denosumab should not be suspended pending a 5-year review unless there is a clinical reason for doing so. Please also see MHRA Drug Safety update about increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment, found here.

5. Monitoring requirements

Monitoring parameters	Frequency of monitoring	Action (adjustment and referral back to hospital)
For patients with a Creatinine Clearance of ≤ 35ml/min or those receiving dialysis. *This is calculated using the Cockcroft-Gault Equation which requires the patient's height weight and creatinine level.*	**Check serum calcium weekly for at least one month and until calcium normalised post each injection.** Check creatinine clearance and serum calcium before each dose.	Seek specialist advice if calcium level low and /or patient is symptomatic. Ensure compliance with calcium and vitamin D supplementation.
For patients with a Creatinine clearance of > 35ml/min. *This is calculated using the Cockcroft-Gault Equation which requires the patient's height weight and creatinine level (see next page)*	**Clinical monitoring of calcium levels is recommended before each dose and at four weeks post each denosumab injection.**	If serum calcium level is low, check compliance with calcium/vitamin D supplement and re-check serum calcium in 2 weeks providing patient is asymptomatic. If patient is symptomatic seek specialist advice. Should the **Creatinine Clearance** fall to ≤35ml/min, please contact specialist for advice before going ahead with the injection.

6. Cautions and contraindications

Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.

- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients.

This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be considered.

Adequate calcium & vitamin D intake is important for all patients. Hypocalcaemia and insufficient/deficient serum vitamin D levels must be corrected by adequate intake of

	calcium and vitamin D before initiating therapy. Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia. Patients with 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. Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. **ONJ** has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however, some have occurred in patients with osteoporosis. MHRA July 2015 Patient reminder cards about the risk of osteonecrosis of the jaw should be used. Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic 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) and previous treatment with bisphosphonates. 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. Good oral hygiene practices should be maintained during treatment with Prolia. For patients who develop ONJ while on denosumab therapy, dental surgery may exacerbate the condition. If ONJ occurs during treatment with denosumab, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation. **Atypical femoral fractures** have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. 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. 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 or in those with suspected cholesteatoma. Possible risk factors include steroid use and chemotherapy, with or without local risk factors such as infection or trauma. Advise patients to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment (MHRA 2017).
7. Significant medicine and food interactions and management For a comprehensive list, consult the BNF or Summary of Product Characteristics (SPC)	• In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolised by CYP3A4. • There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is low. • In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

	Adverse Effect	**Action to be taken if detected**

8. Adverse effects and management Include details of incidence, identification, importance and management.	• Very common (≥ 1/10): pain in extremity, musculoskeletal pain. • Common (≥ 1/100 to <1/10): Urinary tract infection, Upper respiratory tract infection, sciatica, constipation, rash, eczema. • Uncommon (≥ 1/1,000 to <1/100): Diverticulitis, cellulitis, ear infection. • Rare (≥ 1/10,000 to < 1/1,000): Hypocalcaemia.	• Refer patient back to the specialist if any of these side-effects cause concern.
9. Advice to patients and carers The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.	• Denosumab (Prolia®) patient reminder card (safety information) can be found here: https://www.medicines.org.uk/emc/product/568/rmms	
10. Pregnancy and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	• There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity. • Denosumab is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with denosumab. Any effects of denosumab are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Breast-feeding • It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, considering the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.	
11. Specialist contact information		

	Telephone	**E-mail:**
SFT		
Dr Zoe Cole	01722 336262 ext 4791	Zoe.cole@salisbury.nhs.uk
RUH		
Dr Sarah Hardcastle	01225 821644	sarahhardcastle@nhs.net
Dr Tehseen Ahmed	01225 821644	tehseen.ahmed@nhs.net
Jackie Webb osteoporosis nurse	01225 473413	Jackie.Webb1@nhs.net
Dr Katrina Hicks	01225 821267	khicks1@nhs.net
Dr Celia Gregson	01225 821267	celia.gregson@nhs.net

	Dr Veronica Lyell	01225 821267	v.lyell@nhs.net
	GWH		
	Dr David Collins	01793 604317 (secretary)	david.collins@nhs.net
	Other Specialist Contact Information		
	• Cynapsis app		
12. Additional information For example, process for when Specialist or GP changes roles; specific issues related to patient age/ capacity/ specific monitoring.			
13. References	• Summary of Product Characteristics for Denosumab (Prolia®) via https://www.medicines.org.uk/emc/product/568/smpc • BNF online via https://bnf.nice.org.uk/ • NICE TA 204 October 2010. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. https://www.nice.org.uk/Guidance/TA204 • MHRA Drug Safety Update 25/9/14. Denosumab: Updated recommendations. https://www.gov.uk/drug-safety-update/denosumab-updated-recommendations • MHRA Drug Safety Update 20/7/15. Denosumab (Xgeva▼, Prolia); intravenous bisphosphonates: osteonecrosis of the jaw—further measures to minimise risk - GOV.UK (www.gov.uk) • MHRA Drug Safety Update 21/6/17. https://www.gov.uk/drug-safety-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditory-canal?UNLID=917937221202112311297 • MHRA Drug Safety Update 26/8/20. Denosumab 60mg (Prolia): increased risk of multiple vertebral fractures after stopping or delaying ongoing treatment - GOV.UK (www.gov.uk)		
14. To be read in conjunction with the following documents	• NHS England: Responsibility for Prescribing Between Primary & Secondary/ Tertiary Care. Ref 07573, Version 1.0, Published January 2018. Accessed via: https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/		

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Date Last Updated:	September 2016
Date Approved by BSW:	25th January 2022
Review Date:	January 2025
Document Version:	V2

Shared Care Agreement template adapted with agreement from AWP by Rachel Hobson, October 2020. Version 0.1