All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Prescribing of Denosumab (Prolia®) in Wales: Review

Shared care protocol

October 2013

This report has been prepared by a multiprofessional collaborative group, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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NHS WALES GIG CYMRU

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1.0 RECOMMENDATION

When denosumab (Prolia®) is used for the prevention of osteoporotic fractures in postmenopausal women, it should be prescribed in accordance with the guidelines (National Institute for Health and Care Excellence [NICE] Technology Appraisal 204 [TA204])[1].

It is proposed that denosumab (Prolia®) should be initiated, and the first dose administered, by a specialist team. Thereafter, prescribing and administration can be undertaken in primary care with a shared care agreement (see pages 3–8).

The shared care proposal includes the use of denosumab (Prolia®) for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures where oral therapies are contraindicated or not tolerated.

A local enhanced service would support the necessary monitoring requirements to improve the uptake of the shared care proposal by primary care prescribers.

2.0 BACKGROUND

For full information and complete document, see Prescribing of Denosumab (Prolia®) in Wales: Review – Full Document.

DENOSUMAB SHARED CARE PROTOCOL

PROTOCOL: DENOSUMAB (PROLIA®) *This document should be read in conjunction with the current Summary of Product Characteristics (SPC)*[2] http://www.medicines.org.uk/	
1. Licensed indications	Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.
2. Therapeutic use and background	Denosumab (Prolia®) has been prescribed for the treatment of osteoporosis/bone loss for this individual. Denosumab is a human monoclonal antibody (IgG2) that decreases bone resorption in cortical and trabecular bone. *Subject to consultation responses, AWMSG will be requested to endorse this shared care of subcutaneous denosumab 60 mg (Prolia®)*, in accordance with the guidelines (National Institute for Health and Care Excellence [NICE] Technology Appraisal 204 [TA204])[1] i.e. when the following conditions are met: • **Primary prevention** of osteoporotic fragility fractures 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 contra-indication to, those treatments **and** who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance (available at www.nice.org.uk/TA204)[1]. • **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 contra-indication to, those treatments. • Bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures: who are unable to comply with the special instructions for administering bisphosphonates, or have an intolerance of, or a contra-indication to bisphosphonates. • The first dose should be administered by the specialist team. Thereafter, prescribing and administration can be undertaken in primary care in accordance with the shared care agreement.
3. Contraindications	Hypocalcaemia. Hypersensitivity to the active substance or to any of the excipients of denosumab (Prolia®).
4. Typical dosage regimen (adults)	1) Administration should be performed by an individual who has been adequately trained in injection techniques. For subcutaneous use. 2) The recommended dose is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Caution: a higher dose preparation of denosumab is available for patients with bone metastases and is not covered by this protocol. 3) Denosumab (Prolia®) is not recommended in paediatric patients (age < 18) as the safety and efficacy of denosumab (Prolia®) in these patients have not been established. 4) Duration of treatment: review therapy by specialist team after 5 years.
5. Drug interactions – Consult the British National Formulary (BNF) or SPC	Patients being treated with denosumab (Prolia®) should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal-related events in adults with bone metastases from solid tumours)[2]. http://www.medicines.org.uk/
6. Adverse drug reactions For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event is uncertain, consult SPC or BNF	**BNF summary:** **Diarrhoea, constipation, dyspnoea, urinary tract infection, upper respiratory tract infection, pain in extremity, sciatica, hypocalcaemia (fatal cases reported), hypophosphataemia, cataracts, rash, sweating; less commonly diverticulitis, cellulitis (seek prompt medical attention), ear infection; rarely osteonecrosis of the jaw, atypical femoral fractures (see Medicines and Healthcare Products Regulatory Agency [MHRA]/Commission on Human Medicines [CHM] advice)[3].**

	Hypocalcaemia: Hypocalcaemia (rare) is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance < 30 ml/min; estimated glomerular filtration rate [eGFR] 15–29 ml/min/1.73 m^2) or receiving dialysis. Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60 mg. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time[4]. Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment. **Infections:** Urinary tract infection (common), respiratory infection (common) and cellulitis (uncommon). **Osteonecrosis of the jaw:** Osteonecrosis of the jaw (rare) has been reported in patients treated with denosumab or bisphosphonates. Most cases have been in cancer patients; however, some have occurred in patients with osteoporosis. **Musculoskeletal:** Pain in the extremities reported (common). **Atypical fractures of the femur:** (Rare) If suspected, bilateral hip X-rays should be performed and the patient referred to the specialist team. **Cataracts:** (Common). **Drug-related hypersensitivity reactions:** In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab (Prolia®). Prescribers should be aware that oral bisphosphonate therapy is also associated with a risk of hypocalcaemia (rare), atypical femoral fractures (rare) and osteonecrosis of the jaw (rare). **IF YOU SUSPECT AN ADVERSE REACTION HAS OCCURRED, PLEASE STOP THE DRUG/CONTACT THE SPECIALIST DEPARTMENT. (*Delete as appropriate*)** All serious adverse reactions should be reported to the CHM via the "Yellow Card" scheme.	
7. Baseline investigations	**To be undertaken by secondary care** Ensure calcium and vitamin D replete (vitamin D deficiency and hypocalcaemia must be corrected before initiation of therapy): Renal function, bone profile (serum calcium, alkaline phosphatase, phosphate, albumin) and serum hydroxyvitamin D (25OHD).	
8. Monitoring	**(a) Blood monitoring** Prior to each denosumab injection: Renal profile, vitamin D and bone profile (serum calcium, alkaline phosphatase, phosphate, albumin). **(b) Clinical monitoring** **Assess for adverse effects (listed above) prior to each injection** MHRA Feb 2013: Atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving long-term (≥ 2.5 years) treatment with denosumab 60 mg (Prolia®) in a clinical trial[5].	Do not administer denosumab if patient has hypocalcaemia or low vitamin D levels; refer to initiating consultant for advice. Subsequent injection should be given by the specialist team. Do not administer denosumab if eGFR < 30 ml/min; refer to specialist clinic for advice. If denosumab is considered for patients with eGFR < 30 ml/min, administration should remain in the hospital setting. Irrespective of who administered the injection: if a patient becomes acutely unwell such that renal function may be impaired, clinicians should consider the risk of hypocalcaemia and the need to check calcium/renal function.

		During denosumab treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated.
9. Pharmaceutical aspects	Store in a refrigerator (2–8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. 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, denosumab (Prolia®) must be used within this 30-day period.	
10. Secondary care contact information	**If stopping medication or needing advice, please contact:** **Dr** **……..** **Contact number:** **……..** **Hospital:**	
11. Criteria for shared care	Prescribing responsibility will only be transferred when: • Treatment is for a specified indication and duration. • Treatment has been initiated and established by the secondary care specialist. • The patient's initial reaction to and progress on the drug is satisfactory. • The GP has agreed in writing in each individual case that shared care is appropriate. • The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.	
12. Responsibilities of initiating consultant	• Initiate treatment with first dose of denosumab. In patients with calcium or vitamin D deficiency at first injection, administration of the second dose of denosumab (at 6 months) is also the responsibility of initiating consultant. • Undertake baseline monitoring to ensure calcium and vitamin D replete. • Ensure that the patient can tolerate calcium supplements before administering denosumab. • Correct vitamin D deficiency prior to treatment. • Monitor patient's initial reaction to the drug. • Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug. Provide GP with: • Diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review. • Details of outpatient consultations, ideally within 14 days of seeing the patient *or* inform GP if the patient does not attend appointment. • Advice on when to stop this drug and management of hypocalcaemia. Provide patient with relevant drug information to enable: • Informed consent to therapy. • Understanding of potential side effects and appropriate action.	
13. Responsibilities of primary care	• To monitor, prescribe and administer denosumab (Prolia®) every 6 months following initial dose from specialist according to this protocol. • To ensure that the monitoring and dosage record is kept up to date. Prescribing records should demonstrate that denosumab has been administered within the last 6 months. • To ensure that symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary. *Delete as appropriate:* Provision of shared care is in accordance with a local enhanced service (LES), where available. Near-patient testing is in accordance with the service outline of the General Medical Services contract.	

14. Responsibilities of patients	• To attend hospital and GP clinic appointments. • To maintain adequate intake of calcium and vitamin D. • Keep an up to date record of medicines administered and alert clinicians that denosumab has been administered within the last 6 months. • To report adverse effects to their specialist or GP.
15. Additional responsibilities	Responsibilities of all prescribers: Any serious reaction to an established drug should be reported to CHM.
16. Supporting documentation	Include patient information leaflet: http://www.medicines.org.uk/emc/medicine/23128/XPIL/Prolia/
17. Patient counselling	Before administration give counselling on risk of atypical femoral fractures. (During denosumab treatment, patients should be advised to report new or unusual thigh, hip, or groin pain and discontinuation of denosumab treatment should be considered if an atypical femur fracture is suspected, while the patient is evaluated.) Adequate intake of calcium and vitamin D is important in all patients receiving 60 mg denosumab (Prolia®). Good oral hygiene practices should be maintained during treatment with denosumab. For patients who develop osteonecrosis of the jaw while on denosumab therapy, dental surgery may exacerbate the condition. If osteonecrosis of the jaw occurs during treatment with denosumab, use clinical judgement and guide the management plan of each patient based on individual benefit/risk evaluation. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
18. GP letter	Attached below
19. Guideline date	October 2013 (to be confirmed)
20. Guideline review date	October 2015 (to be confirmed)

SHARED CARE AGREEMENT – NEXT PAGE

SHARED CARE AGREEMENT FORM: CONSULTANT REQUEST

Dear Dr ***IMPORTANT: ACTION NEEDED**

Patient name:
Date of birth:
Diagnosis:

This patient is suitable for treatment with (*insert drug name*) for the treatment of *(insert indication)*.

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by health board/trust/AWMSG). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on (insert date denosumab administered) (insert dose).

If you are in agreement, please undertake monitoring and treatment. The next dose will be due on (insert date in 6 months).

Baseline tests	
Renal function	*Insert information*
Hydroxyvitamin D (25OHD)	*Normal/abnormal*
Bone profile (serum calcium, alkaline phosphatase, phosphate, albumin)	*Normal/abnormal*

Next review with this department: *(add date)*
OR
Routine review in hospital is not required. However, the medical staff of the department are available to give you advice. If the patient continues on denosumab 60 mg for 5 years, please notify this department so that review can be arranged.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

Signature

Consultant name

SHARED CARE AGREEMENT FORM: GP RESPONSE

Dear Dr

Patient *(Insert patient's name)*

Identifier *(Insert patient's date of birth/address)*

I have received your request for shared care of this patient who has been advised to start denosumab.

A I am willing to undertake shared care for this patient as set out in the protocol.

B I wish to discuss this request with you.

C I am unable to undertake shared care of this patient.

GP signature Date

GP address/practice stamp

REFERENCES

1 National Institute for Health and Care Excellence. Technology Appraisal 204. Denosumab for the prevention of osteoporotic fractures in postmenopausal women. 2010. Available at: http://guidance.nice.org.uk/TA204. Accessed May 2013.

2 Amgen Ltd. Prolia®. Summary of Product Characteristics. 2010. Available at: http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/. Accessed May 2013.

3 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. No. 64. Jul 2013. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP4691-denosumab.htm. Accessed Jul 2013.

4 Medicines and Healthcare Products Regulatory Agency. Drug Safety Update. Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment – monitoring recommended. Oct 2012. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560. Accessed May 2013.

5 Medicines and Healthcare Products Regulatory Agency. Drug Safety Update: Denosumab 60 mg (Prolia®): rare cases of atypical femoral fracture with long-term use. Feb 2013. Available at: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON239411. Accessed May 2013.