

All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



# Prescribing of Denosumab (Prolia<sup>®</sup>) in Wales: Review

**Full document**

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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This document should be cited as:

All Wales Medicines Strategy Group. Prescribing of Denosumab (Prolia®) in Wales: Review. October 2013.



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## 1.0 RECOMMENDATION

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When denosumab (Prolia<sup>®</sup>) 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])<sup>1</sup>.

It is proposed that denosumab (Prolia<sup>®</sup>) 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 11–16).

The shared care proposal includes the use of denosumab (Prolia<sup>®</sup>) 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 PURPOSE

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The All Wales Medicines Strategy Group (AWMSG) guidance document "[Prescribing of Denosumab \(Prolia<sup>®</sup>\) in Wales](#)" (2011) requires review<sup>2</sup>. The guidance relates to the use of denosumab at a dose of 60 mg for the prevention of osteoporotic fractures in postmenopausal women, in accordance with the guidelines (NICE TA204)<sup>1</sup>.

This paper is pertinent to recommendation 46 of the AWMSG Medicines Strategy for Wales: "*AWMSG will examine the applicability of shared care arrangements to specialist areas of prescribing and where appropriate, develop shared care templates.*"<sup>3</sup>

### Scope

This paper does not consider denosumab XGEVA<sup>®</sup> 120 mg, which is used for the reduction of bone damage in patients with bone metastases from solid tumours.

### 2.1 Process

- Discussion of initial draft by AWPAG: June 2013
- Multi-professional subgroup meeting: July 2013
- National consultation on recommendation and shared care protocol: August 2013
- Discussion of review document by AWPAG: September 2013
- Consideration of review document by AWMSG Steering Committee: October 2013
- Consideration of review document by AWMSG: October 2013

### 2.2 Stakeholders

Consultation and dissemination list:

- All Wales Rheumatology Audit Group
- Wales Osteoporosis Advisory Group (WOAG)
- Medicines and Therapeutics Committees
- Local Medical Committees
- General Practitioners Committee (GPC) Wales
- Amgen Ltd
- Network of Orthogeriatricians in Wales (NOW)
- National Osteoporosis Society
- Patient groups

### 3.0 CONSIDERATIONS

#### 3.1 Current situation

AWMSG recommendation 2011: Denosumab (Prolia®) should be initiated by a specialist within secondary care for the first two doses (one year) and thereafter prescribing and administration responsibility may be transferred to primary care<sup>2</sup>.

Health board	Recommendation	Enhanced service?
Abertawe Bro Morgannwg University Health Board	As AWMSG recommendation; however, in practice hospital-only prescribing	Has been proposed
Aneurin Bevan Health Board	As AWMSG	Yes
Betsi Cadwaladr University Health Board	Under discussion (possibly shared care)	No
Cardiff & Vale University Health Board	Specialist only	Under consideration
Cwm Taf Health Board	As AWMSG, poor uptake in primary care	Yes
Hywel Dda Health Board	As AWMSG	Yes
Powys Teaching Health Board		

Currently denosumab (Prolia®) is administered by professionals. Current prescribing in primary care is limited. Two health boards reported approximately 40–45 injections administered in primary care in the last year, with approximately five times as many administered in the hospital setting. The prescribing volume may increase following the Medicines and Healthcare Products Regulatory Agency (MHRA) Drug Safety Update relating to strontium ranelate (Protelos)<sup>4</sup>.

#### 3.2 Population covered by AWMSG guidance

The AWMSG guidance currently covers the prevention of osteoporotic fractures in postmenopausal women, per NICE TA204<sup>1,2</sup>.

Denosumab (Prolia®) is recommended as a treatment option for the *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](http://www.nice.org.uk/TA204))<sup>1</sup>.

Denosumab (Prolia®) 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 contra-indication to, those treatments<sup>1</sup>.

Denosumab (Prolia®) is also licensed for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. It is recommended that the prescribing responsibility guidance should be extended to include this group. This does not include patients with bone metastases; in the case of these patients, NICE TA265 states: “Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer”<sup>5</sup>.

Denosumab is a human monoclonal antibody that inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption<sup>6</sup>. Denosumab (Prolia<sup>®</sup>) is not recommended in paediatric patients (age < 18) as the safety and efficacy of denosumab (Prolia<sup>®</sup>) in these patients have not been established<sup>7</sup>.

### 3.3 Consultation

The document was forwarded to stakeholders. Comments received related to the following themes:

(i) The use of a shared care protocol and recommendations for prescribing responsibility were appropriate.

(ii) The need for an enhanced service. It is unlikely that shared care will be taken up by primary care prescribers unless there is an accompanying local enhanced service (LES) to support the necessary monitoring requirements.

(iii) Monitoring. The consultation draft shared care protocol recommended the monitoring currently undertaken by specialist teams, i.e. at baseline and pre-injection: renal function, bone profile (includes calcium) and vitamin D level.

The documentation recognised that renal monitoring is not a requirement according to the Summary of Product Characteristics (SPC); however, it is consistent with current practice in specialist clinics and would be undertaken at the same time as the bone/calcium profile.

The availability and appropriateness of testing of vitamin D in addition to calcium levels prior to each denosumab injection, was raised. Further advice was sought from biochemists across Wales. Some respondents supported focused testing of vitamin D levels pre-injection where the patient has not been taking vitamin D supplements or to confirm normalisation after supplementation if the preceding vitamin D level was low.

The final advice is a consensus statement and supports baseline and pre-injection monitoring of renal function, bone profile (includes calcium) and vitamin D.

### 3.4 Place of prescribing (Recommendation)

General Medical Council (GMC) guidance (2013) outlines the responsibilities of clinicians when prescribing at the recommendation of a professional colleague or undertaking shared care<sup>8</sup>:

*“Prescribing at the recommendation of a professional colleague*

*37. If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.*

*38. If you delegate assessment of a patient's suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required. You must also make sure that they follow the guidance in [paragraphs 21 – 29 on Consent](#).*

*39. In both cases, you will be responsible for any prescription you sign.”<sup>8</sup>*

**Table 1. AWMSG shared care criteria: Denosumab (Prolia®)**

Indication: Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Denosumab (Prolia®) significantly reduces the risk of vertebral, non-vertebral and hip fractures.

A general practitioner may rarely encounter medicines commonly used by a specialist. Lack of familiarity with medication is an important cause of medication errors. It is therefore essential that care is only shared where it is in the best interests of the patient. The following criteria may be helpful when considering whether medicines are suitable for shared care agreements:

	AWMSG criteria	Notes	AWMSG criteria outcome Suitable for:		
			Primary care	Shared care	Hospital only
1	Therapy is for a licensed indication for a chronic condition. Occasionally a drug that has a recognised (but unlicensed) indication may be considered suitable for shared care.	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.	Y	Y	Y
2	Statements in the SPC relating to the most appropriate place for prescribing (usually Section 4.2) should normally be followed.	No statement.	Y	Y	Y
3	There is sufficient evidence for its use over existing preparations. Shared care is therefore not appropriate where clinical experience is limited or side effects have yet to be established.	Endorsed by NICE TA204 (Oct 2010) <sup>1</sup> .  MHRA (Oct 2012) outlines risk of hypocalcaemia (see criteria 7) <sup>9</sup> . MHRA (Feb 2013) outlines risk of atypical femoral fractures <sup>10</sup> . Not suitable for initiation in primary care.	N	Y	Y
4	The professional signing the prescription takes legal responsibility*. Consideration will need to be given to professional opinion such as Medicines and Therapeutics Committees and Local Medical Committees, as to whether shared care of this drug is appropriate.	Primary care initiation unlikely to be supported. Professional opinion to be established at consultation.	N	Y	Y

\*Prescribing guidance: Shared care (2013) GMC:

Prescribing at the recommendation of a professional colleague

37. If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

38. If you delegate assessment of a patient's suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required. You must also make sure that they follow the guidance in [paragraphs 21 – 29 on Consent](#).

39. In both cases, you will be responsible for any prescription you sign.<sup>8</sup>

5	<p>Therapy is initiated and stabilised in secondary/tertiary care. The need for stabilisation will vary with different drugs, patients and local agreement. Adequate follow-up can be provided by secondary/tertiary care.</p>	<p>Specialist initiation is appropriate. Follow-up in secondary care not normally needed; however, prescribers need advice on proposed duration of treatment.</p> <p>If patients are hypocalcaemic prior to the first injection, the second should be administered within the hospital setting (Consensus statement of subgroup).</p> <p>If denosumab (Prolia<sup>®</sup>) is considered for patients with estimated glomerular filtration rate (eGFR) &lt; 30 ml/min, administration should remain in the hospital setting.</p>	N	Specialist initiation/ shared care.	N
6	<p>Drug administration and monitoring does not require specialist equipment or skills. <i>List monitoring requirement</i></p>	<p><b>Administration</b> Denosumab (Prolia<sup>®</sup>) 60 mg solution for injection in a pre-filled syringe. The recommended dose of denosumab (Prolia<sup>®</sup>) is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm. Normally administered by a healthcare professional.</p> <p><b>Monitoring requirements – background</b> Cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (XGEVA<sup>®</sup>▼) or 60 mg (Prolia<sup>®</sup>). Some of these cases were fatal in those receiving the 120 mg dose. Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypercalcaemia is present. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time<sup>9</sup>. SPC: hypocalcaemia is a contra-indication to use. Adequate intake of calcium and vitamin D is important in all patients (anecdotal note that supplementation often poorly tolerated). Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Patients with severe renal impairment (creatinine clearance &lt; 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.</p>	Y	Y	N



		<p>Patients under 75 years may require dual-energy X-ray absorptiometry (DEXA) monitoring.</p> <p><b>SUMMARY</b>                  At baseline and pre-injection: renal function, bone profile (includes calcium), vitamin D level.                  This advice reflects the monitoring currently undertaken by specialist teams.</p> <p>Prescribers require guidance on monitoring requirements. Blood and clinical monitoring do not require specialist skills.</p>			
7	<p>The safety profile of the drug is such that inadequate monitoring may have serious implications.</p> <p><i>List potential toxicity (common adverse drug reactions (ADRs) and other ADRs likely to be of clinical interest)</i></p>	<p>This section considers the safety profile of denosumab (Prolia®) and how potential adverse effects can be monitored by prescribers. Side-effects as listed in the British National Formulary (BNF): diarrhoea, constipation, dyspnoea, urinary tract infection, upper respiratory tract infection, pain in extremity, sciatica, hypocalcaemia (fatal cases reported), hypophosphataemia, cataracts, rash, sweating; <i>less commonly</i> diverticulitis, cellulitis (seek prompt medical attention), ear infection; <i>rarely</i> osteonecrosis of the jaw, atypical femoral fractures (see <a href="#">MHRA/Commission on Human Medicines [CHM] advice</a>)<sup>6</sup>.</p> <p>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. During denosumab (Prolia®) treatment, patients presenting with new or unusual thigh, hip or groin pain should be evaluated for an incomplete femoral fracture. Discontinuation of denosumab (Prolia®) therapy should be considered if an atypical femur fracture is suspected, while the patient is evaluated<sup>10</sup>.</p> <p>Oral bisphosphonates can cause the following undesirable effects<sup>11</sup>:                  Rare: Hypocalcaemia.                  Very common: Musculoskeletal (bone, muscle or joint) pain which is sometimes severe.                  Rare: Osteonecrosis of the jaw, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction)<sup>11</sup>.</p>		Y	Y

		<p><b>Summary</b>  <b>Prescribers require guidance on clinical monitoring for adverse effects and the need to investigate hip or thigh pain. Specialist advice needed after 5 years of therapy.</b>          Blood and clinical monitoring do not require specialist skills and can be carried out in primary care. The safety profile is such that inadequate monitoring may have serious implications. Shared care promotes the safe handover of care and will clearly identify roles and responsibilities.</p>			
8	The service to the patient is convenient and appropriate to their needs.	<p>Frail elderly patients currently have to come into hospital for the second injection. As specialists have had experience of denosumab (Prolia<sup>®</sup>), the orthogeriatricians considered that there is no change in management and no gain in undertaking the second injection in the hospital environment.</p> <p>Patient representative on subgroup.</p> <p>Patient groups invited to comment on consultation.</p>		Y	N
9	If the patient must attend the specialist on a regular basis (for reasons other than obtaining a prescription) then it may be safer and more appropriate for prescribing to be undertaken by secondary/tertiary care.	<p>Patients with osteoporosis are not routinely followed up within hospitals, therefore it is likely that primary care or shared care prescribing would be appropriate. Younger patients may require repeat DEXA scanning.</p>	Y	Y	N
10	Responsibility for prescribing should remain with consultants where drugs are undergoing or included in a hospital-based clinical trial. Welsh Health Circular (WHC) 91(94)	Not applicable.			
11	A comprehensive shared care protocol for the drug is available that clearly identifies the areas of care for which each partner has responsibility.	Enclosed.			
12	The use of resources by NHS Wales is efficient. Transferring prescribing between primary and secondary/tertiary care for purely budgetary reasons is not appropriate.	The recommendations have addressed the clinical requirements of a safe and effective system.			

	<p><b>SUMMARY: BALANCE OF REPOSSES</b></p>	<p>To be agreed.</p>	<p><b>Specialist initiation (1 injection) with shared care. Specialist review after 5 years.</b></p> <p><b>Exclusions: Patients with eGFR &lt; 30 ml/min. Patients with hypocalcaemia/low vitamin D prior to first injection should remain under specialist care for at least two injections.</b></p>
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#### 4.0 IMPLEMENTATION

Previous uptake of denosumab (Prolia®) prescribing and administration in primary care has been limited. The proposal to provide the service under a shared care agreement should give confidence to prescribers by clarifying responsibilities, necessary monitoring requirements and possible adverse effects.

A consensus across Wales would reduce cross-border issues; however, English border issues would require addressing separately.

Inclusion within enhanced service structures is likely to increase uptake.

## REFERENCES

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- 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 All Wales Medicines Strategy Group. Prescribing of denosumab (Prolia<sup>®</sup>) in Wales. 2011. Available at: <http://awmsg.org/docs/awmsg/medman/Prescribing%20of%20Denosumab%20%28Prolia%29%20in%20Wales.pdf>. Accessed May 2013.
- 3 All Wales Medicines Strategy Group. A Medicines Strategy for Wales: Executive summary. 2008. Available at: <http://www.wales.nhs.uk/sites3/Documents/371/Strategy%20Exec%20Summary%20endorsed%20AWMSG%20April08.pdf>. Accessed May 2013.
- 4 Medicines and Healthcare Products Regulatory Agency. Drug Safety Update: Strontium ranelate (Protelos): risk of serious cardiac disorders-restricted indications, new contraindications, and warnings. Apr 2013. Available at: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON266148>. Accessed Jul 2013.
- 5 National Institute for Health and Care Excellence. Technology Appraisal 265. Bone metastases from solid tumours - denosumab: guidance. 2012. Available at: <http://guidance.nice.org.uk/TA265>. Accessed May 2013.
- 6 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.
- 7 Amgen Ltd. Prolia<sup>®</sup>. Summary of Product Characteristics. 2010. Available at: <http://www.medicines.org.uk/EMC/medicine/23127/SPC/Prolia/>. Accessed May 2013.
- 8 General Medical Council. Prescribing guidance: Shared care. 2013. Available at: [http://www.gmc-uk.org/guidance/ethical\\_guidance/14321.asp](http://www.gmc-uk.org/guidance/ethical_guidance/14321.asp). Accessed May 2013.
- 9 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.
- 10 Medicines and Healthcare Products Regulatory Agency. Drug Safety Update: Denosumab 60 mg (Prolia<sup>®</sup>): 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.
- 11 Actavis. Alendronic Acid 70 mg Tablets Summary of Product Characteristics. Jun 2013. Available at: <http://www.medicines.org.uk/emc/medicine/23733/SPC/Alendronic+Acid+70+mg+Tablets/>. Accessed Jul 2013.

DENOSUMAB SHARED CARE PROTOCOL

<p><b>PROTOCOL: DENOSUMAB (PROLIA®)</b>  <i>This document should be read in conjunction with the current Summary of Product Characteristics (SPC)<sup>7</sup></i>  <a href="http://www.medicines.org.uk/">http://www.medicines.org.uk/</a></p>	
<p><b>1. Licensed indications</b></p>	<p>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.</p>
<p><b>2. Therapeutic use and background</b></p>	<p>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.</p> <p><i>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])<sup>1</sup> i.e. when the following conditions are met:</i></p> <ul style="list-style-type: none"> <li>• <b>Primary prevention</b> 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 <b>and</b> 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 <a href="http://www.nice.org.uk/TA204">www.nice.org.uk/TA204</a>)<sup>1</sup>.</li> <li>• <b>Secondary prevention</b> 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>
<p><b>3. Contraindications</b></p>	<p>Hypocalcaemia.                      Hypersensitivity to the active substance or to any of the excipients of denosumab (Prolia®).</p>
<p><b>4. Typical dosage regimen (adults)</b></p>	<p>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 &lt; 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.</p>
<p><b>5. Drug interactions – Consult the British National Formulary (BNF) or SPC</b></p>	<p>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)<sup>7</sup>.  <a href="http://www.medicines.org.uk/">http://www.medicines.org.uk/</a></p>
<p><b>6. Adverse drug reactions</b>                      For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event is uncertain, consult SPC or BNF</p>	<p><b>BNF summary:</b>  <b>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)<sup>6</sup>.</b></p>

	<p><b>Hypocalcaemia:</b> Hypocalcaemia (rare) is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance &lt; 30 ml/min; estimated glomerular filtration rate [eGFR] 15–29 ml/min/1.73 m<sup>2</sup>) 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<sup>9</sup>.</p> <p>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.</p> <p><b>Infections:</b> Urinary tract infection (common), respiratory infection (common) and cellulitis (uncommon).</p> <p><b>Osteonecrosis of the jaw:</b> 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.</p> <p><b>Musculoskeletal:</b> Pain in the extremities reported (common).</p> <p><b>Atypical fractures of the femur:</b> (Rare) If suspected, bilateral hip X-rays should be performed and the patient referred to the specialist team.</p> <p><b>Cataracts:</b> (Common).</p> <p><b>Drug-related hypersensitivity reactions:</b> 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<sup>®</sup>).</p> <p>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).</p> <p><b>IF YOU SUSPECT AN ADVERSE REACTION HAS OCCURRED, PLEASE STOP THE DRUG/CONTACT THE SPECIALIST DEPARTMENT. (Delete as appropriate)</b> All serious adverse reactions should be reported to the CHM via the “Yellow Card” scheme.</p>	
<p><b>7. Baseline investigations</b></p>	<p><b>To be undertaken by secondary care</b> 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).</p>	
<p><b>8. Monitoring</b></p>	<p><b>(a) Blood monitoring</b> Prior to each denosumab injection:  Renal profile, vitamin D and bone profile (serum calcium, alkaline phosphatase, phosphate, albumin).</p> <p><b>(b) Clinical monitoring</b> <b>Assess for adverse effects (listed above) prior to each injection</b> 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<sup>®</sup>) in a clinical trial<sup>10</sup>.</p>	<p>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.</p> <p>Do not administer denosumab if eGFR &lt; 30 ml/min; refer to specialist clinic for advice.</p> <p>If denosumab is considered for patients with eGFR &lt; 30 ml/min, administration should remain in the hospital setting.</p> <p>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.</p>

		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.
<b>9. Pharmaceutical aspects</b>	<p>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.</p>	
<b>10. Secondary care contact information</b>	<p><b>If stopping medication or needing advice, please contact:</b> <b>Dr</b> ..... <b>Contact number:</b> ..... <b>Hospital:</b></p>	
<b>11. Criteria for shared care</b>	<p>Prescribing responsibility will only be transferred when:</p> <ul style="list-style-type: none"> <li>• Treatment is for a specified indication and duration.</li> <li>• Treatment has been initiated and established by the secondary care specialist.</li> <li>• The patient's initial reaction to and progress on the drug is satisfactory.</li> <li>• The GP has agreed in writing in each individual case that shared care is appropriate.</li> <li>• The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.</li> </ul>	
<b>12. Responsibilities of initiating consultant</b>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• Undertake baseline monitoring to ensure calcium and vitamin D replete.</li> <li>• Ensure that the patient can tolerate calcium supplements before administering denosumab.</li> <li>• Correct vitamin D deficiency prior to treatment.</li> <li>• Monitor patient's initial reaction to the drug.</li> <li>• Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug.</li> </ul> <p>Provide GP with:</p> <ul style="list-style-type: none"> <li>• Diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review.</li> <li>• Details of outpatient consultations, ideally within 14 days of seeing the patient or inform GP if the patient does not attend appointment.</li> <li>• Advice on when to stop this drug and management of hypocalcaemia.</li> </ul> <p>Provide patient with relevant drug information to enable:</p> <ul style="list-style-type: none"> <li>• Informed consent to therapy.</li> <li>• Understanding of potential side effects and appropriate action.</li> </ul>	
<b>13. Responsibilities of primary care</b>	<ul style="list-style-type: none"> <li>• To monitor, prescribe and administer denosumab (Prolia®) every 6 months following initial dose from specialist according to this protocol.</li> <li>• 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.</li> <li>• To ensure that symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary.</li> </ul> <p><i>Delete as appropriate:</i> 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.</p>	



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<b>14. Responsibilities of patients</b>	<ul style="list-style-type: none"> <li>● To attend hospital and GP clinic appointments.</li> <li>● To maintain adequate intake of calcium and vitamin D.</li> <li>● Keep an up to date record of medicines administered and alert clinicians that denosumab has been administered within the last 6 months.</li> <li>● To report adverse effects to their specialist or GP.</li> </ul>
<b>15. Additional responsibilities</b>	Responsibilities of all prescribers: Any serious reaction to an established drug should be reported to CHM.
<b>16. Supporting documentation</b>	Include patient information leaflet: <a href="http://www.medicines.org.uk/emc/medicine/23128/XPIL/Prolia/">http://www.medicines.org.uk/emc/medicine/23128/XPIL/Prolia/</a>
<b>17. Patient counselling</b>	<p>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.)</p> <p>Adequate intake of calcium and vitamin D is important in all patients receiving 60 mg denosumab (Prolia®).</p> <p>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.</p> <p>Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.</p>
<b>18. GP letter</b>	Attached below
<b>19. Guideline date</b>	October 2013 (to be confirmed)
<b>20. Guideline review date</b>	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	<i>Insert information</i>
Hydroxyvitamin D (25OHD)	<i>Normal/abnormal</i>
Bone profile (serum calcium, alkaline phosphatase, phosphate, albumin)	<i>Normal/abnormal</i>

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