BNSSG Shared Care Guidance

Section 1: Heading

Drug	Denosumab
Amber *three months*	
Indication	To reduce risk of osteoporotic fractures in post-menopausal women and men Denosumab is recommended as a treatment option for the primary prevention of osteoporotic fragility fractures **in postmenopausal women and men** 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 (as detailed in NICE guidance (for post-menopausal women), age and number of independent clinical risk factors for fracture. Denosumab is recommended as a treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women and men 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. See NICE guidance for further information http://guidance.nice.org.uk/TA204 July 2013 updated - the BNSSG Joint Formulary Group has approved the use of denosumab in men as per the NICE TA204 guidance.
Speciality / Department	Rheumatology
Trust(s)	NBT
	UHBristol
	WHAT

Section 2: Treatment Schedule

Usual dose and frequency of administration	60mg as a sub-cutaneous injection into the thigh, abdomen or back of arm every six months (as prefilled syringe). Patients must be calcium and vitamin D replete (serum vitamin D 50nmol/l or greater).

Route and formulation	Sub cutaneous injection
Duration of treatment	The first injection will be given in the Rheumatology Department who will check the patient's GP is willing to prescribe and administer the second and subsequent injections at 6 month intervals. The GP will be sent written confirmation of injection (and the patient offered a copy). Denosumab doses should be at regular 6 monthly intervals. Do not stop or withhold Denosumab without considering an alternative treatment plan to prevent the likely rebound increased risk of fractures.

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
Patients with severe renal impairment (creatinine clearance <30ml/min) or receiving dialysis are at greater risk of developing transient symptomatic hypocalcaemia. The serum calcium is considered to be at its lowest 10 days after denosumab injection, and on average will reduce pre-existing serum calcium levels by 5.5% Patients must be calcium and vitamin D replete (serum vitamin D 50nmol/l or greater) prior to initiating thereapy. Pre-existing hypocalcaemia must be corrected prior to initiating denosumab.
Subsequent tests - where appropriate
Monitoring of calcium levels should be conducted: • prior to each dose of Denosumab • within two weeks after the initial dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min) • if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient

Section 4: Side Effects

Please list the most common side effects and management. Please provide guidance on when the GP should refer back to the specialist.

Side effects and management	Patients receiving denosumab may develop skin infections (predominantly cellulitis, that may arise distant to the injection site) leading to hospitalisation (0.4%). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis. Osteonecrosis of the jaw (ONJ) is rare (<1/10000 to <1/1000) but may occur following tooth extraction or other oral surgery in patients receiving 60mg injections every 6 months. [NB: ONJ is likely to be more frequent in patients with advanced cancer treated with denosumab at 120mg administered monthly, and with other

	known risks such as poor oral hygiene, (oral) infection, receiving corticosteroids or chemotherapy] Osteonecrosis of the external auditory canal has been reported very rarely (< 1 in 10 000 patients) with bisphosphonates, mainly in association with long-term therapy (2 years or longer). Denosumab causes a transient fall in serum calcium but symptomatic hypocalcaemia (<1.88mmol/l) is rare (0.05%). This drug has only been available since 2010, and it may be that as yet unrecognised side effects are yet to emerge. GPs are asked to remain vigilant and to contact the rheumatology department if they have any concerns.
Referral back to specialist	Any side effects that are concerning

Section 5: Drug Interactions

Please list clinically significant drug interactions (eMC link please click here)

Significant Drug Interactions	Should not be administered concurrently with bisphosphonates.
Reminder to ask patient about specific problems	Click here to enter details

Section 6: Contra-indications, Cautions and Special Recommendations

1. Patients with renal impairment: No dose adjustment is required in patients with renal impairment.
2. Patients with hepatic impairment: The safety and efficacy of denosumab have not been studied in patients with hepatic impairment
3. Adequate intake of calcium and vitamin D is important in all patients. Hypocalcaemia (corrected serum calcium below quoted range) must be corrected by adequate intake of calcium and vitamin D before initiating therapy.
4. A dental examination with appropriate preventative dentistry is recommended prior to treatment with denosumab in patients with concomitant risk factors (malignancy, high dose corticosteroid use, poor dental hygiene) for ONJ.
5. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
6. The optimum duration of denosumab treatment is currently unknown. The risk benefit balance of continuing with denosumab should normally be checked after 5 years treatment.

Section 7: Advice to the patient

Advice for prescribing clinician to inform patient

1. Denosumab is sometimes associated with pain in the extremities (1/10)
2. To contact their doctor if you have any skin rash or infection (1/100-1/10), or any other medical problem out of the ordinary which may be related to your denosumab injection.
3. Osteonecrosis of the jaw (ONJ) is a rare side effect of treatment to reduce risk of osteoporotic fracture. The overall risk of a patient developing osteonecrosis of the jaw over a

typical 3 year treatment cycle is about 1 in 800. Patients who undergo invasive dental procedures (dental implants, tooth extraction, natural tooth loss, scaling or root planing) during that time have a higher risk of developing ONJ (1 in 350 over 3 years), compared to those who do not (1 in 3400 over 3 years). Patients should be advised to maintain good oral hygeine under these circumstances and inform their dental practitioner of their treatment. Denosumab should be discontinued if any features of osteonecrosis of the jaw develop and the treating rheumatologist contacted, who will liaise with secondary dental care. All patients should be advised to keep good oral hygiene, inform their dentist of their denosumab use, and avoid dental extractions where possible.

4. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during treatment
5. Encourage concordance by ensuring the patient is aware of the need for regular injections
6. Patients should be encouraged to report symptoms indicative of hypocalcaemia – paresthesias or muscle stiffness, twitching, spasms, and muscle cramps.

Section 8: Responsibilities for Secondary Care

1. Confirm suitability of patients for denosumab and ensure patient is calcium and vitamin D replete prior to initiation of therapy.
2. Evaluate for ONJ risk factors prior to treatment.
3. Advise patients of potential benefits and adverse reactions, the method of administration and interval of treatment.
4. Evaluate for osteonecrosis risk factors prior to treatment
5. Prescribe and administer the first dose (and subsequent doses if the patient's GP is unable or unwilling to do so).
6. Provide written confirmation of the first dose and any relevant clinical information (for example the requirement to check serum calcium) to the GP (and patient where requested).
7. Provide on-going advice and support to patients and GPs in relation to any side effects which may emerge.
8. Report side-effects through MHRA Yellow Card Scheme

Section 9: Responsibilities for Primary Care

1. Refer patients to the department who may be suitable for denosumab under NICE TA204 where appropriate
2. Take over the prescribing and administration from the second dose (i.e. after 6 months).
3. Reconfirm suitability of patients for denosumab prior to continuation of therapy at 6 monthly intervals.
4. Check the patient maintains adequate dental hygiene and has informed their dentist of denosumab therapy at routine visits.
5. Review patients for any unexpected side effects or concerns.
6. Seek advice from secondary care when appropriate (see sections 3, 4 and 6 above). Reassess the need for on-going treatment after 10 injections (five years treatment). This may involve a repeat DXA scan, or a re-referral to secondary care according to individual circumstances. Denosumab doses should be at regular 6 monthly intervals. Do not stop or withhold Denosumab without considering an alternative treatment plan to prevent the likely rebound increased risk of fractures.
7. Report side-effects through MHRA Yellow Card Scheme via: Yellow Card Scheme Tel: Freephone 0808 100 3352 Website: www.mhra.gov.uk/yellowcard

Section 10: Contact Details

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Section 11: Document Details

Date prepared	28th April 2011 minor amendment 26th November 2012 **Reviewed August 2013 and November 2014 post MHRA recommendations** **Updated November 2015** **Updated July 2017** **Updated May 2018**
Prepared by	Shane Clarke & Jon Tobias and amended by Nicola Bruce
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Section 12: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. Updated August 2013 after discussion with Dr S Clarke, Dr Stuart Webber (WAHT) Prof. J. Tobias, Dr Karen Harding, Dr Emma Clark (both NBT).
2. Updated November 2014 after MHRA guidance
3. Updated November 2015 after discussion with Prof Tobias
4. Updated July 2017 after MHRA guidance

Section 13: References

1. http://guidance.nice.org.uk/TA204
2. Drug Safety Update, October 2012 accessible via http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560

3. Drug Safety Update, September 2014, accessible via http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452540
4. Drug Safety Update, June 2017, accessible via https://www.gov.uk/drug-safetv-update/denosumab-prolia-xgeva-reports-of-osteonecrosis-of-the-external-auditorv-canal