NHS ROTHERHAM CCG

Shared Care Protocol

For

Denosumab 60mg/mL injection (Prolia ®)

Shared care protocol developed by:

Stuart Lakin Head of Medicines Management
NHS Rotherham CCG
Adapted from NHS Sheffield CCG SCP produced by;
Heidi Taylor, Pharmacist Team Leader, SWYBCSU
Dr Nicola Peel, Consultant, MBC, NGH Sheffield

Approved: January 2016
Amended:
Review Date: January 2018

Summary of Shared Care Protocol

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients initiated on denosumab 60mg/mL injection (Prolia ®**)** by the Metabolic Bone Centre (MBC) at the Northern General Hospital.

Denosumab (60 mg 6-monthly subcutaneous injection, Prolia®) is licensed for the treatment of osteoporosis in men and postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer.

Timeline

- Baseline - Metabolic Bone Clinic (MBC)
    - baseline assessment including PINP (N-terminal propeptide of type I collagen (PINP) is a by-product of type I collagen formation released during bone turnover)
    - ensure calcium and vitamin D replete
    - consider dental health and advise patient accordingly
    - monitor calcium levels and identify those patients who are predisposed to hypocalcaemia (patients with severe renal impairment, creatinine clearance <30ml/min) who should also have calcium levels checked within two weeks of the initial dose
    - administer first injection
    - issue patient information including advice to register for reminder service
    - write to patient and GP with result of PINP

    - agreement established with GP for ongoing treatment administration (send link to SCP) using transfer form

- 6 months – GP surgery
    - Monitor serum calcium prior to injection and do not administer treatment if evidence of hypocalcaemia (corrected calcium range 2.2-2.6 mmol\l) contact the metabolic bone clinic (BMC).
    - check patient taking calcium and vitamin D as advised at baseline
    - check there has been a reduction in PINP (reduced by 10ng/ml from baseline and/or the post treatment level is <35ng/ml). If there are any concerns then GPs can contact the MBC to discuss interpretation in individual patients (0114 226 6571)
    - administer second treatment
    - Check for new or unusual symptoms of hip, thigh or groin pain (if present, consider whether evaluation required to look for evidence of atypical femoral fracture)
    - Treatment should be administered within 1 month window around the 6 month due date. Practices are advised to use a robust recall system to ensure patients receive timely treatment
    - Consider measurement of serum calcium if patients develop symptoms suggestive of hypocalcaemia post-treatment

- 12 months onwards – GP surgery
    - Monitor serum calcium levels prior to each injection
    - check patient taking calcium and vitamin D as advised at baseline
    - Check for new or unusual symptoms of hip, thigh or groin pain (if present, consider whether evaluation required to look for evidence of atypical femoral fracture)
    - administer injection
    - Treatment should be administered within 1 month window around each 6-monthly time-point. If outside of this timeframe the risk of bone fracture is increased, administer as soon as possible or contact the BMC for advice.
    - NB. PINP levels are **not** required. Levels are taken at 6 months to assess treatment response, once this has been demonstrated subsequent measurements are not deemed necessary

- After 5 years of treatment, consider referral to MBC for fracture risk assessment. **Treatment effect reverses rapidly so it is not appropriate to consider "drug holiday" in denosumab therapy as can be considered in bisphosphonate treatment**

  If a patient presents with symptoms of hypocalcaemia between doses, measure calcium level and renal function. Consider measurement of PTH, Magnesium, vitamin D

  Denosumab should not be administered if serum calcium is below the reference range. If the reason for this is unclear and/or serum calcium does not normalise, please discuss with the Metabolic Bone Centre.

Shared Care Protocol for Denosumab 60mg/mL (Prolia®)

Statement of Purpose
This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients initiated on denosumab 60mg/mL (Prolia®) by the Metabolic Bone Centre (MBC) at The Northern General Hospital. Primary care will be requested to take over the prescribing of denosumab predominantly within its licensed indication. Occasionally primary care will be asked to prescribe denosumab that has been initiated outside licence on expert opinion by the MBC.

The Metabolic Bone Centre will administer the baseline injection; further treatment will be requested to be administered via the GP surgery.

NB. This SCP does not cover denosumab 120mg (XGEVA®▼**)**

Indication
Denosumab is licensed for the treatment of osteoporosis in men and postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer. Denosumab is a fully humanised monoclonal antibody to RANK ligand. It is a potent anti-resorptive agent and is effective in reducing the risk of vertebral and non-vertebral fractures, including hip fracture. Treatment is administered as a 6 monthly subcutaneous injection, usually in conjunction with calcium and vitamin D supplementation. As highlighted by the MHRA, hypocalcaemia is a known risk with denosumab use. It may occur within 24 hours of administration and is usually transient. The risk is greater in individuals with pre-existing hypocalcaemia and particularly in those with renal impairment. Calcium absorption should be optimised prior to treatment. This is generally achieved by regular use of standard calcium and vitamin D supplements which should be continued regularly. Occasionally, patients with renal impairment or malabsorption may require pre-treatment with a vitamin D metabolite. All patients should have serum calcium levels monitored prior to each injection.

Alendronic acid remains the first line treatment for osteoporosis in post-menopausal women in accordance with NICE guidance. Approximately 25% of patients cannot be treated with alendronic acid because of side effects, inability to comply with dosing instructions or malabsorption leading to inefficacy. Denosumab provides another option for those patients also unable to take risedronate and has been recommended by NICE in this context.
The guidance is available at http://guidance.nice.org.uk/TA204.

Selection of patients
Denosumab is suitable for patients who cannot be treated with alendronic acid or risedronate because of side effects, inability to comply with dosing instructions or malabsorption. Bisphosphonates are excreted by the kidneys and should not be used in the presence of moderate to severe renal impairment. This is particularly important in the case of zoledronate which is administered as an annual infusion and is not recommended if the eGFR is below 35ml/min/1.73m2. Patients with moderate renal impairment requiring parenteral therapy may be considered for 3-monthly injections of ibandronate.

Denosumab may be particularly suitable for patients who have mild to moderate renal impairment (CKD3) where bisphosphonate treatment is contra-indicated. However, these patients are at greater risk of developing hypocalcaemia following the injection, monitoring of serum calcium levels is recommended prior to each injection.
Denosumab is not suitable for use in patients with renal bone disease unless it has been established that this is associated with high bone turnover on bone biopsy. Use in patients with CKD4-5 should be avoided unless the patient has been evaluated / discussed with a Metabolic Bone or Renal physician.

Dosage
60 mg denosumab is administered as a subcutaneous injection once every 6 months into the thigh, abdomen or back of arm. (See appendix 1). Patients must be calcium and vitamin D replete and in most cases advice will be

given to provide supplementation with calcium and vitamin D (daily dosage: calcium 1g -1.2g and colecalciferol 800 units). Some patients may not be able to tolerate calcium and vitamin D preparations, in such circumstances prescribers should ensure the patient is receiving sufficient dietary calcium (consider using a 'calcium calculator' e.g. http://www.rheum.med.ed.ac.uk/calcium-calculator.php) and consider the need to prescribe vitamin D. (See NHS Rotherham CCG Osteoporosis guidelines).
No dosage adjustment is required in patients with renal impairment. There is insufficient data to recommend use of denosumab in children under 18 years of age.

Contra-indications
Hypocalcaemia or hypersensitivity to the active substance or to any of the product excipients.
Patients with rare hereditary problems of fructose intolerance should not use denosumab.

Side-effects
These details are not a complete list and the current BNF and the SPC remain authoritative

- Common (≥ 1/100 to < 1/10) urinary tract infection, upper respiratory tract infection, sciatica, cataracts, constipation, rash and pain in extremity.
- Uncommon (≥ 1/1000 to < 1/100): diverticulitis, skin infections requiring hospitalisations were reported in postmenopausal women receiving denosumab.
- Rare (≥ 1/10,000 to < 1/1,000): osteonecrosis of the jaw (ONJ), hypocalcaemia (< 1.88 mmol/l), atypical femoral fractures.

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

Interactions
These details are not a complete list and the current BNF and SPC remain authoritative

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (HRT), however the potential for pharmacodynamic interactions would be considered low. Pharmacokinetics and pharmacodynamics were not altered by previous alendronate therapy.

There are no clinical data on the co-administration of denosumab with other biologic agents.

Monitoring
Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiation of therapy. Monitoring of serum calcium levels is recommended prior to every injection and for patients predisposed to hypocalcaemia calcium levels should also be taken within two weeks of the initial injection. Patients should also be advised to report symptoms of hypocalcaemia, e.g. muscle spasms, twitches or cramps; numbness or tingling in the fingers, toes or around the mouth. If hypocalcaemia is suspected calcium levels and renal function should be taken. Also consider measurement of PTH, magnesium and vitamin D.
Denosumab should not be administered if serum calcium is below the reference range. If the reason for this is unclear and/or serum calcium does not normalise, please discuss with the Metabolic Bone Centre.

Patients receiving denosumab may develop skin infections (predominantly cellulitis) requiring hospitalisation and if symptoms develop then they should contact a health care professional immediately. ONJ has been reported rarely in association with treatment for osteoporosis with denosumab or bisphosphonates. A dental examination with appropriate preventative dentistry is recommended prior to treatment with denosumab in patients with concomitant risk factors (refer to SPC). While on treatment, these patients should avoid invasive dental procedures if possible (see SPC for more details). Good oral hygiene and regular dental check-ups should be

maintained during treatment with denosumab. Prompt referral is needed if a patient presents with oral symptoms during therapy (e.g. pain, swelling, dental mobility)

Denosumab has been associated rarely with the occurrence of atypical femoral fractures. Patients presenting with new or unusual hip, thigh or groin pain should be evaluated for this possibility. Discontinuation of denosumab should be considered while the patient is being evaluated. Evolving atypical femoral fractures may not be apparent on radiographs and if the diagnosis is suspected and not seen on a radiograph, further evaluation with NM or MR imaging should be undertaken.

Patients requiring second or third-line treatment may have severe or complicated osteoporosis and may have failed to achieve a satisfactory response to other agents. It is therefore desirable in this patient cohort to confirm an adequate response which will be evaluated by measurement of PINP at baseline and at 6 months. Suppression of bone turnover at 6 months (demonstrated by the PINP being reduced by 10ng/ml from baseline and/or the post treatment level is <35ng/ml), indicates a positive treatment response.

The Metabolic Bone Centre will make recommendations about the timing of repeat fracture risk assessment and will arrange clinic review with repeat fracture risk assessment at 24 months for more complicated patients. MBC staff are happy to discuss individual patient management whenever relevant. This protocol parallels the management using other anti-resorptive agents such as alendronic acid in the metabolic bone clinics.

Patients will be advised to register with the manufacturer's programme to receive a reminder when their next treatment is due.

It is important that treatment with denosumab is administered on time, with this in mind the 6 month PINP level should be taken in advance of treatment. Treatment should be administered within a one month window around each 6 monthly time point. Practices are advised to use a robust recall system to ensure patients receive timely treatment. In clinical studies examining the effects of discontinuation of denosumab, bone turnover markers temporarily increased to levels greater than baseline values which could be associated with an increase in fracture risk. BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with denosumab is required to maintain the effect of the medicinal product.

When treatment with denosumab is stopped, it is important to institute another bone-protective treatment 6 months after the last injection to avoid a potential increase in fracture risk.

Additional information

- Denosumab must not be mixed with other medicinal products.
- Store at 2ºC to 8ºC (in a refrigerator).
- Denosumab may be exposed to room temperature (up to 25ºC) for a maximum single period of up to 30 days in its original container. Once removed from the refrigerator must be used within this 30 day period.
- Do not freeze.
- Keep in outer carton to protect from light.

Responsibilities of consultant clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent. This is particularly important if treatment is administered outside licensed indications.
- To ensure patient is not hypocalcaemic
- To take a baseline PINP and serum calcium
- Assess and advise about maintenance of dental health
- To initiate denosumab in appropriate patients
- To assess tolerability of treatment in the individual
- To prescribe the first dose or until patient stable
- monitor calcium levels in those patients predisposed to hypocalcaemia within two weeks of initial injection

- To contact patient's GP to request prescribing under shared care and send a link to or copy of the shared care protocol and a transfer form.
- To advise the GP regarding continuation of treatment, including the length of treatment and any additional recommendations about monitoring e.g. serum calcium
- To discuss any concerns with the GP regarding the patient's therapy

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe for patients in line with the shared care agreement
- To report any adverse reaction to the CHM and the referring consultant
- To continue to prescribe for the patient as advised by the consultant
- To undertake monitoring as per shared care protocol
- Continue to advise about maintenance of dental health
- To assess efficacy and tolerability of treatment (Metabolic Bone Centre staff can be contacted for advice if clarification needed)
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient's therapy
- To conduct an annual face to face medication review or more frequent if required

Re-Referral guidelines

The patient is to be re-referred at any time if there are concerns about side effects or inefficacy (e.g. new fractures). For all patients receiving pharmacological therapy for osteoporosis it is recommended that fracture risk assessment is reviewed after 5 years' treatment.

Financial implications

Denosumab 60mg/ml solution in pre-filled syringe, 1ml = £183.00. Please see below on how denosumab can be obtained by GP practices, discounts are available if practices order directly. If purchased the practice then a 'personal administration' fee can be claimed,

The annual treatment cost of denosumab is similar to that of intravenous bisphosphonate therapy. However, once the costs of administration are taken into account, denosumab offers a more cost-effective option than ibandronate (and remains similar to zoledronate). It is also potentially more convenient to the patient as treatment is administered as a SC injection which may be given in the GP surgery or by the district nurse.

Support, education and information

Dr Nicola Peel, Consultant, Metabolic Bone Centre, Northern General Hospital, Sheffield, 0114 226 6571
nicola.peel@sth.nhs.uk
Medicines Management Team, 722 Prince of Wales Road, Sheffield, 0114 3051667
National Osteoporosis Society, www.nos.org.uk, 01761 471771 / 0845 130 3076

How to order

Prolia® can be **delivered** directly to your practice within 24 hours.
To order, contact Movianto UK – Product code 9001231.
Telephone: 01234 248631 (08:30 to 16:30 Mon-Fri)
Fax: 01234 248705
Email: orders.uk@movianto.com
Alternatively, Prolia® can be provided to patients through retail pharmacy by writing an FP10.

References

Denosumab for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women, Technology Appraisal, October 2010. Available at

http://guidance.nice.org.uk/TA204.
Prolia Summary of Product Characteristics. Available at
http://www.medicines.org.uk/emc/medicine/23127
MHRA Drug Safety Advice
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con199577.pdf
http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con239417.pdf
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON452540

Appendix 1

Practices can obtain detailed information on how to administer Prolia® from;
Amgen Limited
240 Cambridge Science Park
Milton Road
Cambridge
CB4 0WD
Telephone - 01223 420305
UK Freephone - 0800 243104

This SCP is an update of the original SCP produced by Louise White (Clinical Practice Pharmacist, NHS Sheffield) and Dr Nicola Peel, Consultant, MBC, STHFT – June 2011
Amended June 2014 – information about eGFR levels added
Amended September 2014 – updated in line with changes to the SPC