SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Denosumab (XGEVA) Solid tumours

PROTOCOL REF: MPHADENXST
(Version No. 1.1

Approved for use in:

- Prevention of skeletal- related events (pathological fractures, radiation to the bone, spinal cord compression or surgery to the bone) in adults with bone metastases associated with breast cancer or other solid tumours.
- **Not recommended for bone metastases from prostate cancer.**
- Prostate cancer patients with renal impairment that precludes bisphosphonate use will be eligible for this treatment.

Dosage:

Drug	Dose	Route	Frequency
Denosumab	**120mg**	Subcutaneous injection	Every 28-42 days*

To continue treatment until the clinician or clinical team managing care consider it appropriate to stop (no longer deriving clinical benefit).

Cycle length is 4 weeks however this can be increased to 6 weeks in the following cases:

- If given with concurrent 3 weekly chemotherapy.
- Persistent hypocalcaemia, despite normal vitamin D levels, with 4 weekly dosing.

Administration + Counselling Points:

- Inspect vial prior to administration, do not use if cloudy or discoloured
- Do not shake excessively.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.
- A 27 gauge needle is recommended for the administration of Denosumab.
- Single subcutaneous injection into the thigh, abdomen or upper arm.
- Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present.
- Calcium and vitamin D doses may be increased, reduced or stopped based on clinical need.
- Patients with rare hereditary problems of fructose intolerance should not use Denosumab.

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in the SPC.
- Severe, untreated hypocalcaemia
- Unhealed lesions from dental or oral surgery

Emetogenic risk:

Mild emetogenic potential.

Supportive treatments:

Adcal D3 - 1 tablet twice a day (patient can be obtaining supply via repeat prescription from the GP)

Dosing in renal and hepatic impairment:

Renal	If creatinine clearance is between 20-30 ml/min then Denosumab can be administered if this is the patients' baseline. However, if there has been a significant drop in creatinine clearance and it has fallen below 30ml/min then administration should be deferred (until next chemotherapy appointment if given alongside) Patients with creatinine clearance < 30 mL/min (Severe renal impairment) or on dialysis are at increased risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels recommended.

Hepatic	No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms.

Interactions:

No interaction studies have been performed.

Please refer to the SPC https://www.medicines.org.uk/emc/product/4675/smpc for more information

Main toxicities:

Very common	
Hypocalcaemia	• Symptoms of hypocalcaemia include; paraesthesias or muscle stiffness, twitching, spasms and muscle cramps. • Symptoms of **severe hypocalcaemia** include; QT interval prolongation, tetany, seizures, altered mental status (including coma)
Musculoskeletal pain **Diarrhoea** **Dyspnoea**	In clinical trials discontinuation due to this side-effect was uncommon.
Other adverse drug reactions	
Osteonecrosis of the jaw (ONJ)	• The jawbone becomes necrotic, exposed, and does not heal within 8 weeks. • Risk factors include invasive dental procedures (e.g., tooth extraction, dental implants, and oral surgery), poor oral hygiene, or other pre-existing dental disease. • Patients should have a dental examination prior to treatment.

	• If any invasive dental procedures need to be undertaken, treatment should be delayed until any oral lesions have healed (recommended duration 6 weeks). • All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling. • If invasive dental work is required then treatment will be withheld for at least 6 weeks or until dentist or oral surgeon confirms that is safe to resume treatment. • Patients who experience ONJ should be managed in collaboration with a dentist or oral surgeon. • Treatment with Denosumab should be interrupted until the condition resolves and the contributing risk factors are mitigated where possible. • Alternatively, the decision to resume treatment can be made by clinical team managing their care in conjunction with the dentist/oral surgeon and the patient.
Hypophosphataemia	Refer to the CCC Hypophosphataemia guidelines for replacement.
Atypical femoral fracture	• Risk increased with longer duration of treatment. • May occur with little or no trauma. • 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.
Skin toxicity/rash	Lichenoid drug eruptions

Osteonecrosis of the external auditory canal	• Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. • Symptoms include the presentation of chronic ear infections.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 day 15	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	X						
Clinical Assessment	X						Every three to six months as clinically indicated
Telephone OTR			X				
SACT Assessment (to include PS and toxicities)	X	X		X	X	X	Every cycle
Bone profile	X	X	X	X	X	X	Every cycle
U&E & serum creatinine (renal profile)	X	X		X	X	X	Every Cycle
Magnesium							If clinically indicated (hypocalcaemia and concurrent chemotherapy that affects magnesium e.g. platinum)
CrCl (Cockcroft and Gault)	X	X		X	X	X	Every cycle
CT scan	X						Every 3-6 months and if clinically indicated
ECG							If clinically indicated (suspected Hypocalcaemia induced QT prolongation)
Main observations (blood pressure, respiratory rate etc.)	X	X		X	X	X	Every cycle
Weight recorded	X	X		X	X	X	Every cycle
Height recorded	X						

Dose Modifications and Toxicity Management:

Prior to cycle 1 day 1- confirm patient has completed baseline dental check.

Proceed on day 1 of cycle 1 and subsequent cycles if:

Adjusted Calcium ≥ Lower Limit Normal (LLN*)	CrCl (creatinine clearance calculated using Cockcroft and Gault equation) ≥ 30ml/min **SEE DOSING IN RENAL IMPAIRMENT ABOVE (PAGE 3) IF CREATININE CLEARANCE <30ml/min**

Delay 1 week** on day 1 if:

Adjusted Calcium < Lower Limit Normal (LLN*)	If creatinine clearance ≤20ml/min. **SEE DOSING IN RENAL IMPAIRMENT ABOVE (PAGE 3) IF CREATININE CLEARANCE <30ml/min**

*Please refer to adjusted calcium range specific to the biochemistry laboratory that has processed the sample.
** Unless a decision is made by a clinical team to continue with treatment with appropriate intervention (monitoring and/or increased supplementation).

When assessing blood results it is important to check for trends in adjusted calcium and creatinine clearance. If the trend denotes a decline in-:

- Adjusted calcium- then provided patient is adherent with supplementation, consult with a medical team or appropriate non-medical prescriber with regards to increasing / decreasing supplementation dose.
- Serum creatinine ≥ 15% then consult with the appropriate clinical team (refer to 'Dosing in Renal and Hepatic impairment' section).

Following any deferral-, confirm patient adherence with calcium and vitamin D supplementation.

- Consider deferring until next chemotherapy appointment if given alongside

- If patient deferred for 2 consecutive weeks despite patient adherence with supplementation- please check vitamin D level. It is important to ensure all patients receiving denosumab treatment are vitamin D replete. Contact clinical team if vitamin D level is low.

Denosumab given via Clatterbridge in the community (CIC)

If patient has had stable bone and renal function for 6 consecutive treatments then blood check will be repeated on the day of treatment, starting with the 6th cycle, and checked within 72 hours for the subsequent cycles that will be administered in 4 weeks' time. Patients who fall into the exclusion criteria outlined the 'Denosumab Risk Assessment- CIC Administration' will have their bloods taken 72 hours prior to each treatment and checked ahead of administration.

References:

1. Amgen Denosumab Health Care Professional Letter. Denosumab 120mg (XGEVA®▼): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia (July 2014).
2. NICE TA265 – Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012). Accessed on 6th February 2023

via https://www.nice.org.uk/guidance/ta265/chapter/1

3. Guidance Prevention of Skeletal-Related Events in Patients with Bone Metastases, CCC Clinical Procedure, v1. Society for Endocrinology. Emergency Management of Acute Hypocalcaemia in Adult Patients (2016). Accessed on 6th February 2023 via www.endocrinology.org
4. Summary of Product Characteristics (SmPC) for Denosumab (Last updated 22nd November 2019). Accessed on 6th February 2023 via https://www.medicines.org.uk/emc/product/4675/smpc
5. Renal Drug Database. Accessed 3rd March 2023. The Renal Drug Database

Circulation/Dissemination

Date added into Q-Pulse	7th September 2023
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Version History

Date	Version	Author name and designation	Summary of main changes
June 2023	1.1	**Anna Burke and Gabriella Langton. Advanced Pharmacists**	Template change and tidied up the wording. Renal information updated.