Denosumab

Indication
Palliative therapy for and prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours, other than prostate cancer, if bisphosphonates would otherwise be prescribed.

(NICE TA265)

ICD-10 codes
Codes with a prefix C15-C80, excluding C61.

Regimen details

Day	Drug	Dose	Route
1	Denosumab	120mg	SC

Cycle frequency
28 days
In some circumstances, to coincide with cycles of chemotherapy it is acceptable to administer every 42 days (unlicensed – discuss with consultant)

Number of cycles
As long as clinical benefit.

Administration
Denosumab is administered as a single subcutaneous injection into thigh, abdomen or upper arm. Before administration, the denosumab solution should be inspected visually. The solution is a clear, colourless to slight yellow solution and may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured. Do not shake excessively.

To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25ºC) before injecting and inject slowly. Inject the entire contents of the vial.

Pre-medication
Nil

Emetogenicity
Nil

Additional supportive medication
Oral calcium and vitamin D supplements – UK chemotherapy board guidelines recommend 1000mg calcium and 800IU vitamin D daily. Dose adjusted according to calcium levels.

Extravasation
N/A

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
Dental examination	3 months, unless ongoing dental issues
FBC	28 days
U+E (including creatinine)	14 days
Corrected calcium	28 days
Vitamin D level	28 days
Phosphate	28 days
Magnesium	28 days

Any pre-existing hypocalcaemia or low vitamin D levels must be corrected before treatment is given.
If hypophosphatemia; phosphate replacement should be prescribed.
If hypomagnesaemia; magnesium replacement should be prescribed.

Investigations - pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
U+E (including creatinine)	Prior to each dose for the first 6 months, three monthly thereafter.
Corrected calcium	2 weeks after first dose then prior to each dose for the first 6 months then three monthly thereafter.
Phosphate	Prior to each dose for the first 6 months, three monthly thereafter.
Magnesium	As indicated
Vitamin D	3 months

Standard limits for administration to go ahead

If blood results within normal range, administer Denosumab as planned. If outside of normal limits refer to below:

Investigation	**Result**	**Action**
Calcium	<2.1mmol/L corrected	DO NOT ADMINISTER – inform prescriber/consultant
	>2.6 -3.0mmol/L corrected	Administer Denosumab and advise patient to stop calcium supplement
	>3.0mmol/L corrected	DO NOT ADMINISTER – refer for urgent management of hypercalcaemia
Magnesium	0.5-0.7mmol/L	Administer Denosumab
	<0.5mmol/L	DO NOT ADMINISTER – Inform prescriber/consultant
Phosphate	0.6-0.8 mmol/L	Administer Denosumab
	<0.6mmol/L	DO NOT ADMINISTER – Inform prescriber/consultant
Vitamin D (prior to 1st dose only)	<35nmol/l	If *prior to starting* denosumab: DO NOT ADMINISTER - Inform prescriber, commence high dose replacement as per local practice, delay treatment to allow at least 2 weeks high dose replacement. No need to recheck level. If patients are *already established* on denosumab: administer denosumab if all other results are within range. Check compliance with calcium/vitamin D supplementation. Inform prescriber and consider high dose replacement or increasing calcium/vitamin D supplementation to twice daily if patient reports compliant.
	35-50nmol/l	Administer Denosumab. Check compliance with calcium/vitamin D supplementation. Inform prescriber - consider increasing calcium/vitamin D supplementation to twice daily if patient reports compliant.
	>50nmol/l	Administer Denosumab
Dental work	Check with patient prior to each treatment. If they have had any dental work done since previous treatment, do not administer denosumab and inform consultant. It is recommended that patients should have a 6 monthly dental assessment	

Dose modifications

- **Renal impairment**

No dose reduction is required in patients with mild- moderate renal impairment.
If CrCl <30mls/min, consultant must give go ahead to proceed as greater risk of hypocalcaemia. Closer monitoring of calcium levels will be required.

- **Hepatic impairment**

The safely and efficacy of denosumab has not been studied in patients with hepatic impairment, denosumab is not thought to be eliminated via hepatic mechanisms.

- **Other toxicities**

Withhold treatment for any Grade 3 or 4 adverse events, or for osteonecrosis of the jaw.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Osteonecrosis of the jaw
Hypersensitivity

- **Frequently occurring side effects**

Flu like symptoms
Pain flare
Hypocalcaemia
Hypophosphataemia
Diarrhoea

- **Other side effects**

Numbness around mouth (sign of low calcium)
Renal impairment
Drug related hypersensitivity reaction
Atypical femoral fracture

Significant drug interactions – for full details consult product literature/ reference texts

No interaction studies have been performed.

In clinical trials, there were no clinically-relevant alterations in trough serum concentration and pharmacodynamics of denosumab by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure.

Additional comments

Osteonecrosis of the jaw is a rare side effect. All invasive dental work such as extractions or oral surgery should have completely healed before initiating therapy, and a minimum of 4 weeks after a dental procedure that exposes or manipulates bone. It is important to obtain a dental assessment prior to treatment and at least 6 monthly thereafter. All patients should be encouraged to maintain good oral hygiene, and immediately report any oral symptoms such as dental mobility, pain, or swelling. If invasive dental work is required while on denosumab then treatment will be withheld for 3 weeks pre and post dental intervention or until dental practitioner confirms it is safe to resume.

Patients with fructose intolerance should not receive denosumab.

Patients should be advised to use adequate contraception methods during treatment.

References

- Summary of Product Characteristics Denosumab (Xgeva) accessed 11th February 2021 via www.medicines.org.uk
- NICE TA265 accessed 10 May 2017 via www.nice.org.uk
- Stopeck, AT et al; Journal of Clinical Oncology 2010; 28:5132-5139
- UK Chemotherapy Board. *Medication-related osteonecrosis of the jaw. Guidance for the oncology multidisciplinary team.* Report of a working party on behalf of the UK Chemotherapy Board. UKCB, 2019.
- BNSGG Vitamin D prescribing guidelines accessed 18/2/2021 available from https://remedy.bnssgccg.nhs.uk/media/3244/ssg-adult-vitamin-d-prescribing-guidance.pdf

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