

ZOLEDRONIC ACID

1. Prevention of skeletal-related events in patients with solid tumours and bone metastases e.g. breast cancer
 2. An option for pain relief in prostate cancer patients with bone metastases.
3. Prevention of skeletal-related events in patients with symptomatic myeloma, or significant silent lytic bone disease detected by imaging investigations.
 4. Management of aromatase inhibitor-induced bone loss
5. For adjuvant use in **post-menopausal** women with **high risk** early stage breast cancer.

Drug/Dosage: Zoledronic acid IV 4mg (if CrCl < 60ml/min, see Renal Function)

Administration: in 100ml 0.9% sodium chloride over 15 minutes

Other drugs: Calcium 500mg and Vitamin D 400iu daily e.g. Calceos tablets, one to be chewed daily

Paracetamol can be recommended for symptom control of flu-like syndrome, fever, myalgia or arthralgia. These symptoms tend to occur with the first two doses, and then are less likely to occur with subsequent treatment.

Frequency:

Solid tumours, in patients with bone metastases:

Minimum frequency is 4-weekly, with patients on 3-weekly chemotherapy usually treated with 6-weekly zoledronic acid.

However, in light of new data supporting 12-weekly dosing in breast cancer³, as well as concerns regarding increased risk of ONJ when used concomitantly with VEGF inhibitors⁴, patients may be treated with zoledronic acid every 8 to 12 weeks.

If in doubt about the required frequency of dosing, always check with the Consultant.

Myeloma:

Current national guidelines¹ lack consensus regarding dosing frequency and duration of treatment. Locally agreed guidance is as follows:

- every 4 weeks while on treatment
- then every 2 months while off treatment
- then, after 2 years total, usually stop zoledronic acid (if no active disease)

Adjuvant use in breast cancer:

Every 6 months for 3 years (i.e. 6 doses in total)

AI-induced bone loss: Every 6 months²

Main Toxicities: fever; flu-like syndrome; nausea; myalgia / arthralgia;
renal impairment; electrolyte imbalances; osteonecrosis of the jaw (see Comments)

Anti-emetics: may need oral domperidone prn with each dose if nausea severe

Extravasation: non-vesicant

Regular Investigations:	U&Es	before every dose (see Comments)
	Corrected Ca ²⁺	before every dose
	Phosphate	before every dose
	Magnesium	if low calcium reported (see Comments)
	Baseline dental check-up	ideally recommended before 1 st dose given
	NB. FBC	Not needed

Reason for Update: Frequency section updated for solid tumours and myeloma	Approved by Chair of Alliance Haematology Group: Dr A Laurie
Version: 8	Approved by Oncology Consultant: Dr T Crook
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Prepared by: S Taylor	Checked by: Man-Chie Chow

Comments:

To avoid delays in administration, biochemistry results from the previous visit may be used if renal function and calcium are within normal limits and stable, **and** if the Consultant is happy for this practice for their patients.

Osteonecrosis of the jaw has been reported in patients on bisphosphonates, mainly associated with dental procedures. For this reason;

- a baseline dental check is advised before initiating zoledronic acid (patients may be given a form for their dentist to complete and return before starting treatment, according to local practice).
- all non-urgent invasive dental procedures should be avoided whilst on treatment.
- For patients requiring urgent dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. It is recommended that any unavoidable dental extractions are performed in hospital by a maxillofacial surgeon.
- For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition.

Dose Modifications

Renal Impairment:

Creatinine clearance should be estimated using the Cockcroft and Gault formula. The appropriate zoledronic acid dose is recommended below. The dosing interval is not affected by renal function.

Baseline CrCl (ml/min)	Dose of Zoledronic Acid	Volume of ZA 4mg/5ml concentrate	Amount to remove from 4mg/100ml soln for inf
> 60	4mg	5ml	-
50 – 60	3.5mg	4.4ml	12 ml
40 – 49	3.3mg	4.1ml	18 ml
30 – 39	3.0mg	3.8ml	25 ml
< 30	Not recommended	-	-

Subsequent doses should remain the same unless serum creatinine rises to > 30% above baseline serum creatinine, in which case, a doctor should be informed and consideration should be given to withholding zoledronic acid until the serum creatinine returns to within 10% of the baseline value. Zoledronic acid may then be resumed at the same dose as prior to treatment interruption.

Hypocalcaemia:

The management of hypocalcaemia may vary between different Consultants as there is no standard agreed practice.

The deficiency is usually asymptomatic and does not require IV treatment, but ensure that the patient is taking daily calcium and vitamin D supplements, at a *minimum* dose as specified above. Also, **serum magnesium** should be checked in these patients to determine whether magnesium replacement is required.

The decision whether to continue or defer the dose of zoledronic acid may depend upon the degree and duration of hypocalcaemia, as well as clinician preference and clinical situation. If in doubt, discuss with Consultant.

Hypophosphataemia:

There is also no standard advice regarding management of hypophosphataemia, but short-term supplemental therapy with Sandophos may be advised to correct the deficiency while zoledronic acid treatment continues. If in doubt, discuss with the prescriber.

References:

¹BCSH Guidelines on the Diagnosis and Management of Multiple Myeloma 2014

²Cancer Treat Rev 2008; 34: S1 – S18 (position statement from UK expert group)

Early Breast Cancer Trialists Collaborative Group; Lancet 2015; 386: 1353 – 1361 (adjuvant use)

³Hortobagyi et al; JAMA Oncol 2017; 3 (7): 906 – 912 (Optimize-2 trial)

⁴Van Cann et al; Support Care Cancer 2017; doi: 10.1007/s00520-017-3903-5. [epub ahead of print]

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