ZOLEDRONIC ACID ADMINISTRATION
APEG PAEDIATRIC DRUG PROTOCOL

DOCUMENT SCOPE / PURPOSE

This document provides a framework for the safe administration of zoledronic acid. The associated APEG consensus guideline[1] provides detailed information on specific indications and treatment rationale.

[1]Simm PJ, Biggin A, Zacharin MR, Rodda CP, Tham E, Siafarikas A, Jefferies C, Hofman PL, Jensen DE, Woodhead H, Brown J, Wheeler BJ, Brookes D, Lafferty A, Munns CF; APEG Bone Mineral Working Group. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health. 2018 Mar;54(3):223-233. doi: 10.1111/jpc.13768.

DOCUMENT SUMMARY/KEY POINTS

- Zoledronic acid (zoledronate) is used predominantly in the management of primary and secondary osteoporosis. It can also have a role in the treatment of avascular necrosis, delayed bone healing, hypercalcaemia, bone pain and other bone-related conditions.
- A comprehensive assessment including baseline blood tests, bone mineral densitometry and dental review is required before commencing zoledronic acid treatment.
- Children and adolescents treated with zoledronic acid require close supervision and monitoring under the care of a treating Paediatric Endocrinologist.
- Adverse reactions including an acute-phase response and hypocalcaemia are commonly associated with the first dose of zoledronate and may recur with subsequent doses. These can be ameliorated with simple analgesia and adequate calcium intake.
- Clinical staff prescribing, dispensing and administering zoledronic acid should read and acknowledge they understand this document.

1. Introduction / Background

Zoledronic acid (zoledronate) is a potent bisphosphonate that inhibits osteoclastic bone resorption. Paediatric patients being considered for bisphosphonate therapy should be referred to an Endocrinologist for assessment before commencing treatment.

This protocol aims to:

- Promote the safe initiation and maintenance use of zoledronate.
- Monitor and mitigate against adverse outcomes of zoledronate administration.

2. Indications

- A low bone density (bone mineral density Z-scores <-2) with two or more long-bone fractures, or vertebral crush fracture irrespective of bone density.

  OR

- A low bone density and significant fracture with minimal trauma (e.g. low trauma femur fracture in a child with cerebral palsy).
- OR
- Moderate to severe osteogenesis imperfecta.

  OTHER

- Avascular necrosis (AVN).
- Delayed bone healing.
- Hypercalcaemia.
- Other bone-related conditions (eg. fibrous dysplasia, chronic recurrent multifocal osteomyelitis, bone cysts, generalised arterial calcification of infancy).

3. Contraindications

- Pregnancy.
- Vitamin D deficiency - serum 25-hydroxyvitamin D <50 nmol/l.
- Hypocalcaemia - serum corrected calcium <2.0 mmol/l.
- Documented allergic reaction to bisphosphonates.
- History of osteonecrosis of the jaw or recent (healing) / imminent dental extraction
- Renal impairment (relative contraindication, dose adjustment can be considered).

4. Precautions

- Acute fracture (delay zoledronate for 6 weeks or until callus formation).
- Recent or planned dental or orthopaedic procedures (delay zoledronate for 6 weeks or until sufficient healing).

5. Pre-Treatment Assessment and Investigations

- Baseline blood tests, bone mineral densitometry and dental review are required before treatment is to commence. Bone density is not usually performed in children <4 years due to the lack of normative data.
- Pre-infusion biochemistry including serum Ca, Mg, PO4, Alk Phos, albumin, electrolytes/urea/creatinine (EUC) and 25-OH-vitamin D should be collected before all zoledronate infusions. Post-infusion bloods should be considered if clinically indicated.

- All patients should have a dental review prior to commencing Zoledronate to assess the need for any major dental interventions. It is important that patients continue to maintain good dental health whilst undergoing therapy and should continue to have annual check-ups. Routine treatment such as scaling and fillings do not pose a risk.
- Height and weight are recorded prior to all zoledronate infusions.
- Consider a lateral thoraco-lumbar spine x-ray at baseline in children with bone density Z-scores <-2 or clinical suspicion of vertebral compression fracture.
- Bone mineral densitometry by DXA is performed prior to zoledronate treatment. This is repeated annually whilst on treatment and following cessation of treatment as per the treating Endocrinologist.
- Lateral Vertebral Assessment (LVA) can be performed as part of the DXA to review vertebral compression fractures. This will reduce the overall patient radiation exposure compared to regular spine x-rays.
- Bone mineral densitometry by peripheral quantitative CT (pQCT) can also be performed where available (in addition to DXA) but this is usually performed every two years. pQCT is not applicable for patients being managed for hypercalcaemia or delayed healing.
- Calcium and 25-OH-Vitamin D must be within normal limits prior to commencement of zoledronate. Children 4 – 8 years of age must have a calcium intake of 800 mg/day and older children 1200 mg/day. If dietary intake is inadequate, supplementation may be necessary.

6. Dose

- The dose of zoledronate is calculated on the child's body weight and is administered via intravenous infusion over 30 minutes.
- In overweight or obese patients, use one of the following methods to obtain the adjusted body weight in order to calculate dose:
    - If age and height are known, use height-for-age chart to identify the percentile at which to read the "ideal" weight from a weight-for-age growth chart
    - If height is not known, use the 50th percentile for age
- The prescribing Endocrinologist will ultimately determine the dose and frequency of zoledronate.
- Adolescents with osteoporosis on annual infusions can receive a maximum dose of 4mg.
- The maximum dose for children on more frequent infusions (eg. 6-monthly) is usually 2mg per infusion.
- The following treatment regimens can be used as a guide:

Zoledronate 6-12 monthly - *Consider for osteoporosis in children ≥2 years of age*

Infusion number	Dose	Frequency
All*	0.025 - 0.05 mg/kg	6-12 monthly

*The first dose may be split into an initial dose of 0.0125mg/kg and a follow-up dose 6 weeks later of 0.0375mg/kg (to make a 'total' dose of 0.05mg/kg) in order to minimise the acute phase reaction.

All treatment should be tailored to the individual, taking into account clinical circumstances and outcomes.

Zoledronate 3 monthly - *Consider for osteoporosis in children <2 years of age or avascular necrosis (AVN)*

Infusion number	Dose	Frequency
All	0.025 mg/kg	3 monthly

Zoledronate 2 doses only – *Consider for delayed bone healing*

Infusion number	Dose	Frequency
1st infusion 4 weeks post-surgery	0.0125 mg/kg	Once
2nd infusion 6 weeks AFTER first dose	0.025 mg/kg	Once

Hypercalcaemia

Infusion	Dose	Frequency
1st infusion	0.0125 mg/kg	Once
Subsequent doses as required	0.0125 - 0.025 mg/kg	PRN

Supplementary medication post <u>first</u> infusion

Medication	Dose	Duration
Paracetamol / Ibuprofen#	PRN	3 days
Elemental Calcium*	1000 mg twice daily	3 days
Ondansetron	0.1mg/kg q 8hr	PRN

*Reduce dose for children < 4 years-old.

Ibuprofen may be contraindicated by orthopedic surgeon.

7. Adverse Reactions

An acute-phase reaction comprising “flu-like” symptoms (i.e. fever, nausea, vomiting, headache and body aches and pains) usually occurs within 24 hours of the first zoledronate infusion and subsides within 48-72 hours.

With subsequent infusions, these symptoms do not usually occur but if they do, it is to a lesser degree. Other reported symptoms are migraines, itchy eyes (iritis), burning sensation on palms of hands and soles of the feet. Hypophosphataemia and hypocalcaemia are commonly observed following the first infusion. Phosphate supplementation is not indicated as it may further decrease serum calcium. Symptoms of numbness or tingling in the fingers or toes is indicative of hypocalcaemia. This should be investigated and reported to the Endocrinologist.

If hypocalcaemia (corrected serum calcium <2.0 mmol/l) does occur, calcium and calcitriol are needed until serum calcium is ≥2.0 mmol/l.

Treatment of hypocalcaemia (Serum calcium <2.0 mmol/l)

Medication	Dose	Duration
Elemental Calcium*	1000 mg three times daily	Until serum Ca ≥2.0
Calcitriol*	0.25 μg three times daily	Until serum Ca ≥2.0

*reduce dose for children < 4 years-old.

8. Duration of Treatment

- Treatment duration is determined by disease severity, clinical progress and changes in serial bone mineral densitometry. In general, treatment should continue for at least 12 months (excluding treatment for hypercalcaemia and delayed bone healing) and be reviewed annually.

9. Authorised Prescribers

- Zoledronate should be prescribed under the advice and supervision of a treating Endocrinologist.

10. Administration

- Zoledronate is usually diluted in 50mL 0.9% saline and infused intravenously over 30 minutes.
- The reconstituted solution is stable at room temperature for 24 hours.
- Please refer to your local hospital drug administration guidelines.

11. Safety and Patient Monitoring

Zoledronate infusions are usually conducted as a day-stay admission and fasting is not required. Children with significant co-morbidities may be admitted for three days for treatment and observation following the first infusion.

12. Appendix 1 – Summary Protocol Tables

6-12 monthly zoledronate

	Pre infusion	Day 0	6 weeks*	6 months	12 months	Thereafter
Zoledronate infusion		+	+	+/-	+	6-12 monthly
Auxology	+	+	+	+	+	at infusion
DXA (+/- lateral vertebral assessment)	+				+	12 monthly
pQCT (where available)	+					2nd yearly
Dental review	+				+	12 monthly
Spine x-ray (lateral)	+					2nd yearly or as indicated
Serum calcium, PO4, Mg, ALP, albumin, EUC	+	+	+	+	+	at infusion
FBC	+				+	12 monthly
PTH	+				+	12 monthly
25 OH Vitamin D	+				+	12 monthly
Bone turnover: Serum CTX, PINP	+				+	12 monthly

*applicable only if 'splitting' the first dose (see section 6)

3 monthly zoledronate (children with AVN are treated for 12 months [5 doses] only)

	Pre infusion	Day 0	3m	6m	9m	12m	Thereafter
Zoledronate infusion		+	+	+	+	+	3 monthly
Auxology	+	+	+	+	+	+	3 monthly
DXA (+/-lateral vertebral assessment)	+					+	12 monthly

pQCT (where available)	+						2nd yearly
Dental review	+					+	12 monthly
Serum calcium, PO4, Mg, ALP, albumin, EUC	+	+	+	+	+	+	3 monthly
FBC	+					+	12 monthly
PTH	+					+	12 monthly
25 OH Vitamin D	+					+	12 monthly
Bone turnover: Serum CTX, PINP	+					+	12 monthly

Zoledronate 2 DOSES ONLY (delayed healing)

	Pre infusion	4 weeks post surgery	6 weeks post 1st infusion
Zoledronate infusion		+	+
Auxology	+		+
Dental review	+		
Calcium, PO4, Mg, ALP, albumin, EUC	+	+	+
FBC	+		
PTH	+		
25 OH Vitamin D	+		
Serum CTX, PINP	+		