MONOGRAPH

ZOLEDRONIC ACID

Scope (Staff):	Medical, Pharmacy, Nursing
Scope (Area):	All Clinical Areas

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

QUICKLINKS

Dosage/Dosage Adjustments	Administration	Prescribing & Calcium/Vitamin D Dosing	Monitoring

DRUG CLASS

Zoledronic acid is a bisphosphonate.[1]

INDICATIONS AND RESTRICTIONS[2, 3]

Indications **not listed** below will require individual patient application (IPA) approval from the Drug and Therapeutics Committee (DTC):

- Primary osteoporosis (osteogenesis imperfecta).
- Secondary osteoporosis or osteopenia.
- Refractory hypercalcaemia.
- Localised reduced bone mineral density due to trauma, slipped epiphyses, internal fixation, steroids, chemotherapy, fracture non-union.
- Idiopathic avascular necrosis or Legge-Calve-Perthes disease.
- Chronic recurrent multifocal osteomyelitis, under the direction of a rheumatologist, as per the WADEP treatment algorithm.[4]

CONTRAINDICATIONS

- Hypersensitivity to zoledronic acid or any component of the formulation.[3]

- Pre-existing hypocalcaemia.[3]
- Pregnancy – patients with childbearing potential should be tested prior to each infusion. Patients/guardians must be advised of contraception requirement if applicable.[3, 5]
- Calcium and 25-Hydroxy-Vitamin D level must be within normal limit prior to commencing zoledronic acid.[2]

PRECAUTIONS

- Patients with significant co-morbidities or risk factors for hypocalcaemia may be admitted for up to three days for treatment and observation for their first infusion, or subsequent infusions if clinically indicated.
- Dehydration.[5]
- Renal disease or impairment (including renal calculi).[5] Consider measured glomerular filtration rate (GFR) via nuclear medicine department, to guide dose adjustments.
- Concurrent use with other nephrotoxic drugs.[5]
- Invasive dental procedures or pre-existing major dental complications – increased risk of osteonecrosis of the jaw (ONJ).[3]
- Recent fracture or osteotomy (within 6 weeks) – may delay bone healing.[2, 5]
- Active rickets.[2]

FORMULATIONS

- 4 mg/5 mL vial.[6]

DOSAGE & DOSAGE ADJUSTMENTS

Dosing in Overweight and Obese Children: Dose based on patient's ideal body weight.[7]

Dosage and frequency are dependent on the indication and may deviate from usual recommendations at the discretion of the treating consultant.

- Minimum recommended age: 2 years old. For children < 2 years, consult an endocrinologist.[7]
- Refer to prescribing section for pre-infusion calcium and vitamin D supplementation dosing recommendations.
- ##Bisphosphonate **naïve** patients (for primary or secondary osteoporosis) – consider using lower initial dose for **first dose** to reduce risk of hypocalcaemia.[2] Suggested dosing:
  - 0.025 mg/kg IV daily for 2 days, OR
  - 0.025 mg/kg IV at 0 and 3 months, OR
  - 0.025 mg/kg IV once, then 0.05 mg/kg at 6 months.

Primary osteoporosis[2, 7, 8]

See previous page (##) for first dose.

Patients **previously tolerated** bisphosphonate infusion: 0.05 mg/kg/dose, repeat in 6 months (0.1 mg/kg/**year**, max 5 mg/**year**).

Repeat DXA (Dual Energy X-ray Absorptiometry) scan after 12 months of therapy then continue treatment as below (max 5 mg/**year**):

- BMD Z score ≤ -2.0 ➜ continue same annual dose.
- BMD Z score ≥ -2.0 but <0 ➜ consider reducing the dose to 0.05 mg/kg/**year,** in 2 divided doses.
- BMD Z score > 0 ➜ 0.025 mg/kg as a **single annual dose**, if maintenance therapy indicated.

Spine or TBLH (total body less head) BMD rather than total BMD, is typically assessed in paediatrics and adolescents.[9]

Secondary osteoporosis[2, 8, 10]

See previous page (##) for first dose.

Subsequent dosing (2nd dose and following doses): 0.05 mg/kg, repeat in 6 months (0.1 mg/kg/**year**, max 5 mg/**year**).

- Consider switching to maintenance therapy or ceasing zoledronic acid therapy (0.025 mg/kg as a single annual dose) after 12 months if DXA and clinical features improve significantly.

Patients under the care of Paediatric Rehabilitation team:

- 0.025 mg/kg/dose at 0, 6, 12 and 18 months (*0.1 mg/kg over 2 years*).
- Consider repeating treatment course as above if BMD Z score remains low or patient develops fractures.

Idiopathic avascular necrosis (AVN), Legg-Calvé-Perthes disease[11]

- 0.025 mg/kg repeated every 3 months (total 0.1 mg/kg/**year**, max 4 mg/**year**).

Refractory hypercalcaemia[12]

- First infusion: 0.0125 mg/kg as a single dose.
- Subsequent infusions: 0.0125 – 0.025 mg/kg as required.
- Reduction in calcium level may be delayed by a few days following bisphosphonate infusion. Consider this before prescribing subsequent doses.

Chronic recurrent multifocal osteomyelitis (CRMO)[13, 14]

- 0.025 – 0.05 mg/kg (max 4 mg) as a single dose.
- Repeat in 6 – 12 months, if necessary, max 4 mg/**year**.

Renal impairment:

- eGFR calculator

- Dosage adjustment may be necessary for zoledronic acid use in renal impairment. Consider using pamidronate instead, in consultation with endocrinologist.[12]

Hepatic impairment: No data available. Not hepatically metabolised.[3]

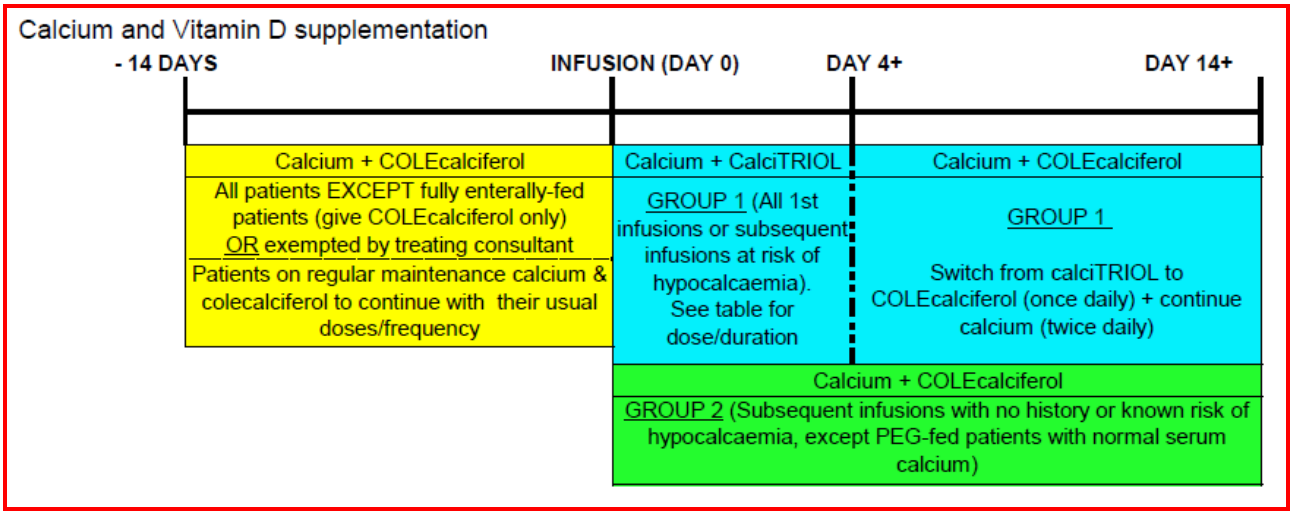
PRESCRIBING[2, 7]

- Prescribe paracetamol or ibuprofen (as required) on National Inpatient Medication Chart (NIMC) to treat acute phase reaction symptoms (flu-like symptoms).
- Prescribe zoledronic acid infusion on MR828 IV Fluid Therapy Order sheet.

The remaining information in this section only applies to patients receiving zoledronic acid for indications other than hypercalcaemia.

COLEcalciferol and **calciTRIOL** are not equivalent. Calcitriol is the active form of vitamin D.
Patients **SHOULD NOT** be taking both forms concurrently
(i.e. withhold colecalciferol when taking calcitriol)

- *Patients at low risk of hypocalcaemia may at the treating consultant's discretion, not require pre- or post-infusion calcium and/or vitamin D (e.g. rheumatology patients using bisphosphonates for CRMO/AVN with no known co-morbidities that may increase their risk of hypocalcaemia).*
- Calcium doses may be rounded to the nearest 150 mg (quarter of a 600 mg tablet) or 125 mg (quarter of a 500 mg tablet), if tablet is preferred.



PRE–infusion calcium and COLEcalciferol supplementation

Patients should receive calcium and colecalciferol supplementation prior to zoledronic acid infusion *(see exceptions below)*

- Non-ambulatory fully enterally–fed patients with normal calcium levels do not require additional pre-infusion calcium supplementation but should be prescribed COLEcalciferol.
- Patients receiving ongoing (regular) calcium and vitamin D supplements, with normal serum calcium and vitamin D levels do not require additional pre-infusion supplementation (i.e. continue on their usual maintenance dose and frequency).
- Patients with normal serum calcium/vitamin D levels and at low risk of bisphosphonate-related

hypocalcaemia may be exempted from pre-infusion calcium/colecalciferol supplementation at the treating consultant's discretion.

- Recommended dose and duration:

Drug	Dose (enteral)	Commence
Elemental calcium	20 mg/kg (max 600 mg) TWICE daily	14 days pre-infusion
COLEcalciferol (Vitamin D_3)	Refer to COLEcalciferol guideline	14 days pre-infusion

- Consider using combination product containing elemental calcium 600 mg + colecalciferol 500 units/tablet if appropriate. ***(Preferred formulation for patients under the care of Paediatric Rehabilitation team)***.

POST–infusion calcium and vitamin D supplementation (Note: Group 1 vs Group 2)

- Intravenous calcium infusion may be necessary in patients with severe symptomatic hypocalcaemia. Refer to calcium monograph.
- Patients with normal serum calcium/vitamin D levels and are at low risk of bisphosphonate-related hypocalcaemia may be exempted from post-infusion calcium/colecalciferol supplementation at the treating consultant's discretion.

Group 1: ALL FIRST infusions or all subsequent infusions at risk of hypocalcaemia

- ➢ Patients with history of zoledronic acid or other bisphosphonate-induced hypocalcaemia should be managed as post-first infusion (i.e. should be prescribed calcium and calcitriol following subsequent infusions).

- Following treatment with calciTRIOL, patients should step down to COLEcalciferol to complete at least 14 days in total of vitamin D therapy post-infusion.
  - ➢ Recommended dose and minimum duration:

Serum calcium level (24hrs post-infusion)	Drug	Dose (enteral)	Duration
≥ 2mmol/L	Elemental calcium	20 mg/kg (max 1 g) **TWICE daily**	14 days
	CalciTRIOL	0.25 microg/**DOSE** (NOT per kg) **TWICE daily**	≥ 4 days, then step down to COLEcalciferol **once daily**
< 2mmol/L	Elemental calcium	20 mg/kg (max 1 g) **THREE times daily**	Until serum calcium ≥2mmol/L, then reduce to **twice daily**
	CalciTRIOL	0.25 microg/**DOSE** (NOT per kg) **THREE times daily**	Until serum calcium ≥ 2mmol/L, then step down to COLEcalciferol **once daily**
It is recommended that patients complete a total of 14 days calcium & vitamin D therapy. Exact duration of treatment to be determined by treating consultant.			

Group 2: SUBSEQUENT infusions (no history or known risk of hypocalcaemia):

- Patients who have previously tolerated zoledronic acid infusion without hypocalcaemia *(see exception below)* should be prescribed calcium and COLEcalciferol for at least 14 days post-infusion.
  - ➢ Non-ambulatory fully enterally–fed patients with normal calcium levels do not require additional post–infusion calcium supplementation.
- Recommended dose:

Drug	Dose (enteral)	Duration
Elemental calcium	20 mg/kg (max 600 mg) bd	14 days post-infusion
COLEcalciferol (Vitamin D_3)	Refer to Colecalciferol guideline	14 days post-infusion

- Consider using combination product containing elemental calcium 600 mg + colecalciferol 500units/tablet if appropriate. ***(Preferred formulation for patients under the care of Paediatric Rehabilitation team)***.

ADMINISTRATION

- During pharmacy operating hours, zoledronic acid infusion is prepared by PCH Pharmacy Compounding Services (PCS).
- Dilute to 50mL or 100mL with compatible fluid and infuse over at least 30 minutes.[15] Smaller volume may be used if patient is fluid restricted **(max concentration 0.04mg/mL)**.
- Ensure patient is adequately hydrated prior to, during and after the infusion.[5, 16]

COMPATIBILITY

Compatible fluids: Sodium chloride 0.9%, glucose 5%.[16]

MONITORING[2, 5, 7]

- **With each infusion** – Baseline temperature, pulse and respiratory rate (TPR), blood pressure; repeat every 30 minutes until 1 – 2 hours post-infusion. Frequency of monitoring for inpatients may then be reduced to standard frequency.
- Monitor serum or ionised calcium levels.

Recommended additional monitoring for all indications **other than hypercalcaemia**:

- **Monitoring requirements may vary at the treating consultant's discretion.**
- In the presence of renal disease and impaired creatinine production/clearance, measurement of glomerular filtration rate (GFR) using radio-contrast may be necessary. Discuss with an endocrinologist.
- **WORKUP prior to FIRST infusion**– serum or ionised calcium (blood gas), phosphate, magnesium, full blood count, UEC (urea, electrolytes and creatinine), renal function, renal

ultrasound, alkaline phosphatase (ALP), serum 25-hydroxy vitamin D, parathyroid hormone, dental review (consider orthopantomogram), baseline ECG (for patients at risk of arrhythmias).

- **Prior to EACH infusion (at time of presentation to PCH)** – serum or ionised calcium, serum 25-hydroxy vitamin D, UEC, estimated renal clearance, urine beta-hCG (pregnancy test). Serum calcium level must be within normal limit prior to starting the infusion.
- **POST–FIRST infusion (all patients)**:
  - Repeat serum calcium level 24 hours post-infusion and adjust calcium/calcitriol dosing frequencies accordingly.
  - Requirement for serum calcium monitoring on **day 2 and 3 is optional** depending on individual patient's clinical status and is to be determined by the treating consultant.
  - Inpatients may be discharged on day 2 if clinically appropriate. Follow up calcium monitoring may occur in an outpatient setting.
- **POST–SUBSEQUENT infusion (Group 1: patients with risk factors for or history of zoledronic acid-induced hypocalcaemia)** – monitor as per first infusion.
- **POST–SUBSEQUENT infusion (Group 2: patients with no known risk factors for hypocalcaemia)**:
  - Routine serum calcium monitoring is not necessary.
- Ongoing long-term monitoring (annually or as deemed appropriate by treating consultant): dental examination, bone density scan (DXA and pQCT), X-ray.
- Consider yearly analysis of bone turnover markers in patients with osteopenia or osteoporosis – serum P1NP (total procollagen type 1 N-terminal propeptide) and serum CTX (c-terminal telopeptide).

ADVERSE EFFECTS[2, 3]

Acute phase reaction may occur up to 24 – 72 hours after the infusion.[8, 12] Signs and symptoms include low-grade fever, headache, bone pain, chest pain or myalgia.[8]

Common: Acute phase reaction, hypocalcaemia, hypophosphataemia, hypertension, infusion site reaction, headache.

Infrequent: Hypomagnesaemia, hypokalaemia, hypotension, seizures, sinus tachycardia, atrial fibrillation.

Rare: Osteonecrosis of the jaw or external auditory canal, atypical fractures, anaphylactic shock, angioedema, Stevens-Johnson syndrome, ocular inflammation, renal impairment, heart failure, hypotension, oedema, iritis.

STORAGE[16]

Vial: Store below 25ºC.

Diluted infusion solution: Stable for 24 hours at 2 to 8ºC.

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g.

Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Please note: The information contained in this guideline is to assist with the preparation and administration of **zoledronic acid**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

Related CAHS internal policies, procedures and guidelines

PCH.MED.Colecalciferol

PCH.MED.Calcium

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