

Alert	Discuss with specialist before starting treatment. Contraindicated in Osteogenesis Imperfecta Type 2. Ensure neonates have normal vitamin D status and are adequately hydrated prior to administration. Serum calcium level should be closely monitored, particularly in the newborn period and with the first infusion. Flu like symptoms are common within 24 hours following first infusion and subside within 48-72 hours. Symptoms are usually less likely with subsequent infusions.
Indication	Severe Osteogenesis Imperfecta (Contraindicated in OI type 2) Children with OI type 2 have very severe bone fragility and respiratory distress secondary to abnormal lung development, neither of which is amenable to bisphosphonate therapy. Severe hypercalcaemia.
Action	Pamidronate, a nitrogenous bisphosphonate, is a potent inhibitor of osteoclastic bone resorption. It adsorbs to calcium phosphate (hydroxyapatite) crystals and disrupts the cytoskeleton of osteoclasts, thereby increasing bone mass. Bisphosphonate increases thickness of the outer shell of long bones and trabecular number, significantly reducing the risk of bone fractures.
Drug type	Bisphosphonate. Active ingredient is disodium-3-amino-1-hydroxypropylidene-1,1-biphosphonate.
Trade name	Pamisol
Presentation	15 mg in 5 mL vial; 30 mg in 10 mL vial; 60 mg in 10 mL vial; 90 mg in 10 mL vial.
Dose	Severe Osteogenesis Imperfecta¹: Dose in neonates and infancy <ul style="list-style-type: none"> • First infusion: 0.25 mg/kg - 0.5 mg/kg • Subsequent doses: 1 to 1.5 mg/kg every 1 to 2 months. Ensure neonates have normal vitamin D status (25-OH vitamin D ≥50 nmol/L) and are adequately hydrated prior to administration. Severe hypercalcaemia^{1,2} Dose: 0.25 mg/kg – 1 mg/kg. May need to be repeated (depending on underlying condition) with minimum dosing interval of 48 hours. ^{1,2}
Dose adjustment	Therapeutic hypothermia: Not applicable. ECMO: Not applicable. Renal: Pamidronate is not metabolised and is exclusively eliminated by renal excretion. Pamidronate is not recommended for patients with severe renal impairment. Hepatic: Not applicable.
Maximum dose	2 mg/kg
Total cumulative dose	
Route	IV infusion
Preparation	Add 5 mg of pamidronate to sodium chloride 0.9% or glucose 5% to make a final volume of 50 mL with a final concentration of 0.1 mg/mL solution.
Administration	IV infusion over 4 hours (2 to 4 hours). Do not infuse over less than 2 hours. NOT FOR BOLUS INJECTION. Pamidronate should never be given as a bolus injection, since severe local reactions and thrombophlebitis may occur. Bolus injection increases risk of renal failure. It should always be diluted and given as a slow intravenous infusion.
Monitoring	UEC, calcium, magnesium, phosphate, PTH and Vitamin D levels – Prior to starting treatment Patients with pre-existing anaemia, leukopenia, or thrombocytopenia - Monitor full blood count closely, particularly in the first 2 weeks following treatment. Monitor UEC and CMP at 48 hours following first infusion, depending on age of child and underlying condition. Monitor UEC and CMP prior to repeat doses.
Contraindications	Severe renal impairment. Documented allergic reactions to bisphosphonates. Hypocalcaemia – Serum calcium <2.1 mmol/L. Serum 25-Hydroxyvitamin D <50 nanomol/L. Osteogenesis Imperfecta Type 2.
Precautions	Mild renal impairment.

Drug interactions	<p>Aminoglycosides: May enhance the hypocalcaemic effect of bisphosphonates.</p> <p>Nonsteroidal anti-inflammatory agents: May enhance the adverse effect of bisphosphonates including risk of gastrointestinal ulceration and nephrotoxicity.</p> <p>Proton Pump Inhibitors: May reduce therapeutic effect of bisphosphonates.</p> <p>Angiogenesis inhibitors (systemic): May increase the adverse effect of bisphosphonates, particularly osteonecrosis of the jaw (not reported in children).</p> <p>Deferasirox: Bisphosphonate derivatives may enhance the adverse effect of deferasirox. Specifically, the risk for gastrointestinal ulceration/irritation or bleeding may be increased.</p>
Adverse reactions	<p>Flu-like symptoms are common and usually occur within 24 hours following the first infusion and subside within 48-72 hours. Symptoms are usually less likely with subsequent infusions.</p> <p>Hypocalcaemia and hypophosphatemia are common side effects following the first infusion.</p> <p>Hypocalcaemic seizures have been reported following treatment.</p> <p>Acute respiratory distress in infants with pre-existing respiratory problems.</p> <p>Local reactions at the infusion site, headaches, abdominal pain, bone and muscle pain, irritation of eyes, burning sensation of hands and feet, rash and lymphopenia.</p> <p>Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is reported in adults but there are no reports of BRONJ in children secondary to bisphosphonates. Nevertheless, all children with or without osteogenesis imperfecta who are treated with bisphosphonates, should be regularly reviewed by dental clinicians as a precaution.</p> <p>Pamidronate may interfere with the bone healing in children with osteogenesis imperfecta. It may be necessary to withhold pamidronate therapy following a fracture or osteotomy until good callus formation is seen on the X-ray.</p>
Compatibility	<p>Fluids: Sodium chloride 0.9%, glucose 5%.</p> <p>Drugs: Consult the pharmacist for advice. It is recommended to administer as a separate infusion, separate from all other drugs.</p>
Incompatibility	<p>Fluids: Calcium containing solutions, e.g. Ringer's solution.</p> <p>Drugs: Calcium folinate, caspofungin.</p>
Stability	<p>Diluted solution should be infused immediately after preparation and any residual amount to be discarded. If the diluted product cannot be used immediately or as soon as practicable after preparation, store between 2° to 8°C for not more than 24 hours.</p>
Storage	<p>Store below 25°C.</p>
Excipients	<p>Mannitol, phosphoric acid, sodium hydroxide and water for injections.</p> <p>Phosphoric acid and sodium hydroxide are added to adjust pH.</p>
Special comments	<p>Ensure infants are adequately hydrated prior to administration.</p> <p>Pamidronate is not metabolised and is exclusively eliminated by renal excretion. Pamidronate is not recommended for patients with severe renal impairment.</p> <p>For infants with OI, measure vitamin D status prior to commencement of treatment. Ensure adequate vitamin D intake.</p>
Evidence	<p>Efficacy</p> <p><u>Osteogenesis Imperfecta (OI)</u></p> <p>A Cochrane review of 819 participants from 14 trials (2003–13) showed a universal improvement in bone density, but data on growth, bone pain, fracture incidence and function were incomplete.³ [LOE I, children and adults] The studies included in this review were insufficiently powered to appropriately assess these secondary outcomes. Intravenous bisphosphonate treatment in infants and children aged 2 months to 3 years was associated with improvement in the number of vertebral fractures in the growing skeleton and modelling.⁴ [LOE IV]. It has been shown to significantly reduce the incidence of long-bone fractures in children.⁵ [LOE I] In mild OI, there was no significant difference in fracture rate in patients treated with oral bisphosphonates compared to intravenous agents.⁵ [LOE I] However, neither was associated with improvements in spinal morphology or bone pain.^{3,6} [LOE I]</p> <p>In neonates, Lin, et al reported the outcomes of treatment with pamidronate in 6 newborns diagnosed with severe OI either born with fractures or sustained fractures in the neonatal period.⁷ The mean age of the patients while starting the treatment was 2.8 months. The dosage and frequency of pamidronate infusion depended on age. In younger populations, the dosage was lower, but the frequency was higher than that in older patients. The dosing and frequency schedule was as follows: 0.5 mg/ kg every 2 months prior to 1 year of age; 1 mg/kg every 2 months between 1 year and 2 years of age; 1.5 mg/kg every 3</p>

	<p>months between 2 years and 4 years of age; and 2 mg/kg every 3-4 months after 4 years of age. The drug was diluted in a sodium chloride 0.9% solution and infused over 4 hours. Oral calcium carbonate (125 mg two times a day) and vitamin D (cholecalciferol 400 international units daily) were also supplied. Symptom relief was seen 1 month after the first infusion.⁷ [LOE IV]</p> <p><u>Hypercalcaemia</u></p> <p>Pamidronate has been used in neonates and young infants in a variety of conditions that cause severe hypercalcaemia including neonatal hyperparathyroidism (NHPT) and neonatal severe hyperparathyroidism (NSHPT)^{1,8}, severe neonatal fat necrosis⁹⁻¹² and vitamin D intoxication.^{2,13} For treatment of NSHPT, pamidronate doses used were 0.5–1 mg/kg body weight or 20 mg/m² body surface area with minimal time to reduction in serum calcium of 12 hours and maximum effect after 2–3 days. Pamidronate was well tolerated but hypocalcaemia was developed in one patient.⁸ In a retrospective case series, 21 children with vitamin D intoxication treated with pamidronate as first line therapy (median dose of 1 mg/kg) had a lower recurrence rate of hypercalcaemia compared to other treatment strategies.²</p> <p><u>Generalised arterial calcification of infancy</u></p> <p>GACI, if untreated, is a generally fatal condition often caused by a mutation in ENPP1 and less commonly ABCC6.^{1,14} In a case series, 11 of 17 (65%) infants treated with bisphosphonates survived compared with 8 of 26 (31%) infants not treated.¹⁵ However, there are concerns regarding the development of hypophosphatemic rickets in infants with GACI treated with prolonged bisphosphonates.¹⁶⁻¹⁹</p> <p>Safety</p> <p>Long-to-medium term bisphosphonate therapy in children with moderate-to-severe OI has been shown to be safe. Adverse effects of bisphosphonates were few and minor (gastrointestinal complaints often comparable to placebo, fever, headache, small decreases in lymphocyte counts).³ Flu-like symptoms described as "acute phase reactions" following the first infusion are common with IV administration of bisphosphonates.³ Hypocalcaemia after pamidronate infusion was observed in all three neonates during their first month of life, although oral calcium and vitamin D supplies were prescribed.⁷ Children should have a serum 25-hydroxy vitamin D level >50 nanomol/L before starting bisphosphonate, and neonates should have daily serum calcium level monitoring for 3 days after the first infusion. A rare but serious side effect of bisphosphonates is osteonecrosis of the jaw, although this has not been reported in children or adults with OI.³</p> <p>In infants with GACI, hypophosphatemia, hyperphosphaturia and hypophosphatemic rickets has been associated with prolonged use of bisphosphonates.^{15,19}</p>
<p>Practice points</p>	<p><u>Australian Paediatric Endocrine Group consensus guidelines 2018¹:</u></p> <p>Osteogenesis imperfecta: Intravenous bisphosphonates should be considered for use in children with severe OI (e.g. type III), children with vertebral compression fractures or children who have had two or more long-bone fractures per year. [LOE 1 GOR B] Oral bisphosphonates should only be considered for those with mild to moderate OI in the absence of vertebral compression fractures. [LOE II GOR B]</p> <p>Children should have a serum 25-hydroxy vitamin D level ≥50 nanomol/L before starting bisphosphonate, and neonates should have daily serum calcium level monitoring for 3 days after the first infusion.</p> <p>Severe hypercalcaemia:</p> <p>When hypercalcaemia is refractory to dietary manipulation and intravenous hydration, low-dose bisphosphonate can be considered (pamidronate at 0.25 mg/kg or zoledronate at 0.0125 mg/kg), with at least 48 hours between doses and serum calcium monitored closely for 72 hours. [LOE IV GOR C] However, higher doses of pamidronate (median of 1 mg/kg) have been used with good effect in infants and children with severe hypercalcaemia.² Hypocalcaemia is a risk with higher dosing.</p> <p>Generalised arterial calcification of infancy: Bisphosphonate therapy can be considered in severe cases of GACI. [LOE IV GOR D]</p>
<p>References</p>	<ol style="list-style-type: none"> 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. Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. <i>Journal of Paediatrics and Child Health</i>. 2018;54:223-33. 2. Demir K, Doneray H, Kara C, Atay Z, Cetinkaya S, Cayir A, Anik A, Eren E, Ucakturk A, Yilmaz GC, Ergur AT, Kendirci M, Aycan Z, Bereket A, Aydin M, Orbak Z, Ozkan B. Comparison of treatment regimens in management of severe hypercalcemia due to vitamin D intoxication in children. <i>JCRPE Journal of Clinical Research in Pediatric Endocrinology</i>. 2019;11:140-8.

3. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev.* 2016;10:CD005088.
4. Alcausin MB, Briody J, Pacey V, Ault J, McQuade M, Bridge C, Engelbert RH, Sillence DO, Munns CF. Intravenous pamidronate treatment in children with moderate-to-severe osteogenesis imperfecta started under three years of age. *Horm Res Paediatr.* 2013;79:333-40.
5. Shi CG, Zhang Y, Yuan W. Efficacy of Bisphosphonates on Bone Mineral Density and Fracture Rate in Patients With Osteogenesis Imperfecta: A Systematic Review and Meta-analysis. *Am J Ther.* 2016;23:e894-904.
6. Bishop N, Adami S, Ahmed SF, Anton J, Arundel P, Burren CP, Devogelaer JP, Hangartner T, Hosszu E, Lane JM, Lorenc R, Makitie O, Munns CF, Paredes A, Pavlov H, Plotkin H, Raggio CL, Reyes ML, Schoenau E, Semler O, Sillence DO, Steiner RD. Risedronate in children with osteogenesis imperfecta: A randomised, double-blind, placebo-controlled trial. *The Lancet.* 2013;382:1424-32.
7. Lin CH, Chien YH, Peng SF, Tsai WY, Tung YC, Lee CT, Chien CC, Hwu WL, Lee NC. Cyclic pamidronate infusion for neonatal-onset osteogenesis imperfecta. *Pediatr neonatol.* 2014;55:306-11.
8. Mayr B, Schnabel D, Do Rr HGN, Schoffl C. Gain and loss of function mutations of the calcium-sensing receptor and associated proteins: Current treatment concepts. *European Journal of Endocrinology.* 2016;174:R189-R208.
9. Charfi M, Amar SB, Hamad AB, Regaieg C, Bouroui A, Regaieg R, Hmida N, Thabet AB, Gargouri A. Neonatal subcutaneous fat necrosis a five cases study. *Arch Dis Child.* 2019;104 (Supplement 3):A402.
10. Bergstein KR, Jacobsen RB, Jacobsen BB, Christesen HT. [Efficient treatment of hypercalcaemia in neonatal subcutaneous fat necrosis]. *Ugeskr Laeger.* 2010;172:2096-7.
11. Alos N, Eugene D, Fillion M, Powell J, Kokta V, Chabot G. Pamidronate: Treatment for severe hypercalcemia in neonatal subcutaneous fat necrosis. *Horm Res.* 2006;65:289-94.
12. Khan N, Licata A, Rogers D. Intravenous bisphosphonate for hypercalcemia accompanying subcutaneous fat necrosis: a novel treatment approach. *Clin Pediatr (Phila).* 2001;40:217-9.
13. Kara C, Cetinkaya S, Gunduz S, Can Yilmaz G, Ayca Z, Aydin M. Efficacy and safety of pamidronate in children with vitamin D intoxication. *Pediatr Int.* 2016;58:562-8.
14. Adiyaman P, Ocal G, Berberoglu M, Evliyaoglu O, Ayca Z, Cetinkaya E. The clinical and radiological assessment of cyclic intravenous pamidronate administration in children with osteogenesis imperfecta. *Turk J Pediatr.* 2004;46:322-8.
15. Rutsch F, Boyer P, Nitschke Y, Ruf N, Lorenz-Depierieux B, Wittkamp T, Weissen-Plenz G, Fischer RJ, Mughal Z, Gregory JW, Davies JH, Loirat C, Strom TM, Schnabel D, Nurnberg P, Terkeltaub R. Hypophosphatemia, hyperphosphaturia, and bisphosphonate treatment are associated with survival beyond infancy in generalized arterial calcification of infancy. *Circulation.* 2008;Cardiovascular genetics. 1:133-40.
16. Akhtar Ali S, Ng C, Votava-Smith JK, Randolph LM, Pitukcheewanont P. Bisphosphonate therapy in an infant with generalized arterial calcification with an ABCC6 mutation. *Osteoporos Int.* 2018;29:2575-9.
17. Edouard T, Chabot G, Miro J, Buhas DC, Nitschke Y, Lapierre C, Rutsch F, Alos N. Efficacy and safety of 2-year etidronate treatment in a child with generalized arterial calcification of infancy. *Eur J Pediatr.* 2011;170:1585-90.
18. Ferreira CR, Ziegler SG, Gupta A, Groden C, Hsu KS, Gahl WA. Treatment of hypophosphatemic rickets in generalized arterial calcification of infancy (GACI) without worsening of vascular calcification. *American Journal of Medical Genetics, Part A.* 2016;170:1308-11.
19. Otero JE, Gottesman GS, McAlister WH, Mumm S, Madson KL, Kiffer-Moreira T, Sheen C, Millan JL, Ericson KL, Whyte MP. Severe skeletal toxicity from protracted etidronate therapy for generalized arterial calcification of infancy. *Journal of Bone and Mineral Research.* 2013;28:419-30.

VERSION/NUMBER	DATE
Original	14/05/2020
REVIEW (5 years)	14/05/2025

Authors Contribution

Original author/s	Dr Ansar Kunjunju, Dr Srinivas Bolisetty
Evidence Review	Assoc Prof David Osborn
Expert review	Dr Craig Munns, Dr Shihab Hameed, Dr Kristen Neville, Dr Jan Walker
Nursing Review	Ms Kirsty Minter, Ms Eszter Jozsa

Pharmacy Review	Mr Mohammed Irfan Azeem, Ms Michelle Jenkins, Ms Cindy Chen, Ms Carmen Burman
ANMF Group contributors	Dr Himanshu Popat, Dr Nilkant Phad, Ms Carmen Burman, Ms Thao Tran, Ms Chantelle Smith, Mr James Marceau, Ms Emily Do, Ms Wendy Huynh
Final editing and review of the original	Dr Srinivas Bolisetty, Assoc Prof David Osborn, Ms Wendy Huynh, Ms Thao Tran
Electronic version	Dr Ian Callander, Ms Cindy Chen
Facilitator	Dr Srinivas Bolisetty