Pamidronate
Newborn use only

2020

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 Imperfecta[1]:** Dose in neonates and infancy • 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	Aminoglycosides: May enhance the hypocalcaemic effect of bisphosphonates. Nonsteroidal anti-inflammatory agents: May enhance the adverse effect of bisphosphonates including risk of gastrointestinal ulceration and nephrotoxicity. Proton Pump Inhibitors: May reduce therapeutic effect of bisphosphonates. Angiogenesis inhibitors (systemic): May increase the adverse effect of bisphosphonates, particularly osteonecrosis of the jaw (not reported in children). Deferasirox: Bisphosphonate derivatives may enhance the adverse effect of deferasirox. Specifically, the risk for gastrointestinal ulceration/irritation or bleeding may be increased.
Adverse reactions	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. Hypocalcaemia and hypophosphatemia are common side effects following the first infusion. Hypocalcaemic seizures have been reported following treatment. Acute respiratory distress in infants with pre-existing respiratory problems. 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. 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. 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.
Compatibility	Fluids: Sodium chloride 0.9%, glucose 5%. Drugs: Consult the pharmacist for advice. It is recommended to administer as a separate infusion, separate from all other drugs.
Incompatibility	Fluids: Calcium containing solutions, e.g. Ringer's solution. Drugs: Calcium folinate, caspofungin.
Stability	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.
Storage	Store below 25°C.
Excipients	Mannitol, phosphoric acid, sodium hydroxide and water for injections. Phosphoric acid and sodium hydroxide are added to adjust pH.
Special comments	Ensure infants are adequately hydrated prior to administration. Pamidronate is not metabolised and is exclusively eliminated by renal excretion. Pamidronate is not recommended for patients with severe renal impairment. For infants with OI, measure vitamin D status prior to commencement of treatment. Ensure adequate vitamin D intake.
Evidence	Refer to full version.
Practice points	Australian Paediatric Endocrine Group consensus guidelines 2018[1]: **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] 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. **Severe hypercalcaemia:** 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.

	Generalised arterial calcification of infancy: Bisphosphonate therapy can be considered in severe cases of GACI. [LOE IV GOR D]
References	Refer to full version.

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