Trust Guideline for the Administration of Bisphosphonate Therapy Disodium Pamidronate or Zoledronic Acid in Children and Young People.

For Use in:	Jenny Lind Children's Department
By:	Named Registered Children's Nurses administering and Advanced Paediatric Endocrinology Nurse and Medical Staff prescribing Intravenous Bisphosphonates
For:	Children/young people with primary or secondary osteoporosis or osteogenesis imperfecta.
Division responsible for document:	Women and Children's Division
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Version and Document Control

Version No.	Date of Update	Change Description	Author
4	March 2021	Amended to include Bisphosphonate passport	Karen Blair

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Objective

- To ensure the safe prescribing, administration and monitoring of intravenous bisphosphonate therapy to children and young people by medical staff, and Advanced Paediatric Endocrinology Nurse.
- To ensure the Named Registered Nurse can safely request and take - pre-infusion bloods and administer as per the patient's Consultant instructions.

Rational

Intravenous bisphosphonates (e.g. disodium pamidronate and zoledronic acid) have been used in children/young people with osteoporosis for over 20 years. They act on osteoclast cells in bone to inhibit bone resorption and thereby increase bone density. Their use is also associated with a temporary drop in serum calcium concentrations

Bisphosphonates are not licensed for use in children/young people but are used in the management of severe forms of osteogenesis imperfecta and other causes of osteoporosis in children/young people to reduce the number of fractures (BNFC 2020). The long-term effect of bisphosphonates in children/young people has not been established. Single doses of bisphosphonates are also used to manage hypercalcaemia. Bisphosphonate therapy should only be used under the direction of a paediatrician experienced in treating children/young people with bone diseases.

Most evidence regarding intravenous bisphosphonate therapy in children/young people comes from disodium pamidronate, which is given as a 2 hour infusion on 2 consecutive days, 3-monthly (8 days/year). More recently, several studies (Bowden and Mahan 2017) have demonstrated that zoledronic acid; a more potent third generation bisphosphonate can be used safely and effectively in childhood osteoporosis. The available evidence suggests no difference in the desired treatment effect, or side effects between disodium pamidronate and zoledronic acid (see Intravenous Bisphosphonates Frequently Asked Questions , Trustdocs is 17818.

Zoledronic acid offers the advantage that it can be given as a single intravenous infusion over a shorter duration of 30-45 minutes, with a longer 3-6 months interval between infusions. Zoledronic acid is therefore our preferred bisphosphonate for children/young people over 2 years, especially for children/young people with osteoporosis due to an underlying chronic disease (like cerebral palsy or cancer), or patients with needle phobia to reduce their overall time spent in hospital.

Indications for use

- Primary structural defects in type I collagen and other structural bone proteins (e.g. osteogenesis imperfecta).
- Fibrous dysplasia of bone (e.g. McCune-Albright syndrome).

- Bone abnormalities resulting from systemic disease or the effects of systemic treatment (e.g. steroid treatment of chronic disease or immobilisation).
- Bone matrix abnormalities (e.g. osteoporosis pseudoglioma syndrome).
- Conditions with a primary defect in bone mineralization (e.g. idiopathic juvenile osteoporosis).
- Malignancy associated hypercalcaemia.
- Reflex Sympathetic Dystrophy (or Localised Idiopathic Pain Syndrome).
- Chronic non-bacterial osteitis (CNO)/Chronic Recurrent Multifocal osteomyelitis (CRMO)

Relative contraindications

- Recent fracture/surgery. Bisphosphonates have been associated with poor healing after osteotomy. If an osteotomy has been performed then bisphosphonates should be withheld for 3-4 months and/or good callus formation or healing demonstrated before next administration. After fractures, treatment can be given if there is good callus formation.
- Hypocalcaemia (serum calcium <2.1 mmol/L)
- Untreated vitamin D deficiency (25(OH) vitamin D <50nmol/L)
- Caution should be exercised with renal impairment, and doses adjusted
- Pregnancy (absolute contraindication).
- Acute illness and fever
- Hypersensitivity to bisphosphonates (or any of excipients).
- Ocular symptoms (uveitis or scleritis)

Treatment Considerations

- Decision to start bisphosphonate therapy will be taken by the patient's lead consultant after counselling of patient and parents. Appropriate information should be provided to the family and patient and decisions documented in the Patient Health Care Records
- The choice of bisphosphonate therapy will be determined by the patient's lead consultant.
- Sexually active teenage girls must use contraception while undergoing active treatment, and for 6 months after treatment cessation, as the risks to unborn children/young people are unknown.

Drug Interactions

- Avoid concurrent use with other bisphosphonates.

Arrangements prior to treatment

Prior to and within 3 months of the first cycle of treatment, **serum calcium, phosphate, urea, creatinine, alkaline phosphatase, 25(OH) vitamin D and parathyroid hormone (PTH)** need to be measured. Serum 25(OH) vitamin D should have been demonstrated to be ≥50nmol/L before the infusion is commenced. Otherwise there should be a plan to treat with vitamin D that has been agreed with one of the consultants.

Dental Health

Responsible consultant will assess need for dental examination prior to treatment and refer to a dentist if a child/young person has known significant dental or gingival disease. Bisphosphonates have been associated with osteonecrosis of the jaw in the adult population, and although this has not been reported in children/young people we ask that the family let their dentist know they are on this medication and they visit a dentist preferably six monthly.

Bone Density Scan

It is usually appropriate to monitor bone mineral density by DEXA scanning in children over 5 years. A baseline DEXA scan should normally be performed prior to initiation of therapy, and then after 12 months, to verify that treatment is effective. Thereafter, the scans may be reduced to 2-3 yearly. The patient's Consultant orders the DEXA scan.

On admission

Infusions are administered on an outpatient basis on children's day ward.

Complete checklist/bisphosphonate treatment passport Trustdocs D 18468 prior to receiving bisphosphonate infusion

Confirm;

- The child/young person does not currently have an infection or fever >38^{o}C
- The child/young person is not currently receiving treatment for an infection
- The child/young person is not allergic to disodium pamidronate/zoledronic acid
- First 2 Infusions-The child/young person has had their renal function blood levels taken within the last week and these have been filed as normal.
- 3rd Infusion onwards-normal renal function documented within the last 6 months.

- Serum 25 (OH) Vitamin D >50 nmol/L
- The child/young person has not had any recent fractures.
- If female the young person is not pregnant
- Current medication documented
- Based on above and general appearance of the child/young person, no concerns noted
- Height, weight and baseline observations BP, HR, RR and Temperature recorded

Investigations

Renal function must be checked before each bisphosphonate infusion. (Baronecelli 2014, Bhatt 2014, George 2015)

For the first two infusions satisfactory renal function results must be obtained within the last week or immediately prior to the commencement of the infusion. If renal function is abnormal, or the most recent 25(OH) Vitamin D is <25nmol/L, you must contact the endocrine team for further advice.

Subsequent infusions of those patients with no known renal compromise may be given as long as satisfactory renal blood results have been obtained within the past 6 months.

Pre-infusion blood tests

The following blood tests should be done prior to the bisphosphonate infusion:

- Full Blood Count (FBC)
- Urea & electrolytes
- Liver function tests
- Bone profile (Calcium, phosphate and alkaline phosphatase)
- Magnesium
- Parathyroid hormone
- CTX and P1NP
- 25-hydroxy-Vitamin D (annually).

For patients on steroid therapy:

- Random glucose, HbA1c.
- Other blood tests as clinically indicated.

- In patients with vitamin D deficiency, an abrupt fall in serum calcium may occur after the infusion. If the patient has any unusual neuromuscular symptoms, particularly after the first infusion, then the calcium should be checked.

Monitoring/Observations

- Height and weight.
- Heart rate, respiratory rate and temperature before and after infusion.
- Baseline PEWS/CEWS and blood pressure, with follow-up observations as clinically indicated.

Ensure good fluid intake and provide a prescription for calcium to be taken with first cycle.

Fluids

In terms of general oral fluid intake, children/young people should be encouraged to drink their daily recommended level of fluid before and 24 hours after their infusion.

Suggested oral fluid intake for child/young person's weight:

Up to 10kg =100mL/kg/day. 10kg to 15kg= 1250mL/day.

15kg to 20kg= 1500mL/day Over 20kg =2000mL/day

Calcium Prescription

All children/young people should receive a prescription for oral calcium supplements for one week after their first infusion. For subsequent infusions consider regular calcium and vitamin D for 7 days if hypocalcaemia with previous bisphosphonate infusions. Treat vitamin deficiency while ensuring that calcium intake is adequate and for those with poor nutritional state suggestive of suboptimal dietary calcium consider supplementary calcium.

The doses of oral calcium supplementation for calcium deficiency in the BNFc are a useful guide:

Age	Oral Calcium Dose
2 to 4 years	0.25mmol/kg (10mg/kg) four times daily
5 to 12 years	0.2mmol/kg (8mg/kg) four times daily
12 to 18 years	10mmol (400mg) four times daily

The following preparations are suitable:

- Cacit 500mg (12.5mmol) effervescent tablets.
- Adcal 1500mg (15mmol) chewable tablets.

Children/young people should be encouraged to drink milk and to consume calcium-rich foods (e.g. dairy produce such as cheese and yoghurt) for at least a week following the infusion.

Vitamin D

Indication	Medication	Replenishment Dose	Duration
Vitamin D deficiency (25-hydroxyvitamin D <50nmol/L)	Colecalciferol 20000iu capsules Colecalciferol 800 iu capsules Colecalciferol 3000 units in 1mL syrup	**Age 1–5 months:** 3,000 international units **once daily for 8 weeks** **Age 6 months–11 years:** 6,000 IU for 8 weeks **Age 12–18 years:** 10,000 IU for 8 weeks	After the initial high dose phase the dose would then be dropped back to a prophylactic dose as per BNFc

First admission

Prescribe Ibuprofen and paracetamol to be given regularly during the admission, to try and ameliorate the acute phase reaction they will otherwise almost inevitably suffer.

Caution

In female patients with childbearing potential it is important to ask whether there is any chance of them being pregnant. This should be clearly documented by the prescriber. If there is any doubt or suspicion then complete a pregnancy test and, if positive, withhold treatment and inform the consultant.

Prescription of Zoledronic acid

Zoledronic acid is dissolved in 0.9% sodium chloride.

The first infusion should be at HALF dose. Full dose should be administered from the 2nd infusion onwards for the next two years. Thereafter, treatment doses vary, based on their condition. Decisions to reduce doses will have been made by endocrine-bone team and documented in most current e-TCI:

Dosage schedule is **0.025-0.05mg/kg/day** (dependent on the age of the child/young person) for 30-45min by IV infusion.

Dosage Table

Age	Dosage*	Frequency
<2 years	0.025 mg/kg	3 months
2-5 years	0.035 mg/kg	4 months
>5 years	0.05 mg/kg	6 months

*The maximum *total dose of Zoledronic acid* is not to exceed 2.0mg for any patient < 5 years and 4mg for patients aged between 5 - 17 years

Preparation of Intravenous Zoledronic Acid – Zometa Brand

mg of zoledronic acid to be infused, based on patient weight and age	Add to sodium chloride 0.9% in a volume of	Duration of Infusion
0.025mg/kg/dose	50mLs sodium chloride 0.9%	45 minutes
0.035mg/kg/dose	100mLs sodium chloride 0.9%	45 minutes
0.05mg/kg/dose	100mLs of sodium chloride 0.9%	30 minutes

The Consultant will make a decision regarding:

A. **Diffuse Osteoporosis** secondary to Cerebral Palsy, Retts and similar central neurological conditions (not primary muscle disorders):

They should have 2 years of full dose every 6 months. (year 1 and 2 of treatment)
Then: 1 year of half dose (1/2) every 6 months. (year 3 of treatment)
Then: one quarter (1/4) of the dose every 6 months. (after 3 years of treatment)

If their BMAD (height adjusted BMD) is >+2 SDS, they should change to ¼ of the dose every 12 months. This will be stated in the latest consultant letter.

B. **Primary bone fragility** such as Osteogenesis Imperfecta – **Primary muscle disorders** such as DMD, or **CMD- Haematological disorders** such as Sickle Cell Anaemia:

They should have full dose every 6 months until their BMAD is more than 0 SDS.

If their BMAD is >0 SDS, give half (1/2) dose of Zoledronic acid every 6 months.

If their BMAD is >+2 SDS, give one quarter (1/4) dose of Zoledronic acid every 12 months.

C. **Conditions where the underlying condition may be controlled or treated** such as ALL- Inflammatory bowel disease- renal transplant:

If commenced, they should have full dose every 6 months, but the duration of treatment will be individualised based on the continuation of steroid treatment, their BMD, pubertal status and their underlying condition.

Prescription of Disodium Pamidronate

A. Primary bone fragility such as Osteogenesis Imperfecta

First Treatment Cycle

1. Dosage schedule is **0.75 – 1.5 mg/kg/day** (dependent on the age of the child/young person) for two consecutive days by IV infusion over 2 hours. Dilute in sodium chloride 0.9% (concentration not to exceed 60 mg in 250 mLs, maximum dose 90mg). There will be deviations for patients with impaired renal function; in these cases contact the Endocrine Consultant for advice.

2. Please ensure the cannula is flushed in accordance with current IV policy. The 2nd infusion may be started 20 hours after the start of the 1st infusion.
3. For the first treatment course, the duration of infusion should be 4 hours, but thereafter may be reduced to 2-4 hours.
4. After the infusion is complete, administer a 30mL flush over 5-10 minutes.
5. Treatment is repeated every three months, for the first year of therapy, but may be reduced thereafter, depending on clinical response.

Administration

Disodium pamidronate is available in 30mg, 60mg or 90mg vials, some brands are supplied as a dry powder others as a concentrate solution. Dry powder forms of disodium pamidronate need to be initially reconstituted with water for injection as per package instruction. Both forms must be further diluted with sodium chloride 0.9% as per table 1 below. The concentration of disodium pamidronate in the final IV solution should be no greater than 12 mg /100 mL

Table 1

Preparation of Intravenous Disodium Pamidronate:

mg of disodium pamidronate to be infused in one day (mg/day) based on patient weight.	Amount of sodium chloride 0.9%to add to obtain a total infusion volume of:	Rate-FIRST INFUSION (mL/hour)	Infusion rate over 2 Hrs (mL/hour)
0 to 5	50 mL	12.5	25
5.1 to 15	100 mL	25	50
15.1 to 60	250 mL	63	125
60.1 to 90	500 mL	125	250

90mg is the maximum dose to be prescribed regardless of a weight in excess of 60kg

Disodium Pamidronate Infusions:

Dosage Table:

Age	Dosage	Frequency
<2.0 years	0.75 mg/kg/day for 2 days	2 months
2.1-3.0 years	1.125 mg/kg/day for 2 days	3 months
>3.1 years	1.5 mg/kg/day for 2 days	3 months

90mg is the maximum dose to be prescribed regardless of a weight in excess of 60kg

The Consultant will make a decision:

B. Hypercalcaemia

1. Persistent serum calcium >3mmol/L may require bisphosphonate treatment.

2. The first dose must be given as an inpatient.

3. If not previously done send bloods for bone profile including 25(OH) vitamin D and parathyroid hormone. Other bloods as advised by endocrinologist.

4. Dosage according to OI above, but only **single day infusion** over 4 hours. No need to half the first dose.

5. Re-test plasma calcium daily. Consider second dose not earlier than 3 days after the first infusion, as advised by endocrinologist.

After Treatment

Patients may be discharged after infusion if afebrile and not vomiting. If the patient becomes unwell in the following days they should seek medical attention and inform the paediatric endocrine team. Ensure follow-up arrangements are in place with the relevant clinician. Arrange the subsequent bisphosphonate infusion, as specified by the referring consultant. bisphosphonate treatment passport Trustdocs D 18468.

Adverse Effects

Bisphosphonates are generally well tolerated in children/young people. Adverse effects generally dose dependent (Hospach 2010, Mietteunen et al. 2009). The risk is slightly higher with the first infusion and those who are bisphosphonate naïve (George et al 2015).

1. Restate the warning to the parents that shortly after or within a few days of the first cycle of zoledronic acid the child/young person may get flu-like side effects lasting around 48 hours. (Intravenous Bisphosphonates Frequently Asked Questions Trustdocs ID 17818 These often settle with paracetamol and/or ibuprofen and do not usually recur on subsequent infusions. This is far less likely to occur in children/young people who have previously received other intravenous bisphosphonates, such as disodium pamidronate (Ward et al 2009). Exclude other causes of fever in immunosuppressed patients.
2. Injection site reactions have been documented at a rate of 6% with a 2 hour infusion time (Body 2001).
3. In neonates, the acute phase reaction may include respiratory distress if there is pre-existing respiratory difficulty. Management is with appropriate supportive care.
4. Transient hypocalcaemia, hypophosphataemia and hyperparathyroidism have been reported following treatment, but is rarely symptomatic. Risk can be reduced by ensuring adequate calcium intake and ensuring vitamin D levels are normal (Ward et al 2009).
5. All intravenous bisphosphonates have the potential to cause acute tubular necrosis, the dose, frequency and speed of infusion being important determinants (Diel et al 2007).
6. Adverse effects reported in adult use of bisphosphonates including uveitis, thrombocytopenia, avascular necrosis of the jaw, oesophageal or oral ulceration are rare in children and adolescents (Bachrach 2007).
7. There is an associated risk of delayed tooth eruption when using zoledronic acid over a prolonged period.

Clinical audit standards

To ensure that this document is compliant with the above standards, the following monitoring processes will be undertaken.
Yearly audit of 4 randomly selected case notes and compliance with:

- Use of routine vitamin D supplementation
- Appropriate laboratory monitoring
- Clinical effectiveness, determined by DEXA
- Administration as per this clinical guideline.
- Bisphosphonate treatment passport completed. Trustdocs D 18468

The audit results will be shared with colleagues in the Jenny Lind Children's Department, including formal presentation at departmental governance meetings to review the results and make recommendations for further action.

Summary of Development

The authors listed above drafted this document on behalf of Jenny Lind Children's Department Endocrinology and Rheumatology Teams who have agreed the final content. During its development it has been circulated for comment to:

Ravi Alanoor Consultant Paediatrician Endocrinology
Kate Armon Consultant Paediatrician Rheumatology
Peter Bale Consultant Paediatrician-Comments received and accepted to add as indication for treatment Chronic non-bacterial osteitis (CNO)/Chronic Recurrent Multifocal osteomyelitis (CRMO)
Vipan Datta Consultant Paediatrician Endocrinology
Rosalind Howe Clinical Pharmacist-Comments received and accepted changes to consistency of terminology of drugs. Changes made to reflect availability of oral calcium preparation in NNUH pharmacy.
Ellada Sotirodou Consultant Paediatrician
Kit Tranter Lead Paediatric Rheumatology Nurse Specialist-comments received and accepted to add CRMO as indication for treatment.

Children's Day Ward Team;
(Hayley Ayers, Karen Berry, Katherine Edgeley, Eleanor Goodale)-Comments received and 'patient clerking' changed to completion of checklist prior to Bisphosphonate infusion.

This version has been endorsed by the Professional Protocols, Policies and Guidelines Committee and clinical Guidelines Assessment Panel.

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Associated Documentation

Trust Docs Standard Operating Procedure for referral and admissions to Children's Day Ward 'Checklist prior to receiving Bisphosphonate infusion.' Trustdocs Id 14056

Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw*: Dental Clinical Guidance*, Scottish Dental Clinical Effectiveness Programme March 2017 https://www.sdcep.org.uk/wp-content/uploads/2017/04/SDCEP-Oral-Health-Management-of-Patients-at-Risk-of-MRONJ-Guidance-full.pdf accessed 19/8/20

For further information on potential side effects, see information leaflet for families; **'Intravenous Bisphosphonate Therapy, Frequently asked questions.' British Paediatric and Adolescent Bone Group. 1st Jan 2020** available Trustdocs Id 17818