INDICATIONS
The treatment of patients with Mucolipidosis with Cyclic Intravenous Pamidronate is experimental and being investigated as part of an international collaborative study. Before patients are commenced on therapy the benefits should be weighed up against the known and potential side-effects of therapy. Therapy could be considered in

Patients with Mucolipidosis type III encompassing attenuated forms of Mucolipidosis. Patients in whom:

i. There is clinical and radiographic evidence of progressive osteodystrophy

ii. Documented osteopenia

iii. At any stage of the disorder recognising that the potential for prevention is greater than the possibility of reversing destructive joint problems

Patients with Mucolipidosis type II

i. After resolution of the secondary neonatal hyperparathyroidism (usually after 3 months of age)

ii. In whom there is progressive osteodystrophy

iii. In whom a suitable intravenous Port can be established

REFERRAL
Patients requiring evaluation for Pamidronate therapy are referred to the Connective Tissue Dysplasia or Genetic Metabolic clinic for assessment. The Geneticist then will involve the Bisphosphonate Treatment Program (BTP) coordinator who will arrange bone densitometry by Dual Energy X-ray Absorbtioometry (DXA), baseline medical imaging including specific skeletal X-rays and renal ultrasound and biochemistry before commencing the BTP.
RATIONALE
Bisphosphonates are chemicals that substitute for the naturally occurring compound of bone, Pyrophosphate. Bisphosphonates are potent inhibitors of osteoclastic bone resorption.

When Bisphosphonates are used, their desired response is to decrease osteoclastic activity by decreasing bone resorption, thus allowing an increase of normal bone mass and balance to occur.

The bisphosphonate being trialled in patients with Mucolipidosis is called Disodium Pamidronate. (Pamisol/Aredia).

In Mucolipidoses the bisphosphonate Pamidronate appears to have a novel metabolic effect which results in decreased bone pain, increased mobility and reversal of some ML joint and bone problems. Therapy is continued for at least 12 months and reviewed every 6 months thereafter.

CONTRAINDICATIONS
i. Pregnancy is contraindicated whilst receiving Bisphosphonate Therapy and for several years following cessation of BTP.

ii. If hypocalcaemia is present then the use of Pamidronate is contraindicated.

ADVERSE REACTIONS
i. “Flu like” symptoms eg fever, nausea, vomiting ,headache and body aches and pains usually occur following the 1st infusion, within 12-24 hours and subside within 48 hours. With subsequent infusions these symptoms do not usually occur but if they do, it is to a lesser degree.

ii. Hypocalcaemia is commonly observed following the 1st infusion of Pamidronate. Treatment of hypocalcaemia is recommended if Ca is < 1.9mmol/L or the patient is symptomatic. (See entry under post infusion for management of hypocalcaemia).

iii. Acute breathing problems (rare)

iv. Irritation of the eyes – usually only after the first few infusions

PREPARATION
No fasting required.
PRIOR TO FIRST INFUSION
The BTP coordinator will arrange for the patient to have several endocrine and biochemistry values to be collected in pathology, eg, Urea, electrolytes and Creatinine, Ca, Mg, PO4, SAP, VIT D, osteocalcin and Hb. These are repeated at intervals throughout the BTP. (see flowchart).

The patient has to provide the second urine specimen of the day for deoxypridoline cross links. The specimen needs to be wrapped in foil, as it is light sensitive and then sent to the testing lab via pathology dept. If this is not possible then the specimen can be frozen in the ward freezer, and then sent to pathology at the next convenient opportunity. The specimen is best collected at home several days before the infusion and frozen and brought frozen on the day of the hospital visit.

These urine collections are repeated at several intervals throughout the BTP, see flowchart.

AUXOLOGY
The BTP coordinator will do several measurements on the patient, eg height, weight, head circumference and span at commencement on the BTP and at 6/12 intervals.

BONE DENSITOMETRY
A total body DEXA scan (bone density) is performed before the BTP is commenced and at 6/12 reviews for 2 years and then annually whilst on the program. Once the BTP has been completed the DEXA scan will be performed either 6/12 or 12/12 at the discretion of the treating doctor.

MEDICAL IMAGING
A baseline renal ultrasound is performed before commencing the BTP to exclude any abnormalities. The ultrasound is repeated at 12 month intervals to exclude nephrocalcinosis. Further renal ultrasounds may be warranted if treatment is ongoing and/or abnormalities are present.

A bone age and thoracolumbar spinal Xray are performed annually.

FORMULATION
Pamidronate is available in 15mg, 30mg and 60mg ampoules.
DOSE
The dose is given as 1mg/kg usually monthly. The infusion is diluted in a concentration of 10mg/100mls of Normal Saline, eg. 30mg in 300mls of N/S.
The infusion is given over a minimum period of at least 2-4 hours.
- Up to 30mg over 2hours.
- Up to 45mg over 2-3 hours.
- Up to 60mg over 3-4 hours.

POST INFUSION
Ca, Mg, PO4, SAP and UEC’s are collected 24 - 48 hours following the first infusion. No further levels are required as it is apparent the Ca level does not decrease with subsequent infusions.

The patient also needs several urine specimens collected for Deoxypridinoline cross link measurement which is performed weekly for one month following the first Pamidronate infusion.
The BTP coordinator will provide yellow topped urine containers. 25-50mls is to be collected; the specimen should be wrapped in foil, as it is light sensitive, and sent to the Endocrine laboratory via the Pathology dept. If this is not possible the specimen can be frozen in the ward freezer and sent to pathology at a more convenient time.

MEDICATIONS
Ibuprofen (Nurofen) 10mg/kg per dose in 3 times daily for 3 days or Paracetamol (Panadol) 15-30mg/kg in 6 divided doses for 3 days should be given as ordered to relieve any side effects.

OBSERVATION WHILST IN HOSPITAL
The patient will be admitted to a general ward for approximately 2 days to have their infusion. TPR should be recorded 4/24 following infusion until the patient is febrile then continued 2/24 until afebrile.

The patient will be discharged if the Ca level is within normal limits 24 hours after the first infusion.
FOLLOW UP.

Each patient will be reviewed by the Genetics/Metabolic team, at 6/12 intervals whilst on the pamidronate infusions and then 6/12 after ceasing treatment for a year then annually until discharged or transferred to follow up in an adult hospital.
### INVESTIGATIONS PERFORMED DURING PAMIDRONATE THERAPY

<table>
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<tr>
<th>Stage</th>
<th>-12 &amp; -6 mths</th>
<th>Pre-infusion</th>
<th>12 hr</th>
<th>7 days</th>
<th>6 mths</th>
<th>9 mths</th>
<th>12 mths</th>
<th>15 mths</th>
<th>18 mths</th>
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