Clinical Consent for Pamidronate Therapy

Introduction: Your child is to start treatment with a medicine called pamidronate. We want you to be aware of possible side effects of pamidronate treatment. Although these side effects are rare, we feel you should be aware of them.

Pamidronate is medication belonging to the class of drugs called bisphosphonates or diphosphonates. These drugs are believed to reduce bone loss. Bisphosphonates appear to increase bone strength and reduce the risk of fractures in adults, but there is less experience with pamidronate in children. Pamidronate has mostly been studied in children with a disease called osteogenesis imperfecta, a genetic disorder leading to "brittle bones". Data from these studies indicate that the number of fractures is reduced in those receiving pamidronate. Pamidronate has also been shown to reduce fractures in other conditions as well.

If you consent for pamidronate therapy, your child will receive pamidronate by intravenous infusion (a small needle in a vein), administered over several hours as an outpatient in our Short Stay Unit. The total yearly dose of the medicine is approximately 4 milligrams per kilogram of body weight (to a maximum of 120 milligrams per year). In children younger than age 3, the infusions are given every 8 weeks. For children over age 3, the infusions are given every 3 months. For patients younger than 2 years or those with a history of breathing problems, we provide the first dose of pamidronate in the hospital over a two day stay. This is to observe for possible breathing problems as described below under the section on risks. We will decide on the length of treatment as we see how bone strength changes during therapy and will stop if your child has any serious side effects. A typical course of treatment is 3 years on the schedule described above followed by a maintenance dosing of treatments given every 6 months. You have the option to discontinue treatment at any time.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with pamidronate. These deserve careful thought. You should talk with the doctor if you have any questions. Below you will find a list of the side effects that have been described in adults using pamidronate. Experience in children has shown some, but not all, of the reactions listed below:

General

- Nearly 40%-60% of people develop **"flu-like"** symptoms beginning a few hours after the first infusion, including muscle aches, fatigue, fever, nausea or weakness. These symptoms usually last up to 48 hours, and often do not happen again with later doses of pamidronate.
- A smaller number of adults complain of **bone pain** after pamidronate.
- About 1 out of 100 patients complain of a **rash**.

Blood and blood vessels

- A small percentage of adults using pamidronate have a **lower-than-normal white blood cell count**, (the cells used for fighting infection). The white blood cells return to normal after stopping the medication.
- 1 in 5 patients treated with high dose pamidronate has **redness, swelling and pain** during treatment **around the skin site** where the needle is placed in the vein.

Central nervous system

- **Seizures** (convulsions) occurred in 4 people during US trials, 2 of whom had seizures before receiving pamidronate.

Metabolic

- A **low level of calcium** may develop in 1 in 20 patients treated with pamidronate. It usually causes no problems, but on rare occasion needs treatment with calcium supplementation.
- **Low potassium, magnesium and phosphate** have been noted, but have not required therapy.

Optic/Eye

- **Redness, irritation, excessive tearing and blurred vision** were reported in 23 out of 50,000 people. These symptoms were seen in the first 2 days in most of the patients and resolved with directed therapy, or with observation alone.

Bone

- In a recent report from another medical center, **delayed healing of bone after insertion of metal rods into bone** was found to occur 2-3 times more commonly in children with osteogenesis imperfecta treated with pamidronate than in similar patients who had not received pamidronate therapy. The dose of pamidronate associated with delayed healing was more than twice the dose your child would receive. No problem of delayed bone healing has been reported with the lower dose your child would receive.
- In another report, a total of 63 cases of avascular necrosis of the jaw (damage to the jaw bone because of poor blood supply) were found in older adults who had received pamidronate or medicines that are like pamidronate (drugs called bisphosphonates). All of the patients were elderly and most had been treated for some type of cancer. Since many thousands of adults have received bisphosphonates, the jaw problem is a very rare occurrence and may or may not be due to the bisphosphonates. This condition has never been observed in any children treated with bisphosphonates. In fact, some physicians have used bisphosphonates to treat avascular necrosis in other parts of the body in children.
- There have been rare reports of atypical fractures of the femur (a break in the long upper leg bone) in adult patients who received bisphosphonate drugs (which includes the drug pamidronate). These occurred only in patients who had received bisphosphonates for a long time and 25% had also received glucocorticoid drugs

that can weaken bone. The risk of this complication for adults is 1 fracture per 1000 patients who are treated for at least two years with these drugs. However, it is estimated that 15 fractures from osteoporosis are prevented for each 1 fracture that might occur as a complication. This type of leg fracture has not been reported in children receiving pamidronate.

Respiratory/Lungs – In Children < Age 2

- Four of 59 infants (under age 2) in one series developed difficult breathing (respiratory distress) within 1-2 days after receiving their first pamidronate treatment cycle. All of these children who became ill after the pamidronate had a history of some periods of breathing problems before they ever received the medication. All recovered from the breathing problems in hospital and the problems did not recur with later pamidronate treatment cycles. Because of this report, we admit patients under age 2 to receive their first pamidronate treatment over two days in the hospital to observe for breathing problems.

Risks of Blood Draws

- To watch for side effects such as low calcium or blood counts, blood will be drawn at various times when children are receiving pamidronate. There is a risk of bruising, bleeding or infection, along with fainting when blood is drawn.

Although most of the risks stated above are infrequent and/or resolve spontaneously, we will be monitoring your child for the duration of the time that they are receiving the medication. In addition to these risks, the pamidronate treatment could involve risks that are currently unforeseeable. Every precaution consistent with the best medical care will be taken with regard to treatment with pamidronate. Although pamidronate has been used for many children with bone fragility, the FDA has not approved its use in pediatrics.

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Signature of Parent or Legally Authorized Representative Date

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this treatment, risks and benefits, or alternative courses of treatment, you should ask your doctors in the Division of Pediatric Endocrinology at 650-723-5791.

STUDY