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Protocol for Mucopolysaccharidosis type IVA (MPS IVA) Patients Started on VIMIZIM® (elosulfase alfa)

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Background:

Definition: Mucopolysaccharidosis type IVA (MPS IVA) or Morquio A Syndrome is a rare, autosomal recessive lysosomal storage disease associated with skeletal and joint abnormalities and significant non-skeletal manifestations including respiratory disease, spinal cord compression, cardiac disease, impaired vision, hearing loss, and dental problems.[1-4]

Causes: It is caused by deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS) due to a mutation in *GALNS* gene.[1-4]

Clinical features: The phenotype is heterogeneous that ranges from a severe and rapidly progressive early-onset form to a slowly progressive later-onset form. Patients have no unique clinical findings at birth. The severe form is usually apparent between ages 1-3 years, Initial manifestation mainly skeletal abnormalities including: kyphoscoliosis, knock-knee (genu valgum), and pectus carinatum; the slowly progressive form may not become evident until late childhood or adolescence often first manifesting as hip problems (pain, stiffness, and Legg Perthes disease). Progressive bone and joint involvement leads to short stature, and pain and arthritis that become disabling. Involvement of other organ systems can lead to significant morbidity, including respiratory compromise, obstructive sleep apnea, valvular heart disease, hearing impairment, visual impairment from corneal clouding, dental abnormalities, and hepatomegaly. Compression of the spinal cord is a common complication that results in neurologic injury. Children with MPS IVA have normal intellectual abilities at the onset of the disease.[1-4]

Diagnosis:

Usually by findings of high keratan sulfate in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dry blood spot or white blood cell and DNA molecular testing of *GALNS* gene. [1-4]

Treatment: includes symptom-based interventions, enzyme replacement therapy with VIMIZIM® (elosulfase alfa) and hematopoietic stem cell transplantation (particularly very young, severely affected patients). [1-4]

Purpose: The purpose of this policy is to dictate the management of patients with Mucopolysaccharidosis type IVA (MPS IVA) who are eligible for enzyme replacement therapy.

Baseline assessments and investigations prior to initiation of enzyme replacement therapy (ERT):[4]

- General examination: Height, Weight, Head circumference
- Vital signs: Blood pressure, Heart rate, respiratory rate and temprature
- Enzyme activity level
- DNA molecular testing for *GALNS* gene
- IgG antibody test
- CBC, diff
- Chem1
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Standardized upper extremity function test (eg. Mallet test see appendix 1)
- Endurance measured by Timed 25-Foot Walking (T25W) or 6 minute walking test(This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes).
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing (developmental quotient (DQ) or intelligence quotient (IQ)
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation(visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey (hips/pelvis: AP pelvis radiograph, Lower extremities: standing AP radiographs and spine X-ray)
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.

Enzyme replacement therapy(ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1mg/kg) IV; _____ (mg) IV.

➢ Vimizim® (Elosulfase alfa)[5-7]

- **Dose:** 2mg/kg IV once weekly.
- **Strength:** 5-mL(5mg/5ml) , single-use vials.
  Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example if the patient Weight 4 kg give 10mg instead of 8mg.
- **Weight:** _____(kg): **calculated dose** _____(mg) IV.
- **Dilution :**
  - For patients < 25 kg – dilute in 100 mL normal saline
  - For patients ≥25 kg – dilute in 250 mL normal saline

Administration of VIMIZIM® should be completed within 48 hours of dilution.

Special Precautions:

- **Stable only in Normal Saline.**
- The diluted Vimizim® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion rate:[5,6]

For less than 25 kg:

- 3 mL/hour for 15 minutes
- 6 mL/hour for 15 minutes
- 12 mL/hour for 15 minutes
- 18 mL/hour for 15 minutes
- 24 mL/hour for 15 minutes
- 30ml/hour for 15 minutes
- 36ml/hour for remainder of infusion (minimum of 3.5 hours)
-

For equal or more than 25 kg:

- 6 mL/hour for 15 minutes
- 12 mL/hour for 15 minutes
- 24 mL/hour for 15 minutes
- 36 mL/hour for 15 minutes
- 48 mL/hour for 15 minutes
- 60ml/hour for 15 minutes
- 72ml/hour for remainder of infusion (minimum of 4.5 hours)

The total volume of the administration should be delivered in approximately 3.5-4.5 hours.

Nurses: Monitor vital signs during (prior to each rate increase) and up to 1 hour following infusion. If abnormal, contact the physician to decrease the rate or temporarily hold the VIMIZIM® infusion.

Undesirable effects: anaphylaxis and allergic reactions, infusion reactions, and immune mediated reactions, headache, nausea, vomiting, abdominal pain, fever, chills and fatigue.

Note:

- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Vimizim® and initiate appropriate medical treatment.
- If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

Immunogenicity:[5]

As with all therapeutic proteins, there is potential for immunogenicity. All patients treated with VIMIZIM® 2 mg/kg once per week in the placebo-controlled trial developed anti-drug antibodies by Week 4. Anti-drug antibody titers were sustained or increased for the duration of VIMIZIM® treatment. Because all patients developed anti-drug antibodies, associations between antibody titers and reductions in treatment effect or the occurrence of anaphylaxis or other hypersensitivity reactions could not be determined.
All patients treated with VIMIZIM® 2 mg/kg once per week tested positive for neutralizing antibodies capable of inhibiting the drug from binding to the mannose-6-phosphate receptor at least once during the

trial. Binding to this receptor is required for VIMIZIM® to be taken into cells where it is active. Neutralizing antibody titers were not determined in the patients. Therefore, the possibility of an association between neutralizing antibody titer and treatment effect cannot be assessed.
Assessment of the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VIMIZIM® with the incidence of antibodies to other products may be misleading.

Monitoring the response to enzyme replacement therapy:[4]

Assessment	Frequency
General	
Medical history Physical examination General appearance Neurological examination	Every visit
Lab test	
CBC, diff Electrolytes Liver enzymes CPK level Bone profile and vitamin D levels	Every 3-6 months
General examination	
Standardized upper extremity function test(Mallet test)	Annually
Hips and lower extremities	
Hips/pelvis: AP pelvis radiograph	As clinically indicated
Lower extremities: standing AP radiographs	As clinically indicated
Spine/spinal cord compression	
MRI of spine	Annually
Palin radiograph spine	Every 1-3 year
ENT evaluation (audiometry and ABR test)	Annually
Ophthalmology evaluation(visual acuity, retinal examination, corneal examination)	As clinically indicated
Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)	Annually
Cardiology evaluation (ECG, Echocardiogram)	Every 1-3 years
Skeletal survey	Every 1-3 years
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life	Annually
6MWT/T25FW	Annually

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Appendix 1:

Table 2: The Mallet grading system for shoulder function.

Grade	Description
I	Flail shoulder
II	Active abduction ≤30° Zero degrees of external rotation Hand to back of neck impossible Hand to back impossible Hand to mouth with marked trumpet sign
III	Active abduction 30–90° External rotation up to 20° Hand to back of neck with difficulty Hand to back with difficulty Hand to mouth possible with partial trumpet sign (over 40° of shoulder abduction)
IV	Active abduction over 90° External rotation over 20° Hand to back of neck easy Hand to back easy Hand to mouth easy with less than 40° of shoulder abduction
V	Normal shoulder