PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Vimizim®

(elosulfase alfa)

Solution for Intravenous Infusion
5 mg/5 mL (1 mg/mL)

Enzyme Replacement Therapy
ATC Code: A16AB12

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion	Concentrate 1 mg/mL Sterile solution 5 mg/5 mL	There are no clinically relevant nonmedicinal ingredients. *For a complete listing of nonmedicinal ingredients see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Vimizim is a formulation of elosulfase alfa, which is a purified human enzyme (N-acetylgalactosamine-6-sulfatase, GALNS) produced by recombinant DNA technology in a Chinese hamster ovary cell line. Human GALNS is a hydrolytic lysosomal glycosaminoglycan-specific enzyme that hydrolyzes sulfate from either galactose-6-sulfate or N-acetyl-galactosamine-6-sulfate on the non-reducing ends of the glycosaminoglycans keratan sulfate (KS) and chondroitin-6-sulfate (C6S).

INDICATIONS AND CLINICAL USE

Vimizim (elosulfase alfa) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis IVA (Morquio A syndrome, or MPS IVA).

Vimizim treatment should be supervised by a physician or health professional experienced in the management of patients with mucopolysaccharidoses. Administration of Vimizim should be carried out by an appropriately trained health professional with the ability to manage medical emergencies. Home administration by a health professional trained in recognising and managing serious infusion reactions may be considered only for patients who are tolerating their infusions well under the direction of the prescribing physician.

Geriatrics (>65 years of age):
The safety and efficacy of Vimizim in patients older than 65 years have not been assessed.

Paediatrics (≤18 years of age):
As for all lysosomal genetic disorders, it is important to initiate treatment as early as possible, before appearance of non-reversible manifestations of the disease. Vimizim has been studied in MPS IVA patients 9 months of age and older. No long term safety data are available beyond 52 weeks in children under the age of 5 years (see WARNINGS AND PRECAUTIONS: Special Populations: Paediatrics, and ADVERSE REACTIONS: Adverse Drug Reaction Overview and CLINICAL TRIALS).

WARNINGS AND PRECAUTIONS

WARNING: RISK OF ANAPHYLAXIS AND HYPERSENSITIVITY

Life-threatening anaphylactic reactions have occurred in some patients during Vimizim infusions. Anaphylaxis, presenting as cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, and gastrointestinal symptoms (e.g., nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria, has been reported during Vimizim infusions, regardless of duration of the course of treatment. Closely observe patients during and after Vimizim administration and be prepared to manage anaphylaxis. Inform patients and parents/caregivers of the signs and symptoms of anaphylaxis and severe hypersensitivity and have them seek immediate medical care should symptoms occur. Patients with acute respiratory illness may be at increased risk of serious acute exacerbation due to hypersensitivity reactions, and require additional monitoring and/or delaying infusion (see WARNINGS AND PRECAUTIONS: Immune and Respiratory and ADVERSE REACTIONS).

General

Spinal Cord Compression
Spinal or cervical cord compression (SCC) is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. In clinical trials, SCC was observed both in patients receiving Vimizim (4.7%) and in patients receiving placebo (3.4%). Patients with MPS IVA should be monitored for signs and symptoms of SCC (including neck or back pain, numbness or loss of sensation, weakness or paralysis, and urinary or fecal incontinence) and given appropriate clinical care.

Driving and Operating Machinery
Dizziness was reported during Vimizim infusions. If dizziness occurs after the infusion, the ability to drive cars and use machines may be affected.

Immune

Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions have occurred in patients treated with Vimizim. In clinical trials, 18 of 235 (7.7%) patients treated with Vimizim experienced signs and symptoms of anaphylaxis including cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnea, chest discomfort, gastrointestinal symptoms (nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria. Anaphylaxis occurred as early as 30 minutes from the start of infusion and up to three hours after infusion. Anaphylaxis occurred as late into treatment as the 47th infusion.

Forty-four of 235 (18.7%) patients had hypersensitivity reactions, including serious (e.g., anaphylaxis) and non-serious reactions. Hypersensitivity reactions occurred as early as 30 minutes from the start of infusion but as late as six days after infusion. The most common hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, peripheral edema, cough, dyspnea, and flushing.

Appropriate medical support should be immediately available during and after Vimizim is administered. Observe patients closely for an appropriate period of time after infusing Vimizim. Inform patients and parents/caregivers of the signs and symptoms of anaphylaxis and hypersensitivity, and instruct them to seek immediate medical care should symptoms occur.

Administer prophylactic antihistamines prior to infusion, with or without antipyretics. Management of hypersensitivity reactions should be based on the severity of the reaction and includes slowing or temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids for mild reactions. However, if severe hypersensitivity reaction symptoms occur, immediately stop the Vimizim infusion and treat the reaction.

Consider the risks and benefits of re-administering Vimizim following a severe anaphylactic or hypersensitivity reaction. Re-administration after a severe reaction should proceed with caution and close monitoring. In clinical trials, subsequent infusions were managed with a slower infusion rate of Vimizim, treatment with additional prophylactic antihistamines and, in the event of a more severe reaction, treatment with prophylactic corticosteroids (see ADVERSE REACTIONS, Adverse Drug Reaction Overview and Clinical Trial Adverse Drug Reactions).

Infusion Reactions

Because of the potential for infusion reactions with Vimizim, administer prophylactic antihistamines with or without antipyretics prior to infusion.

In the pivotal trial, infusion reactions occurred in 52 out of 58 (89.7%) patients treated with Vimizim compared to 91.5% for the placebo group. The majority of infusion reactions were mild to moderate (see ADVERSE REACTIONS, Adverse Drug Reaction Overview)**.** Despite routine pretreatment with antihistamines, serious adverse events during infusion have included anaphylactic reaction, hypersensitivity, status asthmaticus, and vomiting. Severe adverse events during infusion have included anaphylactic reaction, rash, chills, hypersensitivity, and status

asthmaticus. The most common infusion reactions were headache, nausea, vomiting, pyrexia, chills and abdominal pain. Other infusions reactions reported were urticaria, dyspnea, hypotension, cyanosis, bronchospasm and syncope.

Infusion reactions can occur at any time during Vimizim treatment. Management of infusion reactions should be based on the severity of the reaction and include slowing or temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids. If severe infusion reactions occur, immediately stop the infusion of Vimizim and initiate appropriate treatment. Consider the risks and benefits of re-administering Vimizim following a severe reaction. Re-administration after a severe reaction should proceed with caution and close monitoring. In clinical trials, subsequent infusions were managed with a slower rate of Vimizim administration, treatment with additional prophylactic antihistamines and, in the event of a more severe reaction, treatment with prophylactic corticosteroids (see ADVERSE REACTIONS, Adverse Drug Reaction Overview and Clinical Trial Adverse Drug Reactions, and Anaphylaxis and Hypersensitivity Reactions).

Respiratory

Risk of Acute Respiratory Complications

Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions including anaphylaxis. The patient's clinical status should be assessed prior to each administration of Vimizim. Consider temporarily withholding treatment with Vimizim in patients with acute febrile or respiratory illness.

Sleep apnea is common in MPS IVA patients. Airway patency should be assessed before treatment with Vimizim. Patients using supplemental oxygen or continuous positive airway pressure (CPAP) should have these treatments readily available during infusion in the event of an acute reaction, or drowsiness/sleep induced by antihistamine use.

Immunogenicity

All patients treated with Vimizim 2 mg/kg once per week in the placebo-controlled trial developed anti-drug antibodies and tested positive for neutralizing antibodies at least once during the trial (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions: Immunogenicity).

Special Populations

Pregnant Women

There are no studies with Vimizim in pregnant women. It is not known whether Vimizim would cause fetal harm when administered to a pregnant woman or would affect reproductive capacity.

In animal reproduction studies, elosulfase alfa crosses the placental barrier. No effects on embryo-fetal development were observed in rats given daily administration of elosulfase alfa up

to 33 times the human steady-state AUC (area under the curve) at the recommended human weekly dose pre-mating and through the period of organogenesis. No effects on embryo-fetal development were observed in rabbits given daily administration of elosulfase alfa at doses up to 8 times the human steady-state AUC at the recommended weekly dose during organogenesis. Maternal toxicity was observed in rabbits given doses of 1 mg/kg/day and higher (0.1 times the human steady-state AUC at the recommended weekly dose).

A dose-dependent increase in stillbirths was observed when elosulfase alfa was administered daily in rats during organogenesis through lactation at doses 5 times the human steady-state AUC at the recommended human weekly dose. An increase in pup mortality was observed at doses producing maternal toxicity.

Vimizim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and mother. Female patients of reproductive age treated with Vimizim who could become pregnant should use two forms of effective contraception.

There is a Morquio A Registry that collects data on pregnant women with MPS IVA who are treated with Vimizim. Contact MARS@bmrn.com or call 1-800-983-4587 for information and enrollment.

Nursing Women
It is not known whether Vimizim is present in human milk. Elosulfase alfa is present in milk from treated rats (see Impairment of Fertility and Reproductive Toxicity). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Vimizim and any potential adverse effects on the breastfed child from the drug or from MPS IVA.

There is a Morquio A Registry that also collects data on breastfeeding women with MPS IVA who are treated with Vimizim. Contact MARS@bmrn.com or call 1-800-983-4587 for information and enrollment.

Paediatrics (≤ 18 years of age)
Paediatric patients with MPS IVA ages 9 months to 18 years have been treated with Vimizim in clinical trials.

Use of Vimizim in patients 5 years of age and older is supported by a study conducted in 176 paediatric and adult patients. Most patients were in the paediatric age group (53% aged 5-11 years, 27% aged 12-18 years). Serious adverse events were more frequent in children <12 years of age (see ADVERSE REACTIONS: Adverse Drug Reaction Overview).

The safety and efficacy of Vimizim in patients less than 5 years of age is supported by clinical data from an ongoing, open-label trial in 15 paediatric patients. Safety and pharmacodynamics results in these patients are consistent with results observed in paediatric patients 5 to 18 years old in a double-blind placebo-controlled study. No long term safety data are available beyond 52 weeks in children under the age of 5 years (see ADVERSE REACTIONS).

Geriatrics (>65 years of age)
The safety and efficacy of Vimizim in patients older than 65 years have not been assessed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 235 MPS IVA patients aged 9 months to 57 years were exposed to Vimizim in six clinical trials (one placebo-controlled trial and 5 open label trials). The mean exposure to the recommended dose of Vimizim (2 mg/kg/week) was 30 weeks (range 1 to 100 weeks). Eighty percent of patients across clinical trials had an adverse reaction considered related to treatment. Most were infusion reactions, defined as reactions occurring after initiation of infusion until the end of the day following the infusion (see WARNINGS AND PRECAUTIONS and Clinical Trial Adverse Reactions). Infusion reactions were generally mild or moderate (99%), and the frequency of events was higher during the first 12 weeks of treatment and tended to occur less frequently with time. Serious infusion reactions were observed in 8.5% of patients in clinical trials and included anaphylaxis, hypersensitivity and vomiting.

During clinical trials, infusion reactions led to interruption or discontinuation of the infusion in 49% of patients and 54/235 patients (23%) required medical intervention, including antihistamines (16%) and/or corticosteroids (13%) (see WARNINGS AND PRECAUTIONS). Two hundred and three (203) of 235 patients (86.4%) experienced more than one infusion reaction. For patients receiving the recommended dose of Vimizim, serious adverse events were reported in 4/16 (25%) of subjects less than 5 years of age, 27/117 (23%) of subjects 5 to 11 years of age, 5/50 (10%) of subjects 12 to 18 years of age and 3/39 (7.7%) of subjects 19 years of age and older.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Vimizim was studied in a 24-week randomized, double-blind, placebo-controlled trial of 176 patients with MPS IVA, ages 5 to 57 years old (mean age = 14.5 years), 1:1 male:female. Of the 176 patients, 65% were White, 23% Asian, 3% Black and 10% Other race. Patients were randomized to three treatment groups: Vimizim 2 mg/kg once per week (n=58), Vimizim 2 mg/kg once every other week (n=59) or placebo (n=59).

Serious adverse events occurred more frequently in patients receiving Vimizim every week (15.5%) than in patients receiving Vimizim every other week (6.8%) or placebo (3.4%). Serious adverse events in patients treated with Vimizim included anaphylactic reaction, hypersensitivity,

vomiting, pneumonia, infusion site pain, lower respiratory tract infection, otitis media, viral upper respiratory tract infection, urticaria, and Dengue fever.

Ninety percent (90%) of patients in the pivotal trial receiving Vimizim had infusion reactions. The most common symptoms of infusion reactions (occurring in ≥10% of patients treated with Vimizim and ≥5% more when compared to placebo) were headache, nausea, vomiting, pyrexia, chills and abdominal pain.

Infusion reactions requiring medical intervention and infusion interruption or discontinuation occurred in 22% of subjects receiving 2 mg/kg per week of Vimizim. Infusion reactions requiring medical intervention included vomiting, allergic reaction, nausea, shivering, abdominal pain, fever, headache, urticaria, hypotension, bronchospasm, and anaphylaxis. Severe adverse reactions in patients treated with Vimizim were anaphylactic reaction, rash, chills and hypersensitivity.
Table 1 has all adverse events with an incidence of 5% or more than placebo regardless of causal relationship in the placebo-controlled trial.

Table 1: Adverse events with an incidence of 5% or more in Vimizim-treated patients than placebo in the Placebo-Controlled Trial*

MedDRA System Organ Class/Preferred Term	Placebo N = 59 (%)	Vimizim 2 mg/kg/ every other week N = 59 (%)	Vimizim 2 mg/kg/week N = 58 (%)
Cardiac disorders			
Tricuspid valve incompetence	3 (5%)	7 (12%)	4 (7%)
Ear and labyrinth disorders			
Ear pain	5 (8%)	8 (14%)	3 (5%)
Eye disorders			
Corneal opacity	1 (2%)	0	5 (9%)
Gastrointestinal disorders			
Abdominal pain**	5 (8.5%)	8 (13.6%)	14 (24.1%)
Abdominal pain upper**	5 (8.5%)	4 (6.8%)	9 (15.5%)
Diarrhoea**	7 (11.9%)	12 (20.3%)	12 (20.7%)
Nausea**	12 (20.3%)	14 (23.7%)	18 (31.0%)
Vomiting**	21 (35.6%)	21 (35.6%)	26 (44.8%)
General disorders and administration site conditions			
Chest discomfort	0	1 (2%)	3 (5%)
Chills**	1 (1.7%)	6 (10.2%)	6 (10.3%)
Infusion site pain	0	4 (7%)	4 (7%)
Non-cardiac chest pain	0	3 (5%)	1 (2%)
Pyrexia**	17 (28.8%)	22 (37.3%)	25 (43.1%)
Immune system disorders			
Hypersensitivity**	1 (1.7%)	4 (6.8%)	3 (5.2%)

MedDRA System Organ Class/Preferred Term	Placebo N = 59 (%)	Vimizim 2 mg/kg/ every other week N = 59 (%)	Vimizim 2 mg/kg/week N = 58 (%)
Infections and infestations			
Ear infection	1 (2%)	2 (3%)	5 (9%)
Gastroenteritis	4 (7%)	8 (14%)	7 (12%)
Nasopharyngitis	9 (15%)	12 (20%)	10 (17%)
Otitis media	4 (7%)	5 (8%)	9 (16%)
Viral infection	1 (2%)	6 (10%)	3 (5%)
Injury, poisoning and procedural complications			
Fall	1 (2%)	4 (7%)	0
Head injury	0	3 (5%)	2 (3%)
Musculoskeletal and connective tissue disorders			
Back pain	6 (10%)	10 (17%)	7 (12%)
Myalgia**	0	1 (1.7%)	3 (5.2%)
Neck pain	0	3 (5%)	5 (9%)
Pain in extremity	9 (15%)	14 (24%)	9 (16%)
Nervous system disorders			
Dizziness**	3 (5.1%)	4 (6.8%)	7 (12.1%)
Headache**	21 (35.6%)	24 (40.7%)	24 (41.4%)
Paraesthesia	0	0	3 (5%)
Somnolence	0	0	3 (5%)
Psychiatric disorders			
Agitation	0	2 (3%)	3 (5%)
Respiratory, thoracic, and mediastinal disorders			
Asthma	0	3 (5%)	1 (2%)
Dyspnoea**	3 (5.1%)	6 (10.2%)	7 (12.1%)
Oropharyngeal pain**	7 (11.9%)	9 (15.3%)	12 (20.7%)
Throat irritation	0	0	3 (5%)
Skin and subcutaneous tissue disorders			
Petechiae	0	3 (5%)	0
Urticaria	0	4 (7%)	4 (7%)
Vascular disorders			
Flushing	0	1 (2%)	5 (9%)
Hot flush	1 (2%)	4 (7%)	3 (5%)

*Includes events not considered treatment-related by the investigator

** Events identified as drug-related

Less Common Adverse Events (<5%)

Blood and lymphatic system disorders: Eosinophilia, Thrombocytopenia
Cardiac disorders: Aortic valve disease**,** Aortic valve incompetence**,** Bradycardia**,** Cardiac discomfort**,** Cardiac valve disease**,** Mitral valve disease**,** Palpitations, Pulmonary valve incompetence, Ventricular dysfunction, Ventricular tachycardia
Congenital, familial and genetic disorders: Dysmorphism**,** Hydrocele**,** Tooth hypoplasia
Ear and labyrinth disorders: Cerumen impaction**,** Ear disorder**,** External ear inflammation**,** Hearing impaired**,** Motion sickness**,** Tympanic membrane disorder**,** Vertigo
Eye disorders: Conjunctivitis**,** Eye pain**,** Eyelid oedema**,** Eyelids pruritus**,** Myopia**,** Ocular hyperaemia, Vision blurred, Visual acuity reduced
Gastrointestinal disorders: Abdominal discomfort**,** Abnormal faeces**,** Aphthous stomatitis**,** Constipation**,** Diarrhoea haemorrhagic**,** Dry mouth**,** Dysphagia, Enteritis, Eructation, Frequent bowel movements, Gastritis, Gastrointestinal sounds abnormal, Gastrooesophageal reflux disease, Gingival pain, Inguinal hernia, Odynophagia, Tongue ulceration, Toothache
General disorders and administration site conditions: Application site vesicles**,** Asthenia**,** Catheter site haemorrhage**,** Cyst**,** Device occlusion, Effusion, Feeling cold, Feeling hot, Feeling of body temperature change, Gait disturbance, Hypothermia, Infusion site erythema, Infusion site extravasation, Infusion site pruritus, Infusion site swelling, Injection site macule, Injection site movement impairment, Injection site pain, Injection site papule, Injection site pruritus, Injection site rash, Injection site swelling, Irritability, Malaise, Nodule, Nonspecific reaction, Oedema peripheral, Puncture site pain, Sensation of foreign body, Vessel puncture site paraesthesia
Immune system disorders: Anaphylactic reaction**,** Seasonal allergy
Infections and infestations: Acute sinusitis**,** Acute tonsillitis**,** Bronchitis**,** Dengue fever**,** Eye infection**,** Fungal infection**,** Gastroenteritis viral**,** Hordeolum**,** Influenza**,** Lice infestation**,** Lower respiratory tract infection**,** Malaria**,** Mononucleosis syndrome, Oral candidiasis, Oral herpes, Otitis externa, Otitis media acute, Pneumonia, Sinusitis, Tonsillitis, Upper respiratory tract infection, Varicella, Viral rash, Viral upper respiratory tract infection, Vulvovaginal mycotic infection
Injury, poisoning and procedural complications: Arthropod bite, Arthropod sting, Contusion, Excoriation, Infusion related reaction, Joint dislocation, Joint injury, Laceration, Limb injury, Overdose, Procedural pain, Repetitive strain injury, Skin injury, Venous injury, Wound
Investigations: Alanine aminotransferase increased, Blood cholesterol increased, Blood glucose increased, Blood potassium decreased, Blood pressure decreased, Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic increased, Blood urea increased, Blood urine present, Body temperature decreased, Body temperature increased, Cardiac murmur, ECG electrically inactive area, Electrocardiogram QT prolonged, Electrocardiogram normal, Gamma-glutamyltransferase increased, Haematocrit decreased, Haemoglobin decreased, Heart rate increased, Nitrite urine, Oxygen saturation decreased, Platelet count decreased, Transaminases increased
Metabolism and nutrition disorders: Hypoglycaemia**,** Ketoacidosis
Musculoskeletal and connective tissue disorders: Bone lesion, Chondropathy, Hypermobility syndrome, Intervertebral disc space narrowing, Joint lock, Joint stiffness, Kyphosis, Mobility decreased, Muscle spasms, Muscle twitching, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal stiffness, Torticollis
Neoplasms benign, malignant and unspecified (incl cysts and polyps): Melanocytic naevus

Nervous system disorders: Areflexia, Balance disorder, Hypoaesthesia, Hyporeflexia, Lethargy, Migraine, Presyncope, Sciatica, Syncope, Tremor, Vagus nerve disorder
Psychiatric disorders: Aggression, Anxiety, Anxiety disorder, Breathing-related sleep disorder, Panic attack, Restlessness, Social avoidant behavior, Tearfulness
Renal and urinary disorders: Dysuria**,** Haematuria, Ketonuria, Pollakiuria, Polyuria, Proteinuria, Urinary incontinence
Reproductive system and breast disorders: Dysmenorrhoea**,** Menstruation irregular**,** Pruritus genital**,** Testicular pain
Respiratory, thoracic and mediastinal disorders: Allergic cough**,** Asphyxia, Bronchitis chronic, Bronchospasm, Dry throat, Dysphonia, Epistaxis, Hyperventilation, Nasal congestion, Nasal discomfort, Obstructive airways disorder, Pharyngeal erythema, Productive cough, Respiratory failure, Rhinorrhoea, Stridor, Tachypnoea, Throat tightness, Upper respiratory tract inflammation, Wheezing
Skin and subcutaneous tissue disorders: Acne**,** Dermatitis, Dermatitis allergic, Dermatitis contact, Dry skin, Nail disorder, Night sweats, Papule, Pruritus, Rash, Rash maculo-papular, Rash papular, Rash pruritic, Skin depigmentation, Skin irritation, Skin lesion, Sweat gland disorder
Surgical and medical procedures: Cerumen removal, Ear tube insertion, Haemangioma removal, Medical device removal, Mole excision, Suture removal
Vascular disorders: Aortic dilatation, Hyperaemia, Hypotension, Pallor, Peripheral coldness, Vein disorder

In open-label trials with patients older than 5 years of age, serious and severe adverse events observed included rash, allergic reaction, vomiting, hypotension, tetraplegia, spinal cord compression, anaphylactic reaction, status asthmaticus, asthma and cardio-respiratory arrest. One patient experienced an adverse event of type 1 hypersensitivity resulting in study discontinuation.

In an ongoing open-label clinical trial in 15 paediatric patients < 5 years of age (range 9 months to 4.9 years) treated with Vimizim 2.0 mg/kg once per week, the most commonly reported adverse reactions during the first 52 weeks of treatment were pyrexia (100%), vomiting (80%) and cough (73%). Serious and severe adverse events in children < 5 years of age were tonsillar hypertrophy with tonsillectomy, cervical cord compression, hypersensitivity, sepsis and staphylococcal skin infection, spinal cord edema and joint instability. Other adverse reactions occurring in 2 or more patients were diarrhoea, abdominal pain, oropharyngeal pain, headache, and nausea.

Immunogenicity
All patients treated with Vimizim 2 mg/kg per week in the placebo-controlled trial developed anti-drug antibodies by Week 4, which 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 (see WARNINGS AND PRECAUTIONS, Immune). IgE antibodies against elosulfase alfa were detected in ≤ 10 % of treated patients and have not consistently been related to hypersensitivity reactions.

All patients treated with Vimizim 2 mg/kg per week in the placebo-controlled trial tested positive for neutralizing antibodies capable of inhibiting the drug from binding to the cation-independent 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 patients. Therefore, the possibility of an association between neutralizing antibody titer and treatment effect cannot be assessed.

DRUG INTERACTIONS

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Vimizim treatment should be supervised by a physician or health professional experienced in the management of patients with mucopolysaccharidoses. Administration of Vimizim should be carried out by an appropriately trained health professional with the ability to manage medical emergencies. Home administration by a health professional trained in recognising and managing serious infusion reactions may be considered only for patients who are tolerating their infusions well under the direction of the prescribing physician.

Because of the potential for infusion reactions, administer antihistamines with or without antipyretics 30 to 60 minutes prior to the start of the infusion. The infusion rate may be slowed and/or temporarily stopped based on clinical judgment.

Recommended Dose and Dosage Adjustment

The recommended dosage is 2 mg/kg of body weight of Vimizim administered once a week. The total volume of the infusion should be delivered over approximately 4 hours.

Each vial of Vimizim provides 5 mg of elosulfase alfa in 5 mL of solution (1 mg/mL) and contains no preservative. It is intended for single use only: discard the vial and any unused Vimizim immediately. Vimizim is provided as a concentrated solution for infusion and must be

diluted prior to infusion with 0.9% Sodium Chloride Injection, USP, to a total volume of 100 mL or 250 mL based on the patient's weight. Use aseptic techniques.

For patients weighing less than 25 kg:
Dilute in 100 mL saline. The initial infusion rate should be 3 mL per hour. The infusion rate may be increased, as tolerated, every 15 minutes as follows: first increase the rate to 6 mL per hour, then increase the rate every 15 minutes by 6 mL per hour increments until a maximum rate of 36 mL per hour is reached. The infusion rate may be slowed or temporarily stopped in the case of infusion reaction or hypersensitivity. In the clinical trial 36 out of 104 patients (35%) weighing less than 25 kg experienced infusion reactions which led to infusion interruption, discontinuation of the infusion, or reduction in infusion rate.

For patients weighing 25 kg or more:
Dilute in 250 mL saline. The initial rate will be 6 mL per hour. The infusion rate may be increased as tolerated, every 15 minutes as follows: first increase the rate to 12 mL per hour, then increase the rate every 15 minutes by 12 mL per hour increments until a maximum rate of 72 mL per hour is reached. The infusion rate may be slowed or temporarily stopped in the case of infusion reaction or hypersensitivity. In the clinical trial, 25 out of 72 patients (35%) weighing 25 kg or more experienced infusion reactions which led to infusion interruption, discontinuation of the infusion, or reduction in infusion rate.

Table 2: Recommended Infusion Volumes and Rates*

Patient Weight (kg)	Total Infusion Volume (mL)	Step 1 Initial Infusion Rate 0 -15 minutes (mL/hr)	Step 2 15 – 30 minutes (mL/hr)	Step 3 30 – 45 minutes (mL/hr)	Step 4 45 - 60 minutes (mL/hr)	Step 5 60 - 75 minutes (mL/hr)	Step 6 75 - 90 minutes (mL/hr)	Step 7 90+ minutes (mL/hr)
< 25	100	3	6	12	18	24	30	36
≥ 25	250	6	12	24	36	48	60	72

* Infusion rate may be increased as tolerated by patient. Patients experiencing infusion reactions or hypersensitivity may require slowing, temporary cessation of infusion, or discontinuation of the infusion.

Administration

Instructions for Use
Prepare and use Vimizim according to the following steps. Use aseptic techniques. Vimizim must be diluted prior to administration. Administer the diluted Vimizim solution to patients using an infusion set equipped with a 0.2 µm in-line filter. Do not allow vials to remain at room temperature longer than 72 hours before dilution.

a. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 2 mg/kg, using the following calculation:

- Patient weight (kg) multiplied by 2 mg per kg = Patient dose (mg)
- Patient dose (mg) divided by (1 mg/mL concentrate of Vimizim) = Total number of mL of Vimizim
- Total amount (mL) Vimizim divided by 5 mL per vial = Total number of vials

b. Round up to the next whole vial. Remove the appropriate number of vials from the refrigerator. Do not heat or microwave vials.
c. Obtain an infusion bag containing 0.9% Sodium Chloride Injection, USP suitable for intravenous administration. The total volume of the infusion is determined by the patient's body weight.
    - Patients weighing less than 25 kg should receive a total volume of 100 mL.
    - Patients weighing 25 kg or more should receive a total volume of 250 mL.
d. Before withdrawing Vimizim from the vial, visually inspect each vial for particulate matter and discoloration. Because this is a protein solution, slight flocculation (thin translucent fibers) may occur. The Vimizim solution should be clear to slightly opalescent and colorless to pale yellow. Do not use if the solution is discolored or if there is particulate matter in the solution.
e. Withdraw and discard a volume of the 0.9% Sodium Chloride Injection, USP from the infusion bag, equal to the volume of Vimizim concentrate to be added.
f. Slowly withdraw the calculated volume of Vimizim from the appropriate number of vials using caution to avoid excessive agitation.
g. Slowly add Vimizim to the infusion bag using care to avoid agitation.
h. Gently rotate the infusion bag to ensure proper distribution of Vimizim. Do not shake the solution.
i. Discard the Vimizim vial.
j. Administer the diluted Vimizim solution to patients using an infusion set equipped with a 0.2 μm in-line filter.

OVERDOSAGE

In clinical trials, doses of elosulfase alfa were explored up to 4 mg/kg per week and no specific signs or symptoms were identified following the higher doses.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Mucopolysaccharidosis comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). MPS IVA is characterized by the absence or marked reduction in *N*-acetylgalactosamine-6-sulfatase activity. The sulfatase activity deficiency results in the accumulation of the GAG substrates, urine KS and chondroitin 6 sulfate (C6S), in the lysosomal compartment of cells throughout the body. The accumulation leads to widespread cellular, tissue, and organ dysfunction. Elosulfase alfa is intended to provide the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increase the catabolism of the GAGs, KS and C6S. Elosulfase alfa uptake by cells into lysosomes is mediated

by the binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to mannose-6-phosphate receptors.

In the absence of an animal disease model that recapitulates the human disease phenotype, elosulfase alfa pharmacological activity was evaluated using human primary chondrocytes from two MPS IVA patients. Treatment of MPS IVA chondrocytes with elosulfase alfa induced clearance of KS lysosomal storage from the chondrocytes.

Pharmacodynamics

The pharmacodynamic effect of elosulfase alfa was assessed by reductions in urine KS levels. The relationship of urine KS to other measures of clinical response has not been established (see CLINICAL TRIALS). No association was observed between antibody development and urinary KS levels.

Pharmacokinetics

The pharmacokinetic parameters of elosulfase alfa were evaluated in 23 patients with MPS IVA who received weekly intravenous infusions of 2 mg/kg of elosulfase alfa over approximately 4 hours for 22 weeks and the parameters at Week 0 and Week 22 were compared.

Eleven patients were aged 5 to 11 years, six were aged 12 to 17 years, and six were aged 18 to 41 years. Table 3 summarizes the pharmacokinetic parameters at Week 0 and Week 22. Mean $AUC_{0\text{-}t}$ and C_{max} increased to 2.8-fold and 2.9-fold, respectively, at Week 22 compared to Week 0. Mean half life ($t_{1/2}$) increased from 7.52 min at Week 0 to 35.9 min at Week 22. Male and female patients had comparable elosulfase alfa clearance, and clearance did not trend with age or weight at Week 22. These changes are likely related to the development of neutralizing antibodies in all patients.

Table 3: Pharmacokinetic Parameters

Pharmacokinetic Parameter	Week 0 Mean (SD) (N=22**)	Week 22 Mean (SD) (N=22**)
$AUC_{0\text{-}t}$, min x µg/mL[*]	238 (100)	577 (416)
C_{max}, µg/mL[†]	1.49 (0.534)	4.04 (3.24)
CL, ml/min/kg[‡]	10.0 (3.73)	7.08 (13.0) [§]
$t_{1/2}$, min[§]	7.52 (5.48)	35.9 (21.5) [§]
T_{max}, min[¶]	172 (75.3)	202 (90.8)
Vdss, mL/mg[♥]	396 (316)[♦]	650 (1842) [§]

** The pharmacokinetics of elosulfase alfa was evaluated in 23 individual patients. However, 1 patient was not tested at Week 0 and another patient was not tested at Week 22.

* $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time zero to the time of last measurable concentration

† C_{max}, observed maximum plasma concentration

‡ CL, total clearance of drug after intravenous administration

§ $t_{1/2}$, elimination half-life

¶ T_{max}, time from zero to maximum plasma concentration

♥ Vdss, apparent volume of distribution at steady-state

§ N=20
♦ N = 14

STORAGE AND STABILITY

Unopened vials: To be stored at 2 ºC to 8 ºC for up to 3 years or until product vial expiry date.

Store in refrigerator (2 °C-8 °C).

Do not freeze.

Protect from light.

Keep out of reach of children.

Diluted solutions: Diluted Vimizim should be used immediately. If immediate use is not possible, chemical and physical in-use stability has been demonstrated for up to 24 hours at 2ºC-8ºC followed by up to 24 hours at 23ºC-27ºC. Administration of Vimizim should be completed within 48 hours from the time of dilution.

SPECIAL HANDLING INSTRUCTIONS

Any unused product or waste material is to be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each vial of Vimizim is intended for single use only. This product contains no preservatives.

Vimizim is supplied as a sterile solution in clear Type I glass vial, containing 5 mg elosulfase alfa (expressed as protein content) per 5 mL (extractable volume) concentrate for solution for infusion. The closure consists of a chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap.

The concentrate for solution for intravenous infusion must be diluted with 0.9% sodium chloride solution, USP, for infusion using aseptic technique. The diluted Vimizim solution is administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

List of excipients:
Sodium acetate, trihydrate
Sodium phosphate monobasic, monohydrate
L-arginine hydrochloride
Sorbitol
Polysorbate 20
Water for Injection

Pack size: 1 vial

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Elosulfase alfa

Chemical name: Recombinant human N-acetylgalactosamine-6-sulfatase, or recombinant human N-acetylgalactosamine-6-sulfate-sulfatase (rhGALNS)

Molecular formula and molecular mass:

Monomer:

The mature protein contains 496 amino acids. The calculated isotope average molecular mass of the peptide chain is 55412.9 Da., not including post-translational modifications. The molecular formula for the rhGALNS monomer is $C_{2510}H_{3794}N_{682}O_{709}S_{17}$.

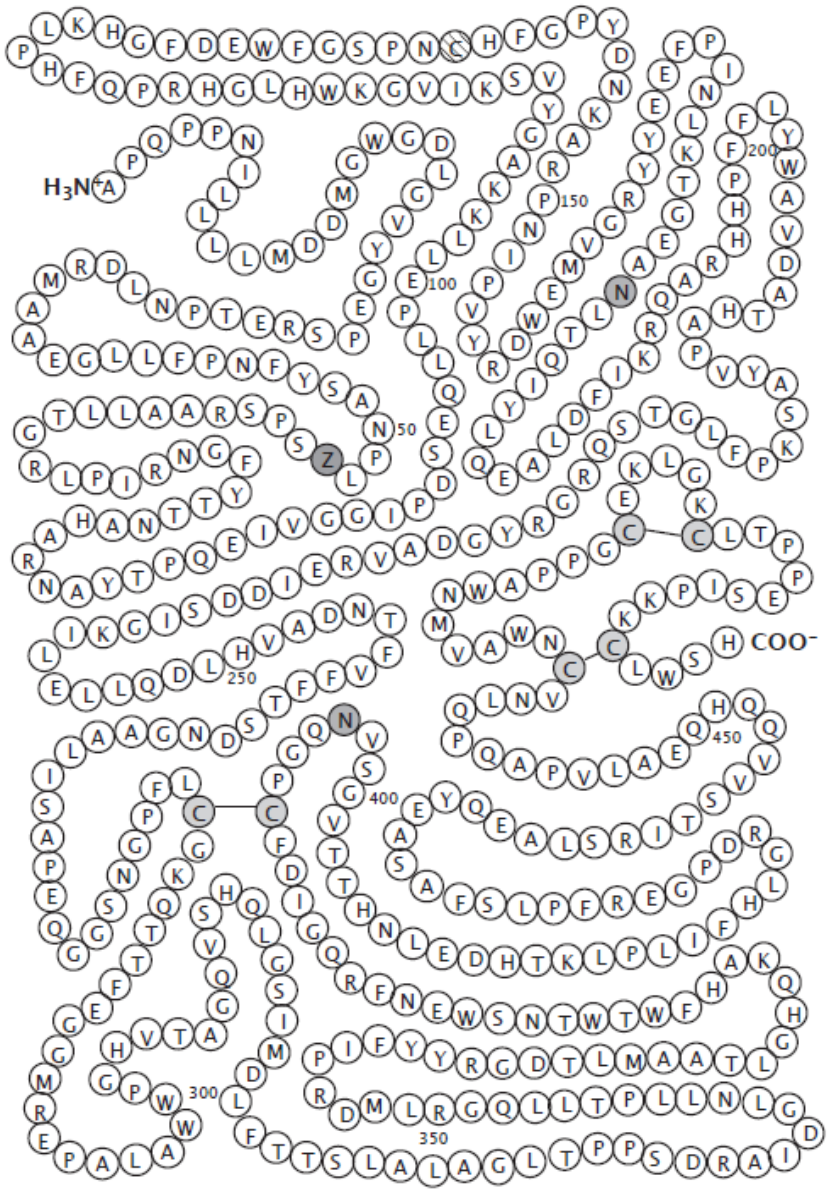
When the conversion of C53 to formylglycine and intra-molecular disulfide linkages are taken into account, the molecular formula for the monomer is $C_{2510}H_{3786}N_{682}O_{710}S_{16}$, with a molecular mass of 55388.2 Da.

Dimer:

In solution, rhGALNS forms a non-covalent dimer with a molecular mass of 110825.8 Da. The chemical formula of the rhGALNS dimer without post-translational modifications is $C_{5020}H_{7588}N_{1364}O_{1418}S_{34}$.

When the conversion of C53 to formylglycine and intra-molecular disulfide linkages are taken into account, the molecular formula for the dimer is $C_{5020}H_{7572}N_{1364}O_{1420}S_{32}$, with a molecular mass of 110776.4 Da.

Structural Formula: N-acetylgalactosamine-6-sulfatase Primary Sequence and Amino Acid



C cysteine in disulfide bond

C free cysteine

Z formylglycine

N N-glycosylation site

Physicochemical properties:

Recombinant human N–acetylgalactosamine 6–sulfatase, or recombinant human N-acetylgalactosamine-6-sulfate-sulfatase (rhGALNS) is a single-chain glycosylated enzyme

involved in the lysosomal degradation of the glycosaminoglycans (GAGs), keratan sulfate (KS) and chondroitin sulfate (CS). The glycosylation of rhGALNS contains high mannose and phosphorylated high mannose oligosaccharide structures. Vimizim (elosulfase alfa) is supplied as a sterile, aqueous solution. Each vial provides 5 mg elosulfase alfa, in a 5 mL extractable solution with pH of approximately 5.4.

Product Characteristics

Vimizim is intended for intravenous infusion and is supplied as a sterile, aqueous solution that must be diluted with 0.9% sodium chloride solution, USP, prior to administration. Each vial of Vimizim provides 5 mg elosulfase alfa, 13.6 mg sodium acetate, trihydrate, 34.5 mg sodium phosphate monobasic, monohydrate, 100 mg sorbitol, 31.6 mg L-arginine hydrochloride, 0.5 mg polysorbate 20, and water for injection, in a 5 mL extractable solution. Elosulfase alfa is a recombinant form of human N-acetylgalactosamine 6-sulfatase (rhGALNS) and is produced in mammalian Chinese Hamster Ovary (CHO) cell culture by recombinant DNA technology.

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and efficacy of Vimizim were assessed in a 24-week randomized, double-blind, placebo-controlled clinical trial of 176 patients with MPS IVA. Fifty-one percent (51%) of patients were female. Of the 176 patients, 65% were White, 23% Asian, 3% Black and 10% Other race. Table 4 summarizes the study demographics.

Table 4 Summary of Patient Demographics for Controlled Clinical Trial in Patients with MPS IVA

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age (range)	Gender
MOR-004 Phase 3 Study	Randomized, double-blind, placebo-controlled study	2.0 mg/kg Vimizim once every week or once every other week or placebo; intravenous infusion; 24 weeks.	MPS IVA Patients n = 177*	14.5 (5 – 57) years	87 M / 89 F

*One patient in the Vimizim 2.0 mg/kg/week group dropped out after one infusion.

Eighty-two percent (82%) of patients presented with a medical history of musculoskeletal conditions, including knee deformity (52%), kyphosis (31%), hip dysplasia (22%), prior spinal fusion surgery (22%) and arthralgia (20%). At baseline, all enrolled patients could walk more than 30 meters (m) but less than 325 m in six minutes.

Patients received Vimizim 2 mg/kg once per week (n=58), 2 mg/kg once every other week (n=59), or placebo (n=59)

The primary endpoint was the change from baseline in the distance walked in six minutes (six minute walk test, (6-MWT) compared to placebo at Week 24. The secondary endpoints were the change from baseline in the rate of stair climbing in three minutes (three-minute stair climb test, 3-MSCT) and change from baseline in urine KS levels at Week 24.

Study Results

At Week 24, the modeled mean treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5 meters (CI95, 4.0, 40.9; p=0.0174) in patients who received Vimizim 2 mg/kg once per week regimen. There was no difference in the mean rate of stair climbing between patients who received Vimizim 2 mg/kg once per week and those who received placebo. Patients who received Vimizim 2 mg/kg once every other week performed similarly in the 6-MWT and 3-MSCT as those who received placebo. The reduction in mean urinary KS levels from baseline was numerically greater in the Vimizim treatment groups compared to placebo. However, the relationship between urinary KS and other measures of clinical response has not been established.

Table 5: Results from Placebo-Controlled Clinical Study

	Vimizim 2 mg/kg once per week			**Placebo**			**Vimizim vs. Placebo**
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Mean Difference in Changes**
N	58	57*	57	59	59	59	
6-Minute Walk Test (Meters)							
Mean ± SD	203.9 ± 76.32	243.3 ± 83.53	36.5 ± 58.49	211.9 ± 69.88	225.4 ± 83.22	13.5 ± 50.63	23.0† (CI_{95}, 2.9, 43.1)
Median Min, Max	216.5 42.4, 321.5	251.0 52.0, 399.9	20.0 -57.8, 228.7	228.9 36.2, 312.2	229.4 50.6, 501.0	9.9 -99.2, 220.5	22.5‡ (CI_{95}, 4.0, 40.9) (p = 0.0174)‡,§

* One patient in the Vimizim group dropped out after 1 infusion

† ANCOVA observed Vimizim mean change- Placebo mean change, adjusted for baseline 6 MWT categories (less than or equal to 200 meters, greater than 200 meters) and age groups (5 – 11, 12- 18, 19 or older)

‡ Model-based mean of Vimizim - Placebo, adjusted for baseline

§ p-value based on the model-based mean difference

Extension Trial

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial. One hundred seventy-three (173) of 176 patients enrolled in the extension trial in which patients received Vimizim 2 mg/kg once per week (n=86) or Vimizim 2 mg/kg once every other week (n=87). Patients who continued to receive Vimizim 2 mg/kg once per week for another 48 weeks (for a total of 72-week exposure) showed no further improvement in walking ability beyond the first 24 weeks of treatment in the placebo-controlled trial.

Paediatric trial in patients < 5 years
In an open-label trial, 15 paediatric patients with MPS IVA under the age of 5 years (9 months to <5 years) received 2 mg/kg of Vimizim once a week for 52 weeks. Patients in this study showed a reduction in mean normalized urinary KS. Efficacy assessment by a 6 minute walk test was not conducted due to the young age of these patients.

DETAILED PHARMACOLOGY

In vitro
The elosulfase alfa pharmacological activity was evaluated *in vitro* in primary human Morquio chondrocytes and a Morquio fibroblast cell line. Elosulfase alfa cellular uptake, trafficking to the lysosomal compartment, and pharmacological activity (clearance of intracellular KS storage) were confirmed in primary human Morquio chondrocytes. Internalization of elosulfase alfa was confirmed within in vitro studies in human Morquio fibroblasts. A K_{uptake} value of ~2.5 nM was measured in human Morquio fibroblasts and the intracellular $t_{1/2}$ was estimated to be 5 to 7 days in these same cells. Incubation of the Morquio chondrocytes with elosulfase alfa resulted in internalization of the enzyme, clearance of stored lysosomal KS, and restored a normal expression profile for some chondrogenic genes such as Sox9, a master transcription factor for the chondrogenic lineage. Extracellular KS was not affected by elosulfase alfa, confirming that elosulfase alfa activity was restricted to the lysosome.

Animal Safety Pharmacology
Safety pharmacology studies evaluated the effects of a single IV dose of elosulfase alfa administered at the 1 mg/kg, 6 mg/kg, and 20 mg/kg dose levels, in rats (respiratory and CNS studies) and telemeterized monkeys (CV study). No elosulfase-alfa related respiratory, CNS or CV parameter changes were observed. The No Observed Effect Level (NOEL) for elosulfase alfa administered IV for all safety pharmacology studies was 20 mg/kg, the highest dose tested.

TOXICOLOGY

Single Dose Toxicity
In a single-dose toxicity and toxicokinetic study in rats given 1, 6, and 20 mg/kg elosulfase alfa, IV bolus (~2 minutes), there were no elosulfase alfa-related changes in any of the standard toxicological parameters measured including clinical observations, macroscopic and microscopic assessments. The study design included CNS safety pharmacology assessments (modified Irving evaluation). The No Observed Adverse Effect Level (NOAEL) following a single IV bolus administration of elosulfase alfa in rats was 20 mg/kg.

Repeated Dose Toxicity
The main findings were related to species-specific anaphylactoid-type reactions observed in rats. These reactions were expected due to the administration of a heterologous protein and were generally mitigated by the diphenhydramine (DPH) pretreatment. Nonetheless, seven mortalities were observed in the repeat-dose and developmental and reproductive toxicity (DART) studies in

rats that may be related to elosulfase alfa -induced anaphylactoid-type reactions based on the timing of these reactions and on the associated clinical signs. No test article-related mortalities were observed in the rabbit embryo-fetal development studies. There were no test article-related mortalities in the repeat-dose toxicity monkey studies. No elosulfase alfa-related target organ toxicity was observed after weekly elosulfase alfa administration up to 20 mg/kg in the repeat-dose toxicology studies. No injection or infusion site reactions were observed in these studies. As expected in these normal animals, no pharmacological or toxicological effects of elosulfase alfa influencing normal bone and cartilage growth or urine KS turnover were observed in the 26-week repeat-dose toxicity rat study or 52-week repeat-dose monkey study. To support the inclusion of a paediatric population, the juvenile cynomolgus monkeys were used in the 52-week repeat-dose toxicity study, and were actively growing during the conduct of the study, allowing the evaluation of elosulfase alfa-related effects on overall development including bone growth.

Carcinogenesis
Long-term studies in animals to evaluate carcinogenic potential have not been performed with elosulfase alfa.

Mutagenesis
Long-term studies in animals to evaluate mutagenic potential have not been performed with elosulfase alfa.

Impairment of Fertility and Reproductive Toxicity
All reproductive studies with rats included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of elosulfase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous (IV) administration of up to 20 mg/kg elosulfase alfa in rats (33 times the human steady-state AUC at the recommended weekly dose of 2 mg/kg) during a 15-day pre-mating period, mating, and the period of organogenesis, produced no maternal toxicity or effects on embryo-fetal development.

Daily intravenous administration of up to 10 mg/kg in rabbits (8 times the human steady-state AUC at the recommended weekly dose) during the period of organogenesis had no effects on embryo-fetal development. However, maternal toxicity (gross changes in liver) was observed in rabbits given doses of 1 mg/kg/day and higher (0.1 times the human steady-state AUC at the recommended weekly dose).

Elosulfase alfa crosses the placental barrier, and due to maternal toxicity, produced an increase in the percentage of stillbirths when administered daily to rats at doses of 6 mg/kg IV and higher (5 times the human steady-state AUC at the recommended weekly dose) during the period of organogenesis through lactation. During the lactation period, daily administration of 20 mg/kg IV (33 times the human steady-state AUC at the recommended weekly dose) produced maternal toxicity and an increase in mortality of offspring. This study lacked a full evaluation of neurodevelopmental milestones; however, no effects of elosulfase alfa were noted in tests for learning and memory.

Animal studies demonstrated the presence of elosulfase alfa in breast milk.

Reproduction studies have revealed no evidence of impaired fertility or reproductive performance in animals.

REFERENCES

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PART III: PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VIMIZIM
(elosulfase alfa)

Read this carefully before you start taking **Vimizim** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Vimizim**.

Serious Warnings and Precautions

- Vimizim may cause severe or life-threatening allergic reactions.
- Tell your doctor or nurse immediately if you experience any of the following symptoms: shortness of breath, coughing, wheezing or trouble breathing, swelling of the face, lips, tongue or other parts of the body, tightness in the throat, chest pain, bluish skin, flushing, rash, itching, or hives.
- Tell your doctor if you have a fever, cough, or cold. These conditions may worsen the symptoms of an allergic reaction.

What is Vimizim used for?
Vimizim is used to treat patients with MPS IVA (Mucopolysaccharidosis Type IVA, Morquio A Syndrome).

People with MPS IVA do not have enough of an enzyme called N-acetylgalactosamine-6-sulfatase, which breaks down specific substances in the body (for example keratan sulfate). As a result, these substances build-up in many tissues in the body which causes the symptoms of MPS IVA.

How does Vimizim work?
This medicine is an enzyme called elosulfase alfa. It can replace the missing enzyme in MPS IVA patients. Treatment with Vimizim in MPS IVA patients has shown improvement in walking ability and reduction in levels of keratan sulfate in the body.

What are the ingredients in Vimizim?
Medicinal ingredients: elosulfase alfa
Nonmedicinal ingredients: L-arginine hydrochloride, polysorbate 20, sodium acetate trihydrate, sodium phosphate monobasic monohydrate, sorbitol, and water for injection.

Vimizim comes in the following dosage forms:
Vimizim is supplied as a concentrated solution for intravenous infusion. One mL of Vimizim contains 1 mg elosulfase alfa. A 5 mL vial contains 5 mg elosulfase alfa.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Vimizim. Talk about any health conditions or problems you may have,

including if you:

- Have ever had an allergic reaction to elosulfase alfa or any other ingredients of Vimizim.
- Have a fever, cough, or cold
- Are pregnant or planning to become pregnant.
- Are breast-feeding or planning to breast-feed

Other warnings you should know about:

- Tell your doctor immediately if you have neck or back pain, numb or weak arms or legs, or any bowel or bladder problems. These symptoms may be caused by pressure on your spinal cord, which is a medical emergency.
- Vimizim given to test animals passes into their unborn babies. Vimizim has not been studied in pregnant patients. Vimizim should not be given during pregnancy unless clearly necessary. Female patients who could become pregnant while taking Vimizim should use two forms of effective birth control.
- Vimizim given to test animals passes into their breast milk. It is not known if Vimizim passes into human breast milk. You and your doctor should discuss the risks and benefits of taking Vimizim while breastfeeding.
- In animal studies, Vimizim had no effects on their sperm quality, but it is not known if Vimizim affects human sperm.

Tell your health professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Studies to test how Vimizim interacts with other medicines have not been done.

How to take Vimizim:

Vimizim is given through a drip into a vein (intravenous infusion). Each infusion takes approximately 4 hours and is supervised by a health professional in case you have a reaction to Vimizim.

Before treating you with Vimizim, your doctor will give you medicine to help prevent allergic reactions. If you have an allergic reaction during your Vimizim treatment, your doctor may slow down or stop the infusion and may give you additional medicines to treat the reaction. You and your doctor will decide whether to continue treatment with Vimizim.

Usual dose:

The dose you receive is based on your body weight. The recommended dose regimen is 2 mg/kg body weight given once every week.

Overdose:

Vimizim is administered under the supervision of a health professional, who will check that the correct dose has been given and treat any overdose.

If you think you have been given too much Vimizim, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed a Vimizim treatment, contact your health professional. If you have any other questions about this medicine, ask your health professional or pharmacist.

What are possible side effects from using Vimizim?
These are not all the possible side effects you may feel when using Vimizim. If you experience any side effects not listed here, contact your health care professional.

Like all medicines, this medicine can cause side effects. Most side effects are mild to moderate and generally are associated with the infusion; however some side effects may be serious and may need treatment. Most side effects happened during the treatment or up to one day later, but some happen up to 6 days later. Side effects may include:

- Headache
- Nausea
- Vomiting (throwing up)
- Fever
- Chills
- Stomach ache
- Diarrhea
- Mouth and throat pain
- Dizziness
- Muscle pain

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Severe allergic reactions (signs and symptoms may include wheezing, shortness of breath, coughing, throat tightness, chest pain, hives, turning red or blue and feeling hot)		√	√
Shortness of breath	√		
Enlarged tonsils (difficulty swallowing or sore throat)	√		
Pressure or swelling on the spinal cord (neck or back pain, numbness in your arms or legs, or any bowel or bladder problems)		√	√
Serious skin infection that may spread to the bloodstream (redness, pain, swelling or blistering of the skin or high fever)		√	√
Weakness or looseness in joints	√		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.
NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Unopened vials: Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
Do not take this medicine after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

Keep out of the sight and reach of children

If you want more information about Vimizim:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for health professionals and includes this Patient Medication Information by visiting the Health Canada website; or by calling BioMarin Pharmaceutical (Canada) Inc, at 1-877-597-6744

This leaflet was prepared by BioMarin Pharmaceutical (Canada) Inc.

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