VIMIZIM- elosulfase alfa injection, solution, concentrate
BioMarin Pharmaceutical Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIMIZIM safely and effectively. See full prescribing information for VIMIZIM.

VIMIZIM (elosulfase alfa) injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS and RISK OF ACUTE RESPIRATORY COMPLICATIONS

***See full prescribing information for complete boxed warning*.**

- **Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. *(5.1)***
- **Initiate VIMIZIM in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. *(5.1)***
- **If a severe hypersensitivity reaction (anaphylaxis) occurs, discontinue VIMIZIM and immediately initiate appropriate medical treatment, including use of epinephrine. *(5.1)***
- **Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions, and require additional monitoring *(5.2)***

RECENT MAJOR CHANGES

Boxed Warning	10/2025
Dosage and Administration (2)	10/2025
Warnings and Precautions (5.1)	10/2025

INDICATIONS AND USAGE

VIMIZIM is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome). (1)

DOSAGE AND ADMINISTRATION

Administration of VIMIZIM should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
2 mg per kg body weight administered once every week as an intravenous infusion over a minimum of 3.5 to 4.5 hours, based on infusion volume. (2.2, 2.4)
See the full prescribing information for administration modifications due to hypersensitivity reactions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 5 mg/5 mL (1 mg/mL) in single-dose vials. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Risk of Acute Respiratory Complications: Patients with acute febrile or respiratory illness may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of VIMIZIM and consider delaying the VIMIZIM infusion. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) are: pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin at 1-866-906-6100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS and RISK OF ACUTE RESPIRATORY COMPLICATIONS

Patients treated with enzyme replacement therapies have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.

Initiate VIMIZIM in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue VIMIZIM and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur *[see Warnings and Precautions (5.1)]*.

Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise due to hypersensitivity reactions and require additional monitoring *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

VIMIZIM (elosulfase alfa) is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Administration of VIMIZIM should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis *[see Warnings and Precautions (5.1)]*.
- Initiate VIMIZIM in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation *[see Warnings and Precautions (5.1)]*.
- This product must be diluted prior to administration and administered using a low-protein binding infusion set equipped with a low-protein binding 0.2 micrometer (µm) in-line filter.
- Consider pre-medicating with antihistamines, with or without antipyretics, 30 to 60 minutes prior to the start of the infusion *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

The recommended dosage of VIMIZIM is 2 mg/kg administered intravenously over a minimum range of 3.5 to 4.5 hours (based on infusion volume) once every week.

2.3 Administration Modifications Due to Hypersensitivity Reaction

In the event of a severe hypersensitivity reaction (e.g., anaphylaxis), discontinue the VIMIZIM infusion and immediately initiate appropriate medical treatment, including use of epinephrine. In the event of a mild to moderate hypersensitivity reaction, consider slowing or temporarily interrupting the infusion, or administering additional antihistamines, antipyretics, and/or corticosteroids *[see Warnings and Precautions (5.1)]*.

2.4 Preparation Instructions

Use aseptic technique during preparation.

1. Determine the number of VIMIZIM vials based on the patient's actual body weight in kg and the recommended dose *[see Dosage and Administration (2.2)]*.
2. Remove vials from the refrigerator.
3. Select the appropriate size 0.9% Sodium Chloride Injection, USP infusion bag and calculate the infusion volume based on patient's actual body weight:
   a. For patients who weigh less than 25 kg, the final infusion volume should be 100 mL
   b. For patients who weigh 25 kg or more, the final infusion volume should be 250 mL.
4. Withdraw and discard a volume of 0.9% Sodium Chloride Injection, USP from either the 100 mL or 250 mL infusion bag equal to the volume of VIMIZIM to be added.
5. Withdraw the required volume of VIMIZIM from the vial(s) and add to the 0.9% Sodium Chloride Injection, USP infusion bag. Gently rotate the infusion bag to mix the diluted solution. Avoid vigorous shaking or agitation. Discard unused portion remaining in the vial(s).
6. Visually inspect the solution for particulate matter and discoloration. The solution should be clear to slightly opalescent and colorless to pale yellow. The diluted VIMIZIM solution may contain proteinaceous particles in the form of translucent fibers which will be removed by the in-line filter during infusion. Discard if opaque particles are present or the solution is discolored.

2.5 Administration Instructions

Use an infusion set equipped with a low-protein binding 0.2 micrometer (µm) in-line filter to administer VIMIZIM.

Do not infuse with other products in the infusion tubing. Compatibility with other products has not been evaluated.

Table 1. Intravenous Infusion Rate for VIMIZIM Based on Patient Weight

Patient Weight (kg)	**Infusion rate (mL/hour)**			
	Initial Rate (first 15 minutes)	**Subsequent Rate (next 15 minutes)**	**Subsequent Rate Increments***	**Maximum Infusion Rate**
Less than 25 kg	3 mL/hour	6 mL/hour	6 mL/hour every 15 minutes	36 mL/hour
25 kg or more	6 mL/hour	12 mL/hour	12 mL/hour every 15 minutes	72 mL/hour

* If tolerated, the infusion rate can be increased incrementally up to the maximum infusion rate.

Table 2. Minimum Infusion Time for VIMIZIM Based on Patient Weight

Patient Weight (kg)	Minimum Infusion Time (hours)
Less than 25 kg	3.5 hours
25 kg or more	4.5 hours

2.6 Storage of the Diluted Solution

- If the diluted VIMIZIM solution is not used immediately:
  - Store the diluted solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature between 23°C to 27°C (73°F to 81°F) for up to 24 hours.
- Diluted VIMIZIM solution must be used within 48 hours, inclusive of total infusion time.
- Discard if not used within 48 hours.
- Do not freeze or shake.

3 DOSAGE FORMS AND STRENGTHS

Injection: 5 mg/5 mL (1 mg/mL) as a clear to slightly opalescent and colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with enzyme replacement therapies, including VIMIZIM. In premarketing clinical trials, 18 of 235 (7.7%) patients treated with VIMIZIM experienced signs and symptoms consistent with anaphylaxis. These 18 patients experienced 26 anaphylactic reactions during infusion with signs and symptoms including 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. These cases of 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 47^{th} infusion.

In clinical trials with VIMIZIM, 44 of 235 (18.7%) patients experienced hypersensitivity reactions, including anaphylaxis. Hypersensitivity reactions have occurred as early as 30 minutes from the start of infusion but as late as six days after infusion. Frequent symptoms of hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, peripheral edema, cough, dyspnea, and flushing.

Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Administration of VIMIZIM should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. Initiate VIMIZIM in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. Observe patients closely for an appropriate period of time after administration of VIMIZIM, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials.

Because of the potential for hypersensitivity reactions, administer antihistamines with or without antipyretics prior to infusion. Management of hypersensitivity reactions should be based on the severity of the reaction and include slowing or temporarily interrupting the infusion, and/or administering additional antihistamines, antipyretics, and/or corticosteroids for mild to moderate reactions. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue VIMIZIM and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.

Consider the risks and benefits of re-administering VIMIZIM following a severe reaction.

5.2 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. Careful consideration should be given to the patient's clinical status prior to administration of VIMIZIM and consider delaying the VIMIZIM infusion.

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

5.3 Spinal or Cervical 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 and patients receiving placebo. Patients with MPS IVA should be monitored for signs and symptoms of SCC (including back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence) and given appropriate clinical care.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity Reactions Including Anaphylaxis *[see Warnings and Precautions (5.1)]*.
- Risk of Acute Respiratory Complications *[see Warnings and Precautions (5.2)]*.
- Spinal or Cervical Cord Compression *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A 24-week, randomized, double-blind, placebo-controlled clinical trial of VIMIZIM was conducted in 176 patients with MPS IVA, ages 5 to 57 years old. Approximately half of the patients (49%) were male. Of the 176 patients, 65% were White, 23% Asian, 3% Black, and 10% Other race. The majority of patients (78%) were non-Hispanic. 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). All patients were treated with antihistamines prior to each infusion.

Table 3 summarizes the most common adverse reactions that occurred in the placebo-controlled trial with an incidence of ≥ 10% in patients treated with VIMIZIM 2 mg/kg once per week and with a higher incidence than in the placebo-treated patients.

Table 3: Adverse Reactions That Occurred in the Placebo-Controlled Trial in At Least 10% of Patients in the VIMIZIM 2 mg/kg Once Per Week Group and with a Higher Incidence than in the Placebo Group

Adverse Reaction	**VIMIZIM 2 mg/kg once per week**	**Placebo**
	N= 58 n (%)	**N= 59 n (%)**
Pyrexia	19 (33%)	8 (14%)
Vomiting	18 (31%)	4 (7%)
Headache	15 (26%)	9 (15%)
Nausea	14 (24%)	4 (7%)
Abdominal pain	12 (21%)	1 (2%)
Chills	6 (10%)	1 (2%)
Fatigue	6 (10%)	2 (3%)

Extension Trial

An open-label extension trial was conducted in 173 patients who completed the placebo-controlled trial *[see Clinical Studies (14)]*. No new adverse reactions were reported.

6.2 Immunogenicity

As with all therapeutic proteins, including VIMIZIM, there is potential for immunogenicity. The detection 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 in other studies or to other elosulfase alfa products may be misleading.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published case reports, a registry with a pregnancy sub-study and pharmacovigilance reports with VIMIZIM use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Limitations of the available data include a small number of exposed cases and missing data.

In animal reproduction studies, 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 concentration-time 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, which produced maternal toxicity. 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.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo/fetal risk

Pregnancy can exacerbate preexisting clinical manifestations of MPS and lead to adverse outcomes for both mother and fetus.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There are no data on the presence of elosulfase alfa in human milk, the effects on the breastfed infant, or the effects on milk production. Elosulfase alfa is present in milk from treated rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. 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 infant from VIMIZIM or from the underlying maternal condition.

Data

Elosulfase alfa was detected in 1 of 5 milk samples from rat dams administered 6 mg/kg/day elosulfase alfa and 4 of 5 milk samples from dams administered 20 mg/kg/day elosulfase alfa. The concentration of drug in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

Safety and effectiveness of VIMIZIM have been established in pediatric patients 5 years of age and older. Use of VIMIZIM in patients 5 years of age and older is supported by an adequate and well-controlled trial in pediatric and adult patients. Clinical trials with VIMIZIM were conducted in 176 patients (median age 12 years, range 5 to 57 years old) with the majority of patients in the pediatric age group (53% aged 5 to 11 years, 27% aged 12 to 17 years) *[see Clinical Studies (14)]*. Safety and effectiveness in pediatric patients below 5 years of age have not been established.

8.5 Geriatric Use

Clinical studies of VIMIZIM did not include any patients aged 65 and over. It is not known whether they respond differently from younger patients.

11 DESCRIPTION

Elosulfase alfa is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. Human N-acetylgalactosamine-6-sulfatase (EC 3.1.6.4) 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).

Elosulfase alfa is a soluble glycosylated dimeric protein with two oligosaccharide chains per monomer. Each monomeric peptide chain contains 496 amino acids and has an approximate molecular mass of 55 kDa (59 kDa including the oligosaccharides). One of the oligosaccharide chains contains bis-mannose-6-phosphate (bisM6P). bisM6P binds a receptor at the cell surface and the binding mediates cellular uptake of the protein to the lysosome. Elosulfase alfa has a specific activity of 2.6 to 6.0 units/mg. One activity unit is defined as the amount of the enzyme required to convert 1 micromole of sulfated monosaccharide substrate D-galactopyranoside-6-sulfate (Gal-6S) to de-sulfated-galactose (Gal) and free sulfate per minute at 37°C.

VIMIZIM (elosulfase alfa) injection is a sterile, preservative-free, nonpyrogenic, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion after dilution. Each single-dose vial contains 5 mL solution of 5 mg elosulfase alfa, 31.6 mg arginine hydrochloride, 34.5 mg monobasic sodium phosphate, 0.5 mg polysorbate 20, 8.2 mg sodium acetate, and 100 mg sorbitol in Water for Injection, USP with a pH between 5 to 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mucopolysaccharidoses comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). Mucopolysaccharidosis IVA (MPS IVA, Morquio A Syndrome) 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, KS and C6S, in the lysosomal compartment of cells throughout the body. The accumulation leads to widespread cellular, tissue, and organ dysfunction. VIMIZIM 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.

12.2 Pharmacodynamics

The pharmacodynamic effect of VIMIZIM was assessed by reductions in urinary KS

levels. The relationship of urinary KS to other measures of clinical response has not been established *[see Clinical Studies (14)]*. No association was observed between antibody development and urinary KS levels.

12.3 Pharmacokinetics

The pharmacokinetics of elosulfase alfa were evaluated in 23 patients with MPS IVA who received intravenous infusions of VIMIZIM 2 mg/kg once weekly, over approximately 4 hours, for 22 weeks. Eleven patients were aged 5 to 11 years, six were aged 12 to 17 years, and six were aged 18 to 41 years. Table 4 summarizes the pharmacokinetic parameters at Week 0 and Week 22. Mean $AUC_{0\text{-}t}$ and C_{max} increased to 2.8- and 2.9-fold, respectively, at Week 22 compared to Week 0. Mean $t_{1/2}$ increased from 7.5 min at Week 0 to 35.9 min at Week 22. These changes are likely related to the development of neutralizing antibodies in all patients.

Table 4: Pharmacokinetic Parameters

Pharmacokinetic Parameter	Week 0 (N = 22)* Mean (SD)	Week 22 (N = 22)* Mean (SD)
$AUC_{0\text{-}t}$, min × mcg/mL†	238 (100)	577 (416)
C_{max}, mcg/mL‡	1.49 (0.534)	4.04 (3.24)
T_{max}, min§	172 (75.3)	202 (90.8)
CL, mL/min/kg¶	10.0 (3.73)#	7.08 (13.0)Þ
V_{dss}, mL/kgß	396 (316) à	650 (1842) Þ
$t_{1/2}$, minè	7.52 (5.48) #	35.9 (21.5) Þ

* 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;
§ T_{max}, time from zero to maximum plasma concentration;
¶ CL, total clearance of drug after intravenous administration;
# N = 15;
Þ N = 20;
ß V_{dss}, apparent volume of distribution at steady-state;
à N = 14;
è $t_{1/2}$, elimination half-life

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with elosulfase alfa. Based on the mechanism of action, elosulfase alfa is not expected to be tumorigenic. Daily intravenous administration of elosulfase alfa in rats at doses up to 20 mg/kg (55 times the human steady-state AUC in male rats and 33 times the human steady-state AUC in female rats at the recommended human weekly dose) had no effects on fertility or reproductive performance.

14 CLINICAL STUDIES

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. The age of patients ranged from 5 to 57 years. The majority of the patients (82%) presented with a medical history of musculoskeletal conditions, which includes 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), VIMIZIM 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) at Week 24. The other endpoints included changes from baseline in the rate of stair climbing in three minutes (three-minute stair climb test, 3-MSCT) and changes from baseline in urine KS levels at Week 24. The treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5 m (CI_{95}, 4.0, 40.9; p=0.0174) in patients who received VIMIZIM 2 mg/kg once per week. There was no difference in the 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 urinary KS levels from baseline, a measure of pharmacodynamic effect, was greater in the VIMIZIM treatment groups compared to placebo. The relationship between urinary KS and other measures of clinical response has not been established.

Table 5: Results from Placebo-Controlled Clinical Trial

	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**	
Six-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	216.5	251.0	20.0	228.9	229.4	9.9	22.5‡ (CI_{95}, 4.0, 40.9)
Min, Max	42.4, 321.5	52.0, 399.9	-57.8, 228.7	36.2, 312.2	50.6, 501.0	-99.2, 220.5	(p = 0.0174)‡,§

* One patient in the VIMIZIM group dropped out after 1 infusion
† Observed VIMIZIM mean change – Placebo mean change
‡ ANCOVA Model-based VIMIZIM mean change – Placebo mean change, adjusted for baseline 6MWT categories (less than or equal to 200 meters, greater than 200 meters) and age groups (5-11, 12-18, 19 or older)
§ p-value based on the model-based difference in means

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 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). In patients who continued to receive VIMIZIM 2 mg/kg once per week for another 48 weeks (for a total of 72-week exposure), walking ability showed no further improvement beyond the first 24 weeks of treatment in the placebo-controlled trial.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VIMIZIM (elosulfase alfa) injection is supplied as a sterile, preservative-free, clear to slightly opalescent, clear to pale yellow solution in a single-dose vial. Each vial contains 5 mg/5 mL (1 mg/mL) of elosulfase alfa. VIMIZIM is available as:

One single-dose vial in a carton (NDC 68135-100-01)

Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylaxis

Advise the patient or caregiver that life-threatening hypersensitivity reactions, including anaphylaxis may occur with VIMIZIM treatment.

Advise the patient or caregiver that anaphylaxis has occurred during the early course of enzyme replacement therapy and after 1extended duration of therapy.

Inform the patient or caregiver of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis, and to seek immediate medical care should symptoms occur. The risks and benefits of re-administering VIMIZIM following a severe reaction should be considered *[see Warnings and Precautions (5.1)]*.

Manufactured by:
BioMarin Pharmaceutical Inc.
Novato, CA 94949
US License Number 1649
1-866-906-6100 (phone)

PRINCIPAL DISPLAY PANEL - 5 mL Vial Carton

NDC 68135-100-01

Vimizim®
(elosulfase alfa)

Injection

5 mg/5 mL (1 mg/mL)

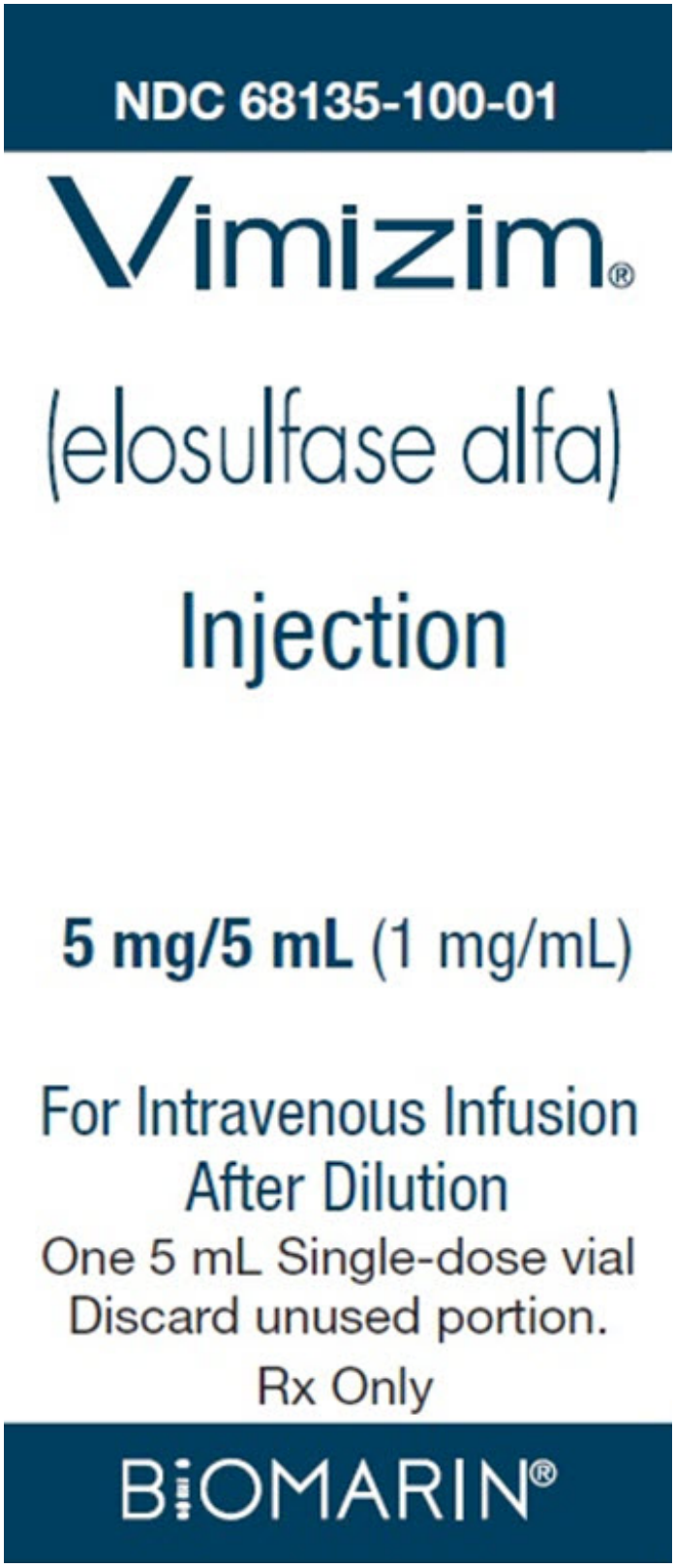
For Intravenous Infusion

After Dilution

One 5 mL Single-dose vial
Discard unused portion.

Rx Only

BiOMARIN®



VIMIZIM

elosulfase alfa injection, solution, concentrate

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68135-100
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ELOSULFASE ALFA (UNII: ODJ69JZG85) (ELOSULFASE ALFA - UNII:ODJ69JZG85)	ELOSULFASE ALFA	5 mg in 5 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68135-100-01	1 in 1 CARTON	02/14/2014	
1		5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125460	02/14/2014	

Labeler - BioMarin Pharmaceutical Inc. (079722386)

Revised: 10/2025 BioMarin Pharmaceutical Inc.