



VIMIZIM[®]
(elosulfase alfa)

VIMIZIM[®] (elosulfase alfa)—
DOSING AND ADMINISTRATION GUIDE



INDICATION

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

Life-threatening anaphylactic reactions have occurred in some patients during VIMIZIM[®] (elosulfase alfa) 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 have been reported to occur 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 of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. 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.

Please see Important Safety Information, including boxed warning, on page 3.

BIOMARIN



INDICATION

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

IMPORTANT SAFETY INFORMATION

Life-threatening anaphylactic reactions have occurred in some patients during VIMIZIM® (elosulfase alfa) 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, have been reported to occur 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 of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. 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.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when VIMIZIM is administered and for an appropriate period of time following administration. In clinical trials, cases of anaphylaxis occurred as early as 30 minutes from the start of infusion and up to 3 hours after infusion, and as late into treatment as the 47th infusion.

In clinical trials, hypersensitivity reactions have been observed as early as 30 minutes from the start of infusion but as late as 6 days after infusion. Frequent symptoms of hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, peripheral edema, cough, dyspnea, and flushing.

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 temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids for mild reactions. However, if severe hypersensitivity 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.

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.

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.

All patients treated with VIMIZIM 2 mg/kg once per week in the placebo-controlled trial developed anti-drug antibodies. The relationship between the presence of neutralizing antibodies and long-term therapeutic response or occurrence of anaphylaxis or other hypersensitivity reactions could not be determined.

VIMIZIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known if VIMIZIM is present in human milk. Exercise caution when administering VIMIZIM to a nursing mother. There is a Morquio A Registry that collects data on pregnant women and nursing mothers with MPS IVA who are treated with VIMIZIM. Contact MARS@BMRN.com for information and enrollment.

Safety and effectiveness in pediatric patients below 5 years of age have not been established and are currently being evaluated.

In clinical trials, the most common adverse reactions ($\geq 10\%$) occurring during infusion included pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue. The acute reactions requiring intervention were managed by either temporarily interrupting or discontinuing infusion, and administering additional antihistamine, antipyretics, or corticosteroids.

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

Please see accompanying full Prescribing Information, including boxed warning, or visit www.VIMIZIM.com.

RECOMMENDED DOSE

- VIMIZIM® (elosulfase alfa) is an injectable solution for infusion; VIMIZIM comes in 5-mL, single-use vials
- The recommended dose of VIMIZIM is 2 mg/kg of body weight given intravenously over a minimum of either 3.5 or 4.5 hours, based on infusion volume, once every week
- Pretreatment with antihistamines (with or without antipyretics) is recommended 30 to 60 minutes prior to the start of the infusion

CALCULATING THE DOSE

- Weigh the patient to accurately calculate the required number of VIMIZIM vials
- Determine the number of vials to be diluted based on the patient's weight and the recommended dose of 2 mg/kg

1 TO GET THE PATIENT DOSE:

Patient weight (kg) \times 2 mg/kg dose = Patient dose = total mL of VIMIZIM^a

2 TO FIND OUT HOW MANY VIALS OF VIMIZIM THE PATIENT NEEDS:

Total mL of VIMIZIM \div 5 mL per vial = Total number of vials

^aMilligrams of VIMIZIM required divided by 1-mg/mL concentrate of VIMIZIM.

Dose calculation example for patient who weighs <25 kg

Always use a 100-mL infusion bag for patients who weigh <25 kg.

Patient weight (20 kg) \times dose (2 mg/kg) = patient dose (40 mL of VIMIZIM)^a

Total amount of VIMIZIM (40 mL) divided by 5 mL per vial = 8 total vials.

^aNote: To convert kilograms (kg) to pounds (lb), multiply by 2.2. Then, use 0.9 mL of VIMIZIM per pound of body weight.

Dose calculation example for patient who weighs \geq 25 kg

Always use a 250-mL infusion bag for patients who weigh \geq 25 kg.

Patient weight (30 kg) \times dose (2 mg/kg) = patient dose (60 mL of VIMIZIM)^a

Total amount of VIMIZIM (60 mL) divided by 5 mL per vial = 12 total vials.

^aNote: To convert kilograms (kg) to pounds (lb), multiply by 2.2. Then, use 0.9 mL of VIMIZIM per pound of body weight.

SUPPLIES NEEDED

- A** VIMIZIM® (elosulfase alfa) 5-mL, single-use vials
- B** 0.9% Sodium Chloride Injection, USP infusion bag (100 mL or 250 mL)
- C** Low-protein binding infusion set equipped with a low-protein binding 0.2-µm in-line filter

DILUTION PRIOR TO ADMINISTRATION

Prepare VIMIZIM for dilution using aseptic technique.

VIMIZIM must be diluted with 0.9% Sodium Chloride Injection, USP to a final volume of 100 mL or 250 mL (based on the patient's weight) prior to infusion and delivered intravenously.

For patients who weigh <25 kg, VIMIZIM should be prepared in 100-mL 0.9% Sodium Chloride Injection, USP bags. For patients who weigh ≥25 kg, VIMIZIM should be prepared in 250-mL 0.9% Sodium Chloride Injection, USP bags.

Administration of VIMIZIM should be completed within 48 hours of dilution. See additional storage information below.



STORAGE AND CARE OF PRODUCT

- Vials are for single-use only
- Discard any unused product
- Do not freeze or shake
- Protect from light
- VIMIZIM does not contain preservatives; therefore, the product should be used immediately after dilution; if immediate use is not possible, the diluted product may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F) followed by up to 24 hours at 23°C to 27°C (73°F to 81°F)

PREPARE AND ADMINISTER VIMIZIM® (elosulfase alfa) ACCORDING TO THE FOLLOWING STEPS

This product should be prepared and administered under the supervision of a healthcare professional with the ability to manage medical emergencies.



AVOID AGITATION DURING PREPARATION

COMPLETE THE DOSE CALCULATION explained on page 4 of this brochure to determine how many vials of VIMIZIM® (elosulfase alfa) you will need.

REMOVE the appropriate number of vials from the refrigerator. Do not heat or microwave vials.



OBTAIN AN INFUSION BAG containing 0.9% Sodium Chloride Injection, USP suitable for intravenous administration. The final volume of the infusion is determined by the patient's body weight.

BODY WEIGHT	VOLUME OF INFUSION
<25 kg	100 mL
≥25 kg	250 mL



INSPECT EACH VIAL for particulate matter or discoloration before withdrawing VIMIZIM from the vial. The VIMIZIM solution should be clear to slightly opalescent and colorless to pale yellow when diluted. Do not use if the solution is discolored or if there is particulate matter in the solution. Note that a diluted solution with slight flocculation (e.g., thin translucent fibers) is acceptable for administration.



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.



SLOWLY WITHDRAW the calculated volume of VIMIZIM from the appropriate number of vials and add to the infusion bag. Gently rotate the infusion bag to ensure proper distribution of VIMIZIM. Do not shake the solution.



ADMINISTER THE DILUTED VIMIZIM solution to patients using a low-protein binding infusion set equipped with a 0.2-µm in-line filter.

The infusion rate may be slowed, temporarily stopped, or discontinued for that visit in the event of hypersensitivity reactions. No other products should be infused in the tubing for VIMIZIM. Compatibility with other products has not been evaluated.

Closely observe patients during and after VIMIZIM administration and be prepared to manage anaphylaxis. Consider the risks and benefits of re-administering VIMIZIM following a severe reaction.

In clinical trials, the most common adverse reactions (≥10%) occurring during infusion included pyrexia, vomiting, headache, nausea, abdominal pain, chills, and fatigue. The acute reactions requiring intervention were managed by either temporarily interrupting or discontinuing infusion and administering additional antihistamines, antipyretics, or corticosteroids.

In clinical trials, 18.7% of patients treated with VIMIZIM experienced hypersensitivity reactions, including 7.7% experiencing anaphylaxis.

To learn more about serious and severe adverse reactions, please see page 11.

To report suspected adverse reactions, contact

- BioMarin Pharmaceutical Inc. at 1-866-906-6100 or email drugsafety@bmrn.com
- FDA at 1-800-FDA-1088 or go to www.fda.gov/medwatch

INFUSION RATES BY PATIENT WEIGHT

For your patient weighing <25 kg

- Prepare VIMIZIM® (elosulfase alfa) in 100-mL 0.9% Sodium Chloride Injection, USP bag
- The initial infusion rate should be 3 mL/h for the first 15 minutes
- The infusion rate may be **increased as tolerated** every 15 minutes. First increase the rate to 6 mL/h, then increase the rate every 15 minutes by 6-mL increments until a maximum rate of 36 mL/h is reached (see table below)
- The total volume of the infusion should be delivered over a **minimum** of 3.5 hours

Time (minutes)	Rate of Infusion (mL/h)
0-15	3
15-30	6
30-45	12
45-60	18
60-75	24
75-90	30
90+	36

For your patient weighing ≥25 kg

- Prepare VIMIZIM in 250-mL 0.9% Sodium Chloride Injection, USP bag
- The initial infusion rate should be 6 mL/h for the first 15 minutes
- The infusion rate may be **increased as tolerated** every 15 minutes. First increase the rate to 12 mL/h, then increase the rate every 15 minutes by 12-mL increments until a maximum rate of 72 mL/h is reached (see table below)
- The total volume of the infusion should be delivered over a **minimum** of 4.5 hours

Time (minutes)	Rate of Infusion (mL/h)
0-15	6
15-30	12
30-45	24
45-60	36
60-75	48
75-90	60
90+	72

WARNINGS AND PRECAUTIONS

Anaphylaxis and hypersensitivity reactions

Anaphylaxis and hypersensitivity reactions have been reported in patients treated with 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 3 hours after infusion. Anaphylaxis occurred as late into treatment as the 47th 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 6 days after infusion. Frequent symptoms of hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, peripheral edema, cough, dyspnea, and flushing.

Due to the potential for anaphylaxis, appropriate medical support should be readily available when VIMIZIM is administered. 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. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur.

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 temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids for mild reactions. If severe hypersensitivity 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.

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 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.

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.

BIOMARIN RARECONNECTIONS™: YOUR PARTNER IN CARE

BioMarin RareConnections™ provides personal support to patients, caregivers, and healthcare professionals, connecting them to valuable resources that complement rare disease therapy.



SUPPORT FOR YOU:

- Helping office staff and treating physicians navigate the reimbursement process
- Infusion-day coordination and logistics
- Providing ongoing product support for BioMarin therapies

SUPPORT FOR PATIENTS:

- Education on Morquio A and VIMIZIM® (elosulfase alfa) single-use vials
- Helping patients understand insurance coverage and financial assistance options
- Working with patients or their caregivers to coordinate delivery of BioMarin therapies

To contact BioMarin RareConnections™, call 1-866-906-6100 or email us at support@biomarin-rareconnections.com.

Please see Important Safety Information, including boxed warning, on page 3.

Reference: VIMIZIM [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2019.