NAGLAZYME® (galsulfase) DOSING & ADMINISTRATION GUIDE

Naglazyme®
(GALSULFASE)

Indication: NAGLAZYME® (galsulfase) is indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). NAGLAZYME has been shown to improve walking and stair-climbing capacity.[1]

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

INDICATION

NAGLAZYME® (galsulfase) is indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). NAGLAZYME has been shown to improve walking and stair-climbing capacity.

IMPORTANT SAFETY INFORMATION

Life-threatening anaphylactic reactions and severe allergic reactions have been observed in some patients during NAGLAZYME (galsulfase) infusions and up to 24 hours after infusion. If these reactions occur, immediate discontinuation of NAGLAZYME is recommended and appropriate medical treatment should be initiated, which may include resuscitation, epinephrine, administering additional antihistamines, antipyretics or corticosteroids. In patients who have experienced anaphylaxis or other severe allergic reactions during infusion with NAGLAZYME, caution should be exercised upon rechallenge; appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) should be available during infusions.

As with other enzyme replacement therapies, immune-mediated reactions, including membranous glomerulonephritis have been observed. In clinical trials, nearly all patients developed antibodies as a result of treatment with NAGLAZYME; however, the analysis revealed no consistent predictive relationship between total antibody titer, neutralizing or IgE antibodies, and infusion-associated reactions, urinary glycosaminoglycan (GAG) levels, or endurance measures.

Caution should be exercised when administering NAGLAZYME to patients susceptible to fluid volume overload because congestive heart failure may result. Consider a decreased total infusion volume and infusion rate when administering NAGLAZYME to these patients.

Consideration to delay NAGLAZYME infusion should be given when treating patients who present with an acute febrile or respiratory illness. Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic episodes. Evaluation of airway patency should be considered prior to the initiation of treatment. 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 infusion reaction, or extreme drowsiness/sleep induced by antihistamine use.

Pretreatment with antihistamines with or without antipyretics is recommended prior to the start of infusion to reduce the risk of infusion reactions. If infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antihistamines and/or antipyretics is recommended.

During infusion, serious adverse reactions included laryngeal edema, apnea, pyrexia, urticaria, respiratory distress, angioedema, and anaphylactoid reaction; severe adverse reactions included urticaria, chest pain, rash, abdominal pain, dyspnea, apnea, laryngeal edema, and conjunctivitis. The most common adverse events (≥10%) observed in clinical trials in patients treated with NAGLAZYME were rash, pain, urticaria, pyrexia, pruritus, chills, headache, nausea, vomiting, abdominal pain, and dyspnea. The most common adverse reactions requiring interventions are infusion-related reactions.

Spinal/cervical cord compression is a known and serious complication that is expected to occur during the natural course of MPS VI. Signs and symptoms of spinal/cervical cord compression include back pain, paralysis of limbs below the level of compression, and urinary or fecal incontinence. Patients should be evaluated for spinal/cervical cord compression prior to initiation of NAGLAZYME to establish a baseline and risk profile. Patients treated with NAGLAZYME should be regularly monitored for the development or progression of spinal/cervical cord compression and be given appropriate clinical care.

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.

RECOMMENDED DOSE[1]

- NAGLAZYME® (galsulfase) is supplied as a sterile injection in clear, type I glass, 5-mL vials containing 5 mg of galsulfase.
- The recommended dose of NAGLAZYME is 1 mg/kg of body weight, administered once weekly as an IV infusion over no less than 4 hours.
- Pretreatment with antihistamines, with or without antipyretics, is recommended 30 to 60 minutes prior to the start of the infusion.

CALCULATING THE DOSE[1]

Determine the number of vials needed based on the individual patient's weight and the recommended dose of 1 mg/kg. Round up to the next whole vial.

STEP 1	Patient weight (kg)	×	1 mL/kg of NAGLAZYME	=	**Total mL NAGLAZYME** (patient dose)
STEP 2	**Total mL NAGLAZYME** (patient dose)	÷	5 mL per vial	=	**Total number of vials needed** (round up to the next whole vial)

NOTE: To convert pounds (lb) to kilograms (kg), divide pounds by 2.2.

Dose calculation example for a patient who weighs ≤20 kg

Consider the use of 100-mL infusion bags for patients who weigh ≤20 kg or are susceptible to fluid overload due to pulmonary disease, cardiac valvular disease, or congestive heart failure.

1	**18 kg** Patient weight	×	1 mL/kg of NAGLAZYME® (galsulfase)	=	**18 mL** NAGLAZYME
2	**18 mL** NAGLAZYME	÷	5 mL per vial	=	**4 vials of NAGLAZYME** (3.6 vials, rounded up to the next whole vial)

Dose calculation example for a patient who weighs >20 kg

1	**42 kg** Patient weight	×	1 mL/kg of NAGLAZYME	=	**42 mL** NAGLAZYME
2	**42 mL** NAGLAZYME	÷	5 mL per vial	=	**9 vials of NAGLAZYME** (8.4 vials, rounded up to the next whole vial)

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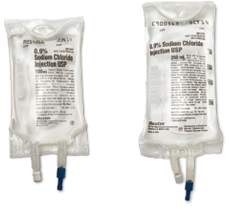
Naglazyme® (GALSULFASE)

GATHERING YOUR SUPPLIES[1]



- NAGLAZYME® (galsulfase) 5-mL, single-use vials
- 0.9% Sodium Chloride Injection, USP, infusion bag (100 mL or 250 mL)
- Low-protein-binding straight IV tubing (no Volutrol or Buretrol) with 0.2-µm in-line filter

STORING NAGLAZYME® (galsulfase)[1]

Store NAGLAZYME vials under refrigeration at 2°C to 8°C (36°F to 46°F).

- **Do not** freeze or shake.
- **Do not** use after expiration date on vial.

DILUTING NAGLAZYME® (galsulfase) PRIOR TO ADMINISTRATION[1,2]

Determine the total infusion volume. All MPS VI study patients, including those with weights as low as 14 kg, were infused using 250-mL total volume.[2]

Consider using 100-mL infusion bags for patients who are ≤20 kg or susceptible to fluid overload due to pulmonary disease, cardiac valvular disease, or congestive heart failure.[1]

For a 250-mL infusion bag[1]

- Withdraw and discard a volume from the 0.9% Sodium Chloride Injection, USP, infusion bag equal to the volume of NAGLAZYME® (galsulfase) to be added.

For a 100-mL infusion bag[1]

- Withdrawing and discarding of dose volume IS NOT necessary.
- Add the dose volume directly to the infusion bag.

- NAGLAZYME contains no preservatives and should be used immediately following preparation.[1]
- Prepared NAGLAZYME must be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 48 hours from the time of preparation to completion of administration.[1]

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PREPARATION AND ADMINISTRATION[1,3]

Prepare and use NAGLAZYME® (galsulfase) according to the following steps. Use aseptic techniques.[1]

Please follow your institution's protocols and prescribing physician's orders for administration.

- **Determine** the number of vials needed by completing the dose calculation outlined on page 4 and remove the required number of vials from the refrigerator to allow them to reach room temperature. **Do not** heat or microwave vials or allow them to remain at room temperature longer than 24 hours prior to dilution.[1]

- **Inspect** each vial for particulate matter and discoloration before withdrawing the NAGLAZYME solution from the vial. The solution should be clear to slightly opalescent and colorless to pale yellow. Some translucency may be present in the solution. **Do not** use NAGLAZYME if the solution is discolored or if there is particulate matter in the solution.[1]

- **Withdraw and discard** from a 250-mL infusion bag of 0.9% Sodium Chloride Injection, USP, a volume equal to the volume of NAGLAZYME solution to be added. If using a 100-mL infusion bag, this step is not necessary.[1]

- **Slowly withdraw** the calculated volume of NAGLAZYME from the appropriate number of vials, then slowly add the NAGLAZYME solution to the 0.9% Sodium Chloride Injection, USP, using care to avoid agitation of the solutions. **Do not** use a filter needle or shake the solution, as this may cause agitation. Agitation may denature NAGLAZYME, rendering it biologically inactive. Gently rotate the infusion bag to ensure proper distribution of NAGLAZYME.[1]

- **Administer** the diluted NAGLAZYME® (galsulfase) solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2-µm in-line filter.[1]
  - » Any unused product or waste material must be discarded and disposed of in accordance with local requirements.

NAGLAZYME must not be infused with other products in the infusion tubing. The compatibility of NAGLAZYME in solution with other products has not been evaluated.[1]

Infusion-rate examples[1,3]

	250-mL volume[1]	120-mL volume[3]
First hour	6 mL	3 mL
Remaining 3+ hours	Increase to 80 mL/h	Increase to 39 mL/h

Patient vital signs should be monitored for signs of infusion reactions.

Can I infuse NAGLAZYME® (galsulfase) at a faster rate?

Although patients and families often ask if the infusion can be administered in a shorter amount of time, NAGLAZYME should NOT be administered at a faster rate than recommended. The safety and efficacy of NAGLAZYME have been established in clinical studies when administered over the specified period of time.[1]

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SPECIAL SAFETY CONSIDERATIONS FOR PATIENTS WITH AIRWAY OBSTRUCTION[1]

Patients with highly compromised upper airway disease warrant close monitoring during infusions.

- Sleep apnea is common in patients with MPS VI and antihistamine pretreatment may increase the risk of apneic episodes.
- Caution should be exercised when administering prophylactic antihistamines as patients may have difficulty breathing during deep sleep.
- Use of CPAP or bi-level positive airway pressure (BiPAP) during infusion should be considered in patients with sleep apnea who are using positive airway pressure machines.
- Evaluation of airway patency should be considered prior to initiation of treatment due to the increased risk of sleep apnea.

OBSERVE THE PATIENT FOR INFUSION-ASSOCIATED REACTIONS (IARs)[1,4]

During infusion, monitor the patient for the following signs that may indicate an IAR[1]:

- Increase or decrease in heart rate
- Increase or decrease in respiratory rate
- Decrease in oxygen saturation (pulse oximetry)
- Increase or decrease in body temperature

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Adverse reactions[1]

Serious or severe

- Laryngeal edema
- Apnea
- Pyrexia
- Urticaria
- Respiratory distress
- Chest pain
- Dyspnea
- Conjunctivitis
- Anaphylaxis
- Shock
- Hypotension
- Bronchospasm
- Respiratory failure

The most common adverse reactions (≥10%) are:

- Rash
- Pain
- Urticaria
- Pyrexia
- Pruritus
- Chills
- Headache
- Nausea
- Vomiting
- Abdominal pain
- Dyspnea

Mild symptoms may progress rapidly to become more severe if the patient is untreated. Monitor patients throughout the infusion.[1]

If an IAR occurs:

- Stop the infusion promptly.[1]
- Assess and appropriately manage the patient's symptoms.[1]
- Consider administering additional antihistamines, antipyretics, and possibly corticosteroids.[1]
- If symptoms subside, consider restarting the infusion at a slower rate.[1]
- Subsequent infusions may be managed with a slower rate (infusion time can be extended to 20 hours if IARs occur), additional prophylactic antihistamines, antipyretics, and possibly prophylactic corticosteroids.[1]
- The physician should evaluate risks and benefits of re-administering NAGLAZYME® (galsulfase) following a severe reaction.[1]
- Caution should be exercised if epinephrine use is being considered in patients with MPS VI due to increased prevalence of coronary artery disease.[1,4]

An IAR may not occur until multiple infusions have been given.[1]

- First IARs occurred as late as 146 weeks in the clinical studies of NAGLAZYME.
- Therefore, it is important that:
  - A physician be available or accessible by phone or pager at time of infusion
  - Nurses monitor the patient closely and observe for IAR symptoms
  - Emergency procedures be in place in the event a severe IAR occurs
  - Patients and/or parents are educated and encouraged to promptly report IAR symptoms. This is especially important for parents of younger patients who may not be able to report IAR symptoms.

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BIOMARIN

BIOMARIN RARECONNECTIONS™: UNCOMMON SUPPORT FOR RARE DISEASES

BioMarin RareConnections provides a wide array of product support services that include an experienced case manager who will work with patients and caregivers to help them understand insurance access and coverage, provide information about final assistance options, coordinate delivery of BioMarin products for therapy, and provide ongoing product support throughout their treatment journey.

BioMarin Rare Connections™

Contact BioMarin RareConnections at 1-866-906-6100 or email support@biomarin-rareconnections.com.

Please see Important Safety Information throughout, and accompanying full Prescribing Information.

References: 1. NAGLAZYME [package insert]. Novato, CA: BioMarin Pharmaceutical Inc; 2019. **2.** Harmatz P, Giugliani R, Schwartz I, et al; MPS VI Phase 3 Study Group. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. *J Pediatr*. 2006;148(4):533-539. doi:10.1016/j.jpeds.2005.12.014. **3.** Data on file. BioMarin Pharmaceutical Inc. **4.** Swiedler SJ, Beck M, Bajbouj M, et al. Threshold effect of urinary glycosaminoglycans and the walk test as indicators of disease progression in a survey of subjects with mucopolysaccharidosis VI (Maroteaux–Lamy syndrome). *Am J Med Genet A*. 2005;134A(2):144-150. doi:10.1002/ajmg.a.30579.

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