
Naglazyme® (galsulfase)

Dosing and Administration Guide

Your guide to using the first and only enzyme replacement therapy for Maroteaux-Lamy syndrome (MPS VI)

Indication

NAGLAZYME® (galsulfase) indicated for patients with mucopolysaccharidosis VI (MPS VI).

NAGLAZYME has been shown to improve walking and stair-climbing capacity.

Important Safety Information

The most common adverse events observed in clinical trials in patients treated with NAGLAZYME were headache, fever, arthralgia, vomiting, upper respiratory infections, abdominal pain, diarrhea, ear pain, cough, and otitis media. Severe reactions included angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea, and urticaria. The most common symptoms of infusion reactions included fever, headache, rash, and mild to moderate urticaria. Nausea, vomiting, elevated blood pressure, retrosternal pain, abdominal pain, malaise, and joint pain were also reported. No patients discontinued for adverse events and all patients who completed the double-blind portion of the trial continued to receive weekly infusions of NAGLAZYME. Nearly all patients developed antibodies as a result of treatment, but the level of immune response did not correlate with the severity of adverse events. Because antihistamine use may increase the risk of apneic episodes, evaluation of airway patency should be considered prior to the initiation of treatment. Consideration to delay infusion of NAGLAZYME should be given when treating patients who present with an acute febrile or respiratory illness.

For more information visit www.naglazyme.com



Naglazyme®
(GALSULFASE)

BIOMARIN™

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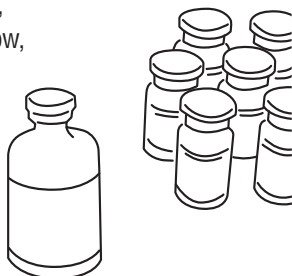
Dosage and administration

Overview

These following steps are recommended for dosing and administration of NAGLAZYME (galsulfase). In addition, please follow your institution's protocols and prescribing physician's orders for administration.

How supplied

- NAGLAZYME is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution
- Each 5-mL single-use vial provides 5 mg of galsulfase (expressed as protein content)

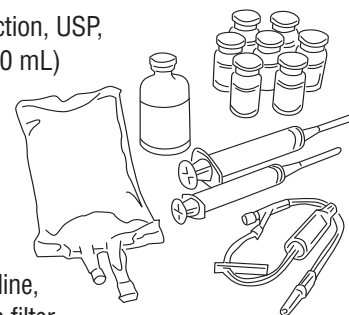


Precautions

- Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion
- It is important to evaluate airway patency prior to initiation of treatment with NAGLAZYME in case of drowsiness caused by antihistamine use. Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic episodes
- Patients using supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these available during infusion in case of an infusion reaction or drowsiness caused by antihistamine use
- Consider delaying infusion in patients who present with an acute febrile or respiratory illness

Supplies needed

- NAGLAZYME 5-mL single-use vials
- 0.9% Sodium Chloride Injection, USP, infusion bag (100 mL or 250 mL)
- Syringes for dilution
- 18-gauge needles without filtering devices for dilution
- PVC straight IV tubing (no Volutrol or Buretrol) in-line, low-protein-binding 0.2- μ m filter
- Additional supplies per institutional protocols



Dosage recommendations

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.

Preparation

1. Determine the number of vials needed using the 2-step formula below. Round to the nearest whole vial. Remove the required number of vials from the refrigerator and allow them to reach room temperature. Do not allow vials to remain at room temperature longer than 24 hours prior to dilution. Do not heat or microwave vials.

Step 1: Patient's weight (kg) x 1 mL/kg of NAGLAZYME
= Total mL NAGLAZYME

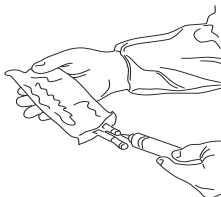
Step 2: Total mL NAGLAZYME ÷ 5 mL per vial
= Total vials needed

Dosage and administration

2. Visually inspect each vial for particulate matter and discoloration. The solution should be clear to slightly opalescent and colorless to pale yellow. A few translucent particles may be present. Do not use if the solution is discolored or if there is particulate matter in the solution.

3. 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. Consider using a 100-mL infusion bag for patients who are: 20 kg and under, or susceptible to fluid overload due to pulmonary disease, cardiac valvular disease, or congestive heart failure.



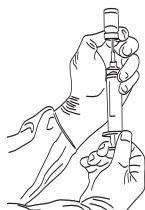
For a 250-mL infusion bag

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

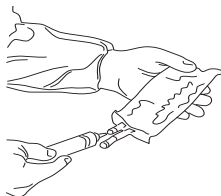
For a 100-mL infusion bag

- Withdrawing and discarding of dose volume is not necessary. Add the dose volume directly to the infusion bag

4. Slowly withdraw the calculated dose of NAGLAZYME from the appropriate number of vials, using caution to avoid excessive agitation, bubbles, and foaming. Agitation may render NAGLAZYME biologically inactive.



5. Add the NAGLAZYME solution to the 0.9% Sodium Chloride, USP, bag, angling the needle tip to ensure slow addition.



6. Gently rotate the infusion bag to mix — do not shake.

7. Label the infusion bag per your institution's policy. Do not mix NAGLAZYME with other medicinal products.



NAGLAZYME does not contain any preservatives; therefore, after dilution with saline in the infusion bag, any unused product or waste material should be discarded and disposed of in accordance with local requirements.

Recommended equipment

- IV infusion pump
- Wall suction (or portable suction machine)
- Oxygen setup
- Pulse oximeter
- Emergency medication such as diphenhydramine, systemic corticosteroids, and epinephrine

Administration

Refer to the package insert, the prescribing physician's orders, and your institution's policies and procedures for additional information and guidance

- Premedication with antihistamines with or without antipyretics 30 minutes to 1 hour prior to infusion is recommended
- NAGLAZYME should be administered with a PVC infusion set equipped with an in-line, low-protein-binding 0.2- μ m filter

Administration, storage, and safety

- Either a 100-mL or a 250-mL infusion bag may be used; 100-mL infusion bags should be considered in patients 20 kg and under who are susceptible to fluid volume overload
- The total dose of NAGLAZYME (galsulfase) should be delivered over **no less than** 4 hours by controlled IV infusion using an infusion pump
- **Infusion rate examples**
 - **250 mL:** 6 mL/hour for the first hour. If the infusion is well tolerated, the infusion rate can be increased to 81 mL/hour for approximately 3 hours
 - **120 mL:** 3 mL/hour for the first hour. If the infusion is well tolerated, the infusion rate can be increased to 39 mL/hour for approximately 3 hours
- **Patient vital signs should be monitored for signs of infusion reactions**

Storage

- 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
- NAGLAZYME contains no preservatives and should be used immediately following preparation
- Prepared NAGLAZYME may be refrigerated at 2°C to 8°C (36°F to 46°F) for no longer than 48 hours between the time of preparation and the time of use

Special safety considerations for patients with airway obstruction

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

- Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic episodes
- Caution should be exercised when administering prophylactic antihistamines as patients may have airway difficulty during deep sleep
- Use of CPAP or Bilevel 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

Infusion rate

Patients and families often ask if the infusion can be administered in a shorter amount of time. The safety and efficacy of NAGLAZYME have been established in clinical studies when administered over the specified period of time. It is not advisable to administer NAGLAZYME at a faster rate than recommended.

Observe for infusion-associated reactions (IARs)

During infusion, monitor the patient for the following signs which may indicate an IAR:

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

In clinical trials, severe symptoms included:

- Angioneurotic edema
- Hypotension
- Dyspnea
- Bronchospasm
- Respiratory distress
- Apnea
- Urticaria

In clinical trials, the most common IARs included:

- Fever
- Chills/rigor
- Headache
- Rash
- Mild to moderate urticaria

- Nausea
- Vomiting
- Elevated blood pressure
- Retrosternal pain
- Abdominal pain
- Malaise
- Joint pain

- Mild symptoms may progress rapidly to more severe if the patient is untreated
- Monitor patients throughout the infusion, especially during the first hour of fast infusion

If an IAR occurs

- **Stop the infusion promptly**
- Assess and appropriately manage the patient's symptoms
- Consider administering additional antihistamines, antipyretics, and possibly systemic corticosteroids
- If symptoms subside, consider restarting the infusion at a slower rate
- 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

Compliance is critical

- The physician should evaluate risks and benefits of re-administering NAGLAZYME (galsulfase) following a severe hypersensitivity or anaphylactic reaction
- Caution should be exercised when considering epinephrine use in patients with MPS VI, due to their increased prevalence of coronary artery disease

An IAR may not occur until multiple infusions have been given

- First IARs occurred as late as 55 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

Patient compliance

- In order for the patient to benefit from treatment, regular enzyme replacement therapy (ERT) is necessary
- If therapy stops, glycosaminoglycan (GAG) builds up and symptoms may return
- Patients and families may have unrealistic expectations about treatment outcomes
- It is important to help patients and families understand that results vary and some improvements occur over a long period of time. Efficacy of ERT for MPS VI seen in the clinical trial was measured over a 6-month period

Proactively address issues that may affect compliance in the long term:

- MPS patients may have difficulty making infusion appointments due to work and school obligations, or frequent illness or hospitalization
 - Be as flexible as possible in scheduling or rescheduling appointments
- Painful IV insertion can be a cause for anxiety which could reduce compliance
 - Consider the use of topical anesthetics to reduce the pain of IV insertion
- Transportation and other problems may arise
 - Utilize social services or call your BioMarin Clinical Sales Specialist for advice