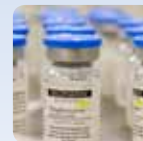


The following steps are recommended for dosing and administration of NAGLAZYME. In addition, please follow your institution's protocols and prescribing physician's orders for administration.



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).

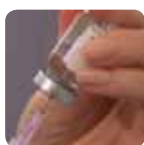
Precautions

- 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
- Low-protein-binding straight IV tubing (no Volutrol or Buretrol) in-line, low-protein-binding 0.2-µm 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 up to the next 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

2. Visually inspect each vial for particulate matter and discoloration. The solution should be clear to slightly opalescent and colorless to pale yellow. Some translucency may be present in the solution. 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 injection, USP, bag, equal to the volume of NAGLAZYME 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.

Please see Important Safety Information on back cover and accompanying full Prescribing Information.

5. Add the NAGLAZYME to the 0.9% Sodium Chloride injection, 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 low-protein-binding infusion set equipped with an in-line, low-protein-binding 0.2- μ m filter.
- 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 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.

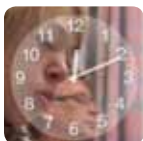
Storage

- 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 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.

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 that 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, serious or severe symptoms during infusion included:

- Laryngeal edema
- Apnea
- Pyrexia
- Urticaria
- Respiratory distress
- Angioedema
- Anaphylactoid reaction
- Chest pain
- Rash
- Abdominal pain
- Dyspnea
- Conjunctivitis

In clinical trials, common symptoms during infusion included:

- Pyrexia
 - Chills
 - Rash
 - Urticaria
 - Dyspnea
 - Nausea
 - Vomiting
 - Pruritis
 - Abdominal pain
 - Pain
 - Headache
- 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 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.
- The physician should evaluate risks and benefits of re-administering NAGLAZYME following a severe reaction.
- Caution should be exercised if epinephrine use is being considered in patients with MPS VI due to increased prevalence of coronary artery disease.

An IAR may not occur until multiple infusions have been given

- 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.

Please see Important Safety Information on back cover and accompanying full Prescribing Information.

NAGLAZYME

Dosing & Administration Guide



Indication

NAGLAZYME 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 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 ($\geq 10\%$) 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.

To report suspected adverse reactions contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information or visit www.Naglazyme.com.