CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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APPROVED LABELING

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NAGLAZYME™ (galsulfase)

Solution for Intravenous Infusion Only

DESCRIPTION

NAGLAZYME (galsulfase) is a normal variant form of the polymorphic human enzyme, *N*–acetylgalactosamine 4-sulfatase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. *N*–acetylgalactosamine 4-sulfatase (glycosaminoglycan *N*–acetylgalactosamine 4-sulfatase, EC 3.1.6.12) is a lysosomal hydrolase that catalyzes the cleavage of the sulfate ester from terminal *N*–acetylgalactosamine 4-sulfate residues of glycosaminoglycans (GAG) chondroitin 4-sulfate and dermatan sulfate.

Galsulfase is a glycoprotein with a molecular weight of approximately 56 kD. The recombinant protein is comprised of 495 amino acids and contains six asparagine-linked glycosylation sites, four of which carry a bis mannose–6–phosphate mannose$_7$ oligosaccharide for specific cellular recognition. Post-translational modification of Cys53 produces the catalytic amino acid residue, Cα-formylglycine, which is required for enzyme activity and is conserved in all members of the sulfatase enzyme family. NAGLAZYME has a specific activity of approximately 70 U/mg protein content. One activity unit (U) is defined as the amount of enzyme required to convert 1 µmole of 4-methylumbelliferyl sulfate to 4-methylumbelliferone and free sulfate per minute at 37°C.

NAGLAZYME, for intravenous infusion, is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted in 0.9% Sodium Chloride Injection, USP, prior to administration. The solution in each vial contains a nominal galsulfase concentration of 1 mg/mL (expressed as protein concentration) at a pH of approximately 5.8. The extractable volume of 5 mL from each vial provides 5 mg galsulfase, 43.8 mg

sodium chloride, 6.20 mg sodium phosphate monobasic monohydrate, 1.34 mg sodium phosphate dibasic heptahydrate, and 0.25 mg polysorbate 80. NAGLAZYME does not contain preservatives; vials are for single use only.

CLINICAL PHARMACOLOGY

Mechanism of Action

Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of GAG. Mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome) is characterized by the absence or marked reduction in *N*–acetylgalactosamine 4-sulfatase. The sulfatase activity deficiency results in the accumulation of the GAG substrate, dermatan sulfate, throughout the body. This accumulation leads to widespread cellular, tissue, and organ dysfunction. NAGLAZYME is intended to provide an exogenous enzyme that will be taken up into lysosomes and increase the catabolism of GAG. Galsulfase uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of galsulfase to specific mannose-6-phosphate receptors.

Pharmacokinetics

The pharmacokinetic parameters of galsulfase were evaluated in 13 patients with MPS VI who received 1 mg/kg of NAGLAZYME as a 4-hour infusion weekly for 24 weeks. The pharmacokinetic parameters at Week 1 and Week 24 are shown in Table 1.

Table 1: Pharmacokinetic Parameters (Median, Range)

Pharmacokinetic Parameter	Week 1	Week 24
Cmax (mcg/mL)	0.8 (0.4 to 1.3)	1.5 (0.2 to 5.5)
AUC_{0-t} (h-mcg/mL)[a]	2.3 (1.0 to 3.5)	4.3 (0.3 to 14.2)
Vz (mL/kg)	103 (56 to 323)	69 (59 to 2,799)
CL (mL/kg/min)	7.2 (4.7 to 10.5)	3.7 (1.1 to 55.9)
Half-life (min)	9 (6 to 21)	26 (8 to 40)

[a]Area under the plasma galsulfase concentration-time curve from start of infusion to 60 minutes post infusion.

Nearly all patients who receive treatment with NAGLAZYME develop antibodies to galsulfase. Of 30 patients with MPS VI who received weekly NAGLAZYME infusions and had pharmacokinetics evaluated, 29 developed antibodies to galsulfase. Four patients with high antibody titers had decreases in plasma AUC between Weeks 1 and 24. One patient with high antibody titers had an increase in plasma AUC between Weeks 1 and 24.

CLINICAL STUDIES

A total of 56 patients with MPS VI were enrolled in three clinical studies. The majority of patients had severe manifestations of the disease as evidenced by poor performance on a test of physical endurance.

In the randomized, double-blind, multicenter, placebo-controlled clinical trial, 39 patients with MPS VI received either NAGLAZYME, 1 mg/kg, or placebo, once-weekly for 24 weeks. The patients' ages ranged from 5 to 29 years. Enrollment was restricted to patients with a 12-minute walk distance of 5 to 400 meters. All patients were treated with antihistamines prior to each infusion.

The NAGLAZYME-treated group showed greater mean increases in the distance walked in 12 minutes (12-minute walk test, 12-MWT) and in the rate of stair climbing in a 3-minute stair climb test, compared to the placebo group (Table 2).

Table 2: Clinical Study Results

	NAGLAZYME			Placebo			NAGLAZYME vs. Placebo
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Difference in Changes**
N	19	19	19	20	19[a]	19	
Results from the 12-Minute Walk Test (Meters)							
Mean±SD	227±170	336±227	109±154	381±202	399±217	26±122	83±45[b] 92±40[c] (p=0.025)[cd]
Median	210	316	48	365	373	34	
Percentiles (25^{th}, 75^{th})	90, 330	125, 483	7, 183	256, 560	204, 573	–3, 89	
Results from the 3–Minute Stair Climb Test (Stairs/Minute)							
Mean ± SD	19.4±12.9	26.9±16.8	7.4±9.9	31.0±18.1	32.6±19.6	2.7±6.9	4.7±2.8[b] 5.7±2.9[c] (p=0.053)[cd]
Median	16.7	22.8	5.2	24.7	29.0	4.3	
Percentiles (25^{th}, 75^{th})	10.0, 26.3	14.8, 33.0	2.2, 9.9	18.1, 51.5	14.2, 57.9	1.0, 6.2	

[a] One subject in the placebo group dropped out before Week 24
[b] Observed mean of NAGLAZYME –Placebo ± SE
[c] Model-based mean of NAGLAZYME – Placebo ± SE, adjusted for baseline
[d] p value based on the model-based mean difference

Bioactivity was evaluated with urinary GAG concentration. Urinary GAG levels decreased in patients treated with NAGLAZYME compared to patients treated with placebo. No subject in the group receiving NAGLAZYME reached the normal range for urinary GAG levels during this 24-week study.

Thirty-eight patients received open-label NAGLAZYME for 24 weeks following the double-blind period. Among patients who were initially randomized to NAGLAZYME and who continued to receive it, increases in the 12-MWT distance and in the rate of stair climbing were observed compared to the start of the open-label period (mean [±SD] change: 36 ± 97 meters and 3 ± 7 stairs /

minute, respectively). Among patients who had been randomized initially to placebo, the increases after 24 weeks of NAGLAZYME treatment compared to the start of the open-label period, were 66 ± 133 meters and 6 ± 8 stairs/minute, for the 12-MWT and the rate of stair climbing, respectively.

Two additional studies enrolled a total of 17 patients who received NAGLAZYME treatment for up to 144 weeks. Baseline demographic and disease characteristics were similar to patients in the randomized, placebo-controlled study. Urinary GAG reductions were sustained in these patients.

INDICATIONS AND USAGE

NAGLAZYME is indicated for patients with Mucopolysaccharidosis VI (MPS VI). NAGLAZYME has been shown to improve walking and stair-climbing capacity.

CONTRAINDICATIONS

None known.

WARNINGS

Infusion Reactions

Because of the potential for infusion reactions, patients should receive antihistamines with or without antipyretics prior to infusion. Despite routine pretreatment with antihistamines, infusion reactions, some severe, occurred in 30 of 55 patients treated with NAGLAZYME. Severe symptoms included angioneurotic edema, hypotension, dyspnea, bronchospasm, respiratory distress, apnea, and urticaria. The most common symptoms of infusion reactions included fever, chills/rigors, headache, rash, and mild to moderate urticaria. Nausea, vomiting, elevated blood pressure, retrosternal pain, abdominal pain, malaise,

and joint pain were also reported. Initial reactions were observed as late as Week 55 of treatment.

Symptoms typically abated with slowing or temporary interruption of the infusion and administration of additional antihistamines, antipyretics, and occasionally corticosteroids. Most patients were able to complete their infusions. Subsequent infusions were managed with a slower rate of NAGLAZYME administration, treatment with additional prophylactic antihistamines, and, in the event of a more severe reaction, treatment with prophylactic corticosteroids. Despite these measures, 13 of 30 patients had additional infusion reactions.

If severe infusion reactions occur, immediately discontinue the infusion of NAGLAZYME and initiate appropriate treatment. The risks and benefits of re-administering NAGLAZYME following a severe reaction should be considered.

No factors were identified that predisposed patients to infusion reactions. There was no association between severity of infusion reactions and titer of anti-galsulfase antibodies.

PRECAUTIONS

General

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 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 anti-histamine use.

Consider delaying NAGLAZYME infusions in patients who present with an acute febrile or respiratory illness.

Information for Patients

Patients should be informed that a Clinical Surveillance Program has been established in order to better understand the variability and progression of the disease in the population as a whole, and to monitor and evaluate long-term treatment effects of NAGLAZYME. The Clinical Surveillance Program will also monitor the effect of NAGLAZYME on pregnant women and their offspring, and determine if NAGLAZYME is excreted in breast milk. Patients should be encouraged to participate and advised that their *participation is voluntary* and may involve long-term follow-up. For more information, visit www.MPSVI.com/CSP or call (866) 906-6100.

Drug Interactions

No formal drug interaction studies have been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the mutagenic and carcinogenic potential of NAGLAZYME have not been conducted.

Reproductive studies in rats have not demonstrated impairment of fertility (see **PRECAUTIONS: Pregnancy**).

Pregnancy: Category B

Reproduction studies have been performed in rats at doses up to 3 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to NAGLAZYME. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether NAGLAZYME is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NAGLAZYME is administered to a nursing woman. (See **PRECAUTIONS: Information for Patients** regarding the Clinical Surveillance Program. Nursing women are encouraged to participate in this program.)

Pediatric Use

The majority of individuals in the clinical studies were pediatric patients; however, patients younger than 5 years of age were not included in the clinical studies. Safety and efficacy in patients younger than 5 years of age have not been evaluated.

Geriatric Use

Clinical studies of NAGLAZYME did not include patients older than 29 years of age. It is not known whether older patients respond differently from younger patients.

ADVERSE REACTIONS

The most frequent serious adverse events related to the use of NAGLAZYME occurred during infusions and included urticaria of the face and neck, bronchospasm, respiratory distress, and apnea (see **WARNINGS: Infusion Reactions**).

The most common adverse reactions observed in the clinical studies were headache, fever, arthralgia, vomiting, upper respiratory infections, abdominal pain, diarrhea, ear pain, cough, and otitis media.

The most common adverse reactions requiring interventions were infusion-related reactions (see **WARNINGS: Infusion Reactions**).

Because clinical trials are conducted under widely varying conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

Table 3 enumerates adverse events that were reported during the 6-month placebo-controlled trial and occurred in at least 2 patients more in the NAGLAZYME group than in the placebo group. Observed adverse events in the Phase 1, Phase 2, and open-label extension studies were not different in nature or severity.

Table 3: Number and Percentage of Patients with Selected Adverse Events in the Placebo-Controlled Study

Adverse Event	NAGLAZYME (n = 19) No. Patients (%)	Placebo (n = 20) No. Patients (%)
All	19 (100)	20 (100)
Abdominal Pain	10 (53)	6 (30)
Ear Pain	8 (42)	4 (20)
Pain	5 (26)	1 (5)
Conjunctivitis	4 (21)	0
Dyspnea	4 (21)	2 (10)
Rigors	4 (21)	0
Chest Pain	3 (16)	1 (5)
Pharyngitis	3 (16)	1 (5)
Areflexia	2 (11)	0
Increased Corneal Opacification	2 (11)	0
Face Edema	2 (11)	0
Gastroenteritis	2 (11)	0
Hypertension	2 (11)	0
Malaise	2 (11)	0
Nasal congestion	2 (11)	0
Umbilical Hernia	2 (11)	0

Immunogenicity

Ninety-eight percent (53/54) of all patients treated with NAGLAZYME developed anti-galsulfase IgG antibodies. Initial evidence of antibody development typically appeared following 4 to 8 weeks of treatment. No association was observed between antibody development and urinary GAG levels.

Five patients with high antibody levels had observable differences in pharmacokinetic parameters (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). Antibodies from one patient were analyzed for neutralizing effect and showed evidence of *in vitro* inhibition of galsulfase activity. Because only one patient sample was analyzed for neutralizing activity, the effects of neutralizing antibodies are unclear.

The data reflect the percentage of patients whose test results were considered positive for antibodies to galsulfase using an enzyme-linked immunosorbent assay (ELISA) for galsulfase-specific IgG-binding antibodies, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to galsulfase with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

There is no experience with overdose of NAGLAZYME.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen of NAGLAZYME is 1 mg/kg of body weight administered once weekly as an intravenous infusion.

Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of the infusion (see **WARNINGS: Infusion Reactions**).

The total volume of the infusion should be delivered over no less than 4 hours. NAGLAZYME should be reconstituted in 0.9% Sodium Chloride Injection, USP, to a final volume of 250 mL and delivered by controlled IV infusion using an infusion pump. The initial infusion rate should be 6 mL/h for the first hour. If the infusion is well tolerated, the rate of infusion may be increased to 80 mL/h for the remaining 3 hours. The infusion time can be extended up to 20 hours if infusion reactions occur.

For patients 20 kg and under who are susceptible to fluid volume overload, physicians may consider diluting NAGLAZYME in a volume of 100 mL. The infusion rate (mL/min) should be decreased so that the total infusion duration remains no less than 4 hours.

Each vial of NAGLAZYME provides 5 mg of galsulfase (expressed in protein content) in 5 mL of solution and is intended for single use only. Do not use the vial more than one time. The concentrated solution for infusion must be diluted in 0.9% Sodium Chloride Injection, USP, using aseptic techniques. NAGLAZYME should be prepared using PVC containers and administered with a PVC infusion set equipped with an in-line, low-protein-binding 0.2 micrometer (μm) filter. There is no information on the compatibility of diluted NAGLAZYME with glass containers.

Preparation and Administration Instructions: Use Aseptic Technique.

1. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 1 mg/kg:

   Patient's weight (kg) × 1 mL/kg of NAGLAZYME = Total # mL of NAGLAZYME

Total # of mL of NAGLAZYME ÷ 5 mL per vial = Total # of vials

Round to the nearest whole vial. Remove the required number of vials from the refrigerator to 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.

2. Before withdrawing the NAGLAZYME from the vial, visually inspect each vial for particulate matter and discoloration. The NAGLAZYME 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. From a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP, withdraw and discard a volume equal to the volume of NAGLAZYME to be added. If using a 100 mL infusion bag, this is not necessary.

4. Slowly withdraw the calculated volume of NAGLAZYME from the appropriate number of vials using caution to avoid excessive agitation. Do not use a filter needle, as this may cause agitation. Agitation may denature NAGLAZYME, rendering it biologically inactive.

5. 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.

6. Gently rotate the infusion bag to ensure proper distribution of NAGLAZYME. Do not shake the solution.

NAGLAZYME does not contain preservatives; therefore, after dilution with saline in the infusion bags, any unused product or waste material should 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.

STORAGE

Store NAGLAZYME under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE OR SHAKE. DO NOT USE NAGLAZYME after the expiration date on the vial. This product contains no preservatives. The diluted solution should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F). Storage after dilution should not exceed 48 hours from the time of preparation to completion of administration. Room temperature storage of diluted solution, other than during infusion, is not recommended.

HOW SUPPLIED

NAGLAZYME is supplied as a sterile solution in clear Type I glass 5 mL vials (5 mg galsulfase [expressed as protein content] per 5 mL). The closure consists of a siliconized chlorobutyl rubber stopper and an aluminum seal with a plastic flip-off cap.

NDC 68135-020-01

Rx Only

NAGLAZYME is manufactured and distributed by:
BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949
US License Number 1649
1-866-906-6100 (phone)

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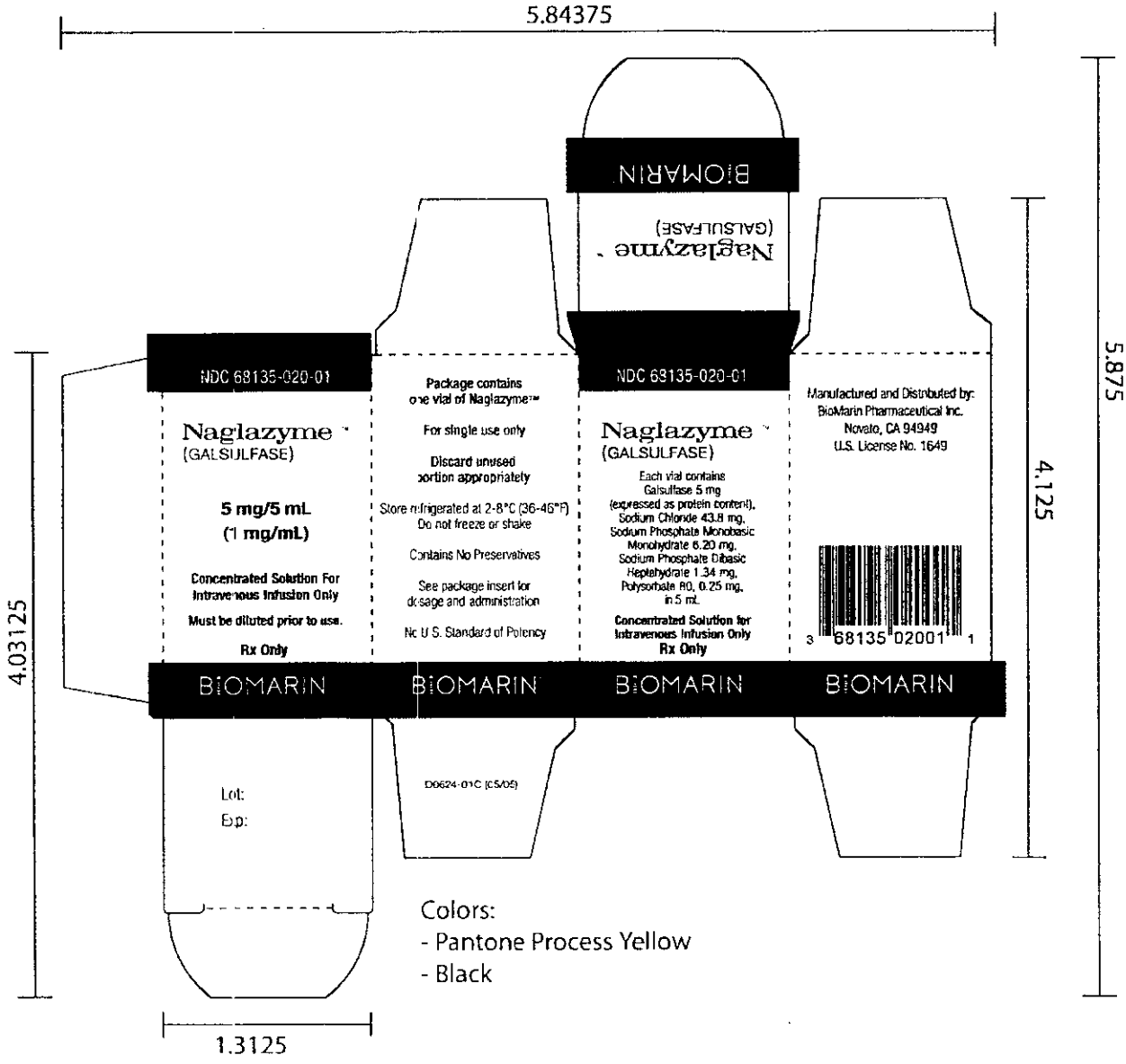
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Naglazyme ™
(GALSULFASE)
NDC 68135-020-01
Naglazyme ™
(GALSULFASE)
5 mg/5 mL
(1 mg/mL)
Concentrated Solution For Intravenous Infusion Only
Must be diluted prior to use.
Rx Only
Package contains one vial of Naglazyme™
For single use only
Discard unused portion appropriately
Store refrigerated at 2-8°C (36-46°F)
Do not freeze or shake
Contains No Preservatives
See package insert for dosage and administration
No U.S. Standard of Potency
Each vial contains
Galsulfase 5 mg
(expressed as protein content),
Sodium Chloride 43.8 mg,
Sodium Phosphate Monobasic Monohydrate 6.20 mg,
Sodium Phosphate Dibasic Heptahydrate 1.34 mg,
Polysorbate 80, 0.25 mg,
in 5 mL
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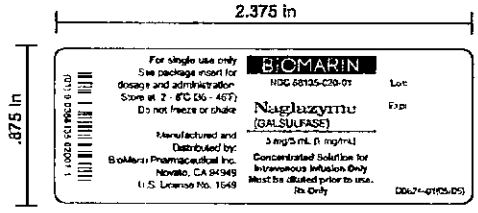

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