

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NAGLAZYME safely and effectively. See full prescribing information for NAGLAZYME.

NAGLAZYME (galsulfase) injection for intravenous use
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Warnings and Precautions, Anaphylaxis and Allergic Reactions (5.1)	04/2011
Warnings and Precautions, Immune-mediated Reactions (5.2)	04/2011
Warnings and Precautions, Risk of Acute Cardiorespiratory Failure (5.3)	04/2011
Warnings and precautions, Acute Respiratory Complications Associated with Administration (5.4)	04/2011
Warnings and Precautions, Infusion Reactions (5.5)	04/2011

INDICATIONS AND USAGE

NAGLAZYME is a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome). NAGLAZYME has been shown to improve walking and stair-climbing capacity (1).

DOSAGE AND ADMINISTRATION

1 mg per kg of body weight administered once weekly as an intravenous infusion (2).

DOSAGE FORMS AND STRENGTHS

Injection: 5 mg per 5 mL vial (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Anaphylaxis and Allergic Reactions:** Life-threatening anaphylactic reactions have been observed in some patients during NAGLAZYME infusions and up to 24 hours after infusion. If anaphylaxis or severe allergic reactions occur, immediately discontinue infusion and initiate appropriate treatment, which may include resuscitation, epinephrine,

administering additional antihistamines, antipyretics or corticosteroids (5.1).

- Immune-mediated Reactions:** Immune-mediated reactions can occur with NAGLAZYME. Monitor patients for the development of immune complex-mediated reactions while receiving NAGLAZYME (5.2).
- Risk of Acute Cardiorespiratory Failure:** Caution should be exercised when administering NAGLAZYME to patients susceptible to fluid volume overload. Consider a decreased total infusion volume and infusion rate when administering NAGLAZYME to these patients. Appropriate medical monitoring and support measures should be available during infusion. (2.1, 5.3)
- Acute Respiratory Complications:** Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic episodes. Appropriate respiratory support should be available during infusion (5.4).
- Infusion Reactions:** 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 (2.1, 5.5).

ADVERSE REACTIONS

The most common adverse reactions ($\geq 10\%$) are: rash, pain, urticaria, pyrexia, pruritus, chills, headache, nausea, vomiting, abdominal pain and dyspnea. The most common adverse reactions requiring interventions are infusion-related reactions (6.1).

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

USE IN SPECIFIC POPULATIONS

- Pregnancy and Nursing Mothers:** Clinical Surveillance Program available (8.1, 8.3, 17.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2011

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1 **FULL PRESCRIBING INFORMATION**

2
3 **1 INDICATIONS AND USAGE**

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

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Recommended Dose**

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

10 Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start
11 of the infusion [see *Warnings and Precautions (5.2)*].

12 The total volume of the infusion should be delivered over a period of time of no less than 4 hours.
13 NAGLAZYME should be diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 250 mL and
14 delivered by controlled intravenous infusion using an infusion pump. The initial infusion rate should be 6 mL
15 per hour for the first hour. If the infusion is well tolerated, the rate of infusion may be increased to 80 mL per
16 hour for the remaining 3 hours. The infusion time can be extended up to 20 hours if infusion reactions occur.

17 For patients 20 kg and under or those who are susceptible to fluid volume overload, physicians may consider
18 diluting NAGLAZYME in a volume of 100 mL [see *Warnings and Precautions (5.1) and Adverse Reactions*
19 *(6.3)*]. The infusion rate (mL per min) should be decreased so that the total infusion duration remains no less
20 than 4 hours.

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

27 **2.2 Instructions for Use**

28 Prepare and use NAGLAZYME according to the following steps. Use aseptic techniques.

- 29 a. Determine the number of vials to be used based on the patient's weight and the recommended dose
30 of 1 mg per kg:

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

32 Total number of mL of NAGLAZYME ÷ 5 mL per vial = Total number of vials

33 Round up to the next whole vial. Remove the required number of vials from the refrigerator to
34 allow them to reach room temperature. Do not allow vials to remain at room temperature longer
35 than 24 hours prior to dilution. Do not heat or microwave vials.

- 36 b. Before withdrawing the NAGLAZYME solution from the vial, visually inspect each vial for
37 particulate matter and discoloration. The NAGLAZYME solution should be clear to slightly
38 opalescent and colorless to pale yellow. Some translucency may be present in the solution. Do
39 not use if the solution is discolored or if there is particulate matter in the solution.

- 40 c. From a 250 mL infusion bag of 0.9% Sodium Chloride Injection, USP, withdraw and discard a
41 volume equal to the volume of NAGLAZYME solution to be added. If using a 100 mL infusion
42 bag, this step is not necessary.

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

- 46 e. Slowly add the NAGLAZYME solution to the 0.9% Sodium Chloride Injection, USP, using care
47 to avoid agitation of the solutions. Do not use a filter needle.
- 48 f. Gently rotate the infusion bag to ensure proper distribution of NAGLAZYME. Do not shake the
49 solution.

50 NAGLAZYME does not contain preservatives; therefore, after dilution with saline, the infusion bags should be
51 used immediately. If immediate use is not possible, the diluted solution must be stored refrigerated at 2°C to
52 8°C (36°F to 46°F) and administered within 48 hours from the time of dilution to completion of administration.
53 Other than during infusion, do not store the diluted NAGLAZYME solution at room temperature. Any unused
54 product or waste material must be discarded and disposed of in accordance with local requirements.

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

57 **3 DOSAGE FORMS AND STRENGTHS**

58 Injection; 5 mL vials (5 mg per 5 mL).

59 **4 CONTRAINDICATIONS**

60 None.

61 **5 WARNINGS AND PRECAUTIONS**

62 **5.1 Anaphylaxis and Allergic Reactions**

63 Anaphylaxis and severe allergic reactions have been observed in patients during and up to 24 hours after
64 NAGLAZYME infusion. Some of the reactions were life-threatening and included anaphylaxis, shock,
65 respiratory distress, dyspnea, bronchospasm, laryngeal edema, and hypotension. If anaphylaxis or other severe
66 allergic reactions occur, NAGLAZYME should be immediately discontinued, and appropriate medical
67 treatment should be initiated. In patients who have experienced anaphylaxis or other severe allergic reactions
68 during infusion with NAGLAZYME, caution should be exercised upon rechallenge; appropriately trained
69 personnel and equipment for emergency resuscitation (including epinephrine) should be available during
70 infusion [see *Adverse Reactions* (6)].

71 **5.2 Immune-mediated Reactions**

72 Type III immune complex-mediated reactions, including membranous glomerulonephritis have been observed
73 with NAGLAZYME, as with other enzyme replacement therapies. If immune-mediated reactions occur,
74 discontinuation of the administration of NAGLAZYME should be considered, and appropriate medical
75 treatment initiated. The risks and benefits of re-administering NAGLAZYME following an immune-mediated
76 reaction should be considered. Some patients have successfully been rechallenged and have continued to
77 receive NAGLAZYME under close clinical supervision. [see *Adverse Reactions* (6.3)].

78 **5.3 Risk of Acute Cardiorespiratory Failure**

79 Caution should be exercised when administering NAGLAZYME to patients susceptible to fluid volume
80 overload; such as in patients weighing 20 kg or less, patients with acute underlying respiratory illness, or
81 patients with compromised cardiac and/or respiratory function, because congestive heart failure may result.
82 Appropriate medical support and monitoring measures should be readily available during NAGLAZYME
83 infusion, and some patients may require prolonged observation times that should be based on the individual
84 needs of the patient. [see *Adverse Reactions* (6.3)].

85 **5.4 Acute Respiratory Complications Associated with Administration**

86 Sleep apnea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apneic
87 episodes. Evaluation of airway patency should be considered prior to initiation of treatment. Patients using
88 supplemental oxygen or continuous positive airway pressure (CPAP) during sleep should have these treatments
89 readily available during infusion in the event of an infusion reaction, or extreme drowsiness/sleep induced by
90 antihistamine use.

91 Consider delaying NAGLAZYME infusions in patients who present with an acute febrile or respiratory illness
92 because of the possibility of acute respiratory compromise during infusion of NAGLAZYME.

93 5.5 Infusion Reactions

94 Because of the potential for infusion reactions, patients should receive antihistamines with or without
95 antipyretics prior to infusion. Despite routine pretreatment with antihistamines, infusion reactions some severe
96 occurred in 33 of 59 (56%) patients treated with NAGLAZYME. Serious adverse reactions during infusion
97 included laryngeal edema, apnea, pyrexia, urticaria, respiratory distress, angioedema, and anaphylactoid
98 reaction. Severe adverse reactions included urticaria, chest pain, rash, dyspnea, apnea, laryngeal edema, and
99 conjunctivitis. [see Adverse Reactions (6)].

100 The most common symptoms of drug-related infusion reactions were pyrexia, chills, rash, urticaria, dyspnea,
101 nausea, vomiting, pruritis, erythema, abdominal pain, hypertension, and headache. Respiratory distress, chest
102 pain, hypotension, angioedema, conjunctivitis, tremor, and cough were also reported. Infusion reactions began
103 as early as Week 1 and as late as Week 146 of NAGLAZYME treatment. Twenty-three of 33 patients (70%)
104 experienced recurrent infusion reactions during multiple infusions though not always in consecutive weeks.

105 Symptoms typically abated with slowing or temporary interruption of the infusion and administration of
106 additional antihistamines, antipyretics, and occasionally corticosteroids. Most patients were able to complete
107 their infusions. Subsequent infusions were managed with a slower rate of NAGLAZYME administration,
108 treatment with additional prophylactic antihistamines, and, in the event of a more severe reaction, treatment
109 with prophylactic corticosteroids.

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

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

115 6 ADVERSE REACTIONS

116 6.1 Clinical Trials Experience

117 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the
118 clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and
119 may not reflect the rates observed in clinical practice.

120 NAGLAZYME was studied in a randomized, double-blind, placebo-controlled trial in which 19 patients
121 received weekly infusions of 1 mg/kg NAGLAZYME and 20 patients received placebo; of the 39 patients 66%
122 were female, and 62% were White, non-Hispanic. Patients were aged 5 years to 29 years. NAGLAZYME-
123 treated patients were approximately 3 years older than placebo-treated patients (mean age 13.7 years versus
124 10.7 years, respectively).

125 Serious adverse reactions experienced in this trial include, apnea, pyrexia, and, respiratory distress. Severe
126 adverse reactions include chest pain, dyspnea, laryngeal edema, and conjunctivitis. The most common adverse
127 reactions requiring interventions were infusion reactions.

128 Table 1 summarizes the adverse reactions that occurred in the placebo-controlled trial in at least 2 patients more
129 in the NAGLAZYME-treated group than in the placebo-treated group.

130 **Table 1: Adverse Reactions that Occurred in the Placebo-Controlled Trial in at least 2 Patients More in**
131 **the NAGLAZYME Group than in the Placebo Group**

MedDRA Preferred Term	NAGLAZYME (n = 19)	Placebo (n = 20 [*])
	No. Patients (%)	No. Patients (%)
All	19 (100)	20 (100)
Abdominal Pain	9 (47)	7 (35)

Ear Pain	8 (42)	4 (20)
Arthralgia	8 (42)	5 (25)
Pain	6 (32)	1 (5)
Conjunctivitis	4 (21)	0
Dyspnea	4 (21)	2 (10)
Rash	4 (21)	2 (10)
Chills	4 (21)	0
Chest Pain	3 (16)	1 (5)
Pharyngitis	2 (11)	0
Areflexia	2 (11)	0
Corneal Opacity	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
Hearing Impairment	2 (11)	0
*One of the 20 patients in the placebo group dropped out after Week 4 infusion		

132

133 Four open-label clinical trials were conducted in MPS VI patients aged 3 months to 29 years with
134 NAGLAZYME administered at doses of 0.2 mg/kg (n = 2), 1 mg/kg (n = 55), and 2 mg/kg (n = 2). The mean
135 exposure to the recommended dose of NAGLAZYME (1 mg/kg) was 138 weeks (range = 54 to 261 weeks).
136 Two infants (12.1 months and 12.7 months) were exposed to 2 mg/kg of NAGLAZYME for 105 and 81 weeks,
137 respectively.

138 In addition to those listed in Table 1, common adverse reactions observed in the open-label trials include
139 pruritus, urticaria, pyrexia, headache, nausea, and vomiting. The most common adverse reactions requiring
140 interventions were infusion reactions. Serious adverse reactions included laryngeal edema, urticaria,
141 angioedema, and other allergic reactions. Severe adverse reactions included urticaria, rash, and abdominal pain.

142 Observed adverse events in four open-label studies (up to 261 weeks treatment) were not different in nature or
143 severity to those observed in the placebo-controlled study. No patients discontinued during open-label treatment
144 with NAGLAZYME due to adverse events.

145 6.2 Immunogenicity

146 Ninety-eight percent (53/54) of patients treated with NAGLAZYME and evaluable for the presence of
147 antibodies to galsulfase developed anti-galsulfase IgG antibodies within 4 to 8 weeks of treatment (in four
148 clinical studies). In 19 patients treated with NAGLAZYME from the placebo-controlled study, serum samples
149 were evaluated for a potential relationship of anti-galsulfase antibody development to clinical outcome
150 measures. All 19 patients treated with NAGLAZYME developed antibodies specific to galsulfase; however, the
151 analysis revealed no consistent predictive relationship between total antibody titer, neutralizing or IgE
152 antibodies, and infusion-associated reactions, urinary glycosaminoglycan (GAG) levels, or endurance measures.
153 Antibodies were assessed for the ability to inhibit enzymatic activity but not cellular uptake.

154 The data reflect the percentage of patients whose test results were considered positive for antibodies to
155 galsulfase using specific assays and are highly dependent on the sensitivity and specificity of the assay.
156 Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including
157 sample handling, timing of sample collection, concomitant medications, and underlying disease. For these
158 reasons, comparison of the incidence of antibodies to galsulfase with the incidence of antibodies to other
159 products may be misleading.

160 **6.3 Postmarketing Experience**

161 The following adverse reactions have been identified during postapproval use of NAGLAZYME. Because these
162 reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably
163 estimate their frequency or establish a causal relationship to drug exposure.

164 In addition to infusion reactions reported in clinical trials, serious reactions which occurred during
165 NAGLAZYME infusion in the worldwide marketing experience include anaphylaxis, shock, hypotension,
166 bronchospasm, and respiratory failure.

167 Additional infusion reactions included pyrexia, erythema, pallor, bradycardia, tachycardia, hypoxia, cyanosis,
168 tachypnea, and paresthesia.

169 During postmarketing surveillance, there has been a single case of membranous nephropathy and rare cases of
170 thrombocytopenia reported. In the case of membranous nephropathy, renal biopsy revealed
171 galsulfase-immunoglobulin complexes in the glomeruli. With both membranous nephropathy and
172 thrombocytopenia, patients have been successfully rechallenged and have continued to receive NAGLAZYME.

173 **8 USE IN SPECIFIC POPULATIONS**

174 **8.1 Pregnancy**

175 Pregnancy Category B.

176 Adequate and well-controlled studies have not been conducted with NAGLAZYME in pregnant women.
177 Reproduction studies have been performed in rats at intravenous doses up to 3 mg/kg/day (about 0.5 times the
178 recommended human dose of 1 mg/kg based on the body surface area) and in rabbits at intravenous doses up to
179 3 mg/kg/day (about 0.97 times the recommended human dose of 1 mg/kg based on the body surface area) and
180 have revealed no evidence of impaired fertility or harm to the fetus due to NAGLAZYME. NAGLAZYME
181 should be used during pregnancy only if clearly needed.

182 Pregnant women with MPS VI who are treated with NAGLAZYME should be encouraged to enroll in the
183 MPS VI Clinical Surveillance Program at 800-983-4587 [*see Patient Counseling Information (17.2)*].

184 **8.3 Nursing Mothers**

185 It is not known whether NAGLAZYME is excreted in human milk. Because many drugs are excreted in human
186 milk, caution should be exercised when NAGLAZYME is administered to a nursing mother. Nursing mothers
187 with MPS VI who are treated with NAGLAZYME should be encouraged to enroll in the MPS VI Clinical
188 Surveillance Program at 800-983-4587 [*see Patient Counseling Information (17.2)*].

189 **8.4 Pediatric Use**

190 Clinical studies with NAGLAZYME were conducted in 56 patients; ages 5 to 29 years, with the majority of
191 these patients in the pediatric age group [*see Clinical Studies (14)*]. In addition, an open-label study was
192 conducted in four infants (3 months to 12.7 months) treated with 1 mg/kg (n = 2) or 2 mg/kg (n = 2) of
193 NAGLAZYME. Safety results in infants were consistent with results observed in patients 5 to 29 years old [*see*
194 *Adverse Reactions (6)*].

195 **8.5 Geriatric Use**

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

198 **11 DESCRIPTION**

199 NAGLAZYME is a formulation of galsulfase, which is a purified human enzyme that is produced by
200 recombinant DNA technology in a Chinese hamster ovary cell line. Galsulfase (glycosaminoglycan *N*-
201 acetylgalactosamine 4-sulfatase, EC 3.1.6.12) is a lysosomal enzyme that catalyzes the cleavage of the sulfate
202 ester from terminal *N*-acetylgalactosamine 4-sulfate residues of glycosaminoglycans (GAG), chondroitin 4-
203 sulfate and dermatan sulfate.

204 Galsulfase is a glycoprotein with a molecular weight of approximately 56 kDa. The recombinant protein
205 consists of 495 amino acids and possesses six asparagine-linked glycosylation sites, four of which carry a
206 bis-mannose-6-phosphate residue for specific cellular recognition. Post-translational modification of Cys53
207 produces the catalytic amino acid residue, C α -formylglycine, which is required for enzyme activity.
208 NAGLAZYME has a specific activity of approximately 70 units per mg of protein content. One activity unit is
209 defined as the amount of enzyme required to convert 1 micromole of 4-methylumbelliferyl sulfate to 4-
210 methylumbelliferone and free sulfate per minute at 37°C.

211 NAGLAZYME is intended for intravenous infusion and is supplied as a sterile, nonpyrogenic, colorless to pale
212 yellow, clear to slightly opalescent solution that must be diluted with 0.9% Sodium Chloride Injection, USP,
213 prior to administration. NAGLAZYME is supplied in clear Type I glass 5 mL vials. Each vial provides 5 mg
214 galsulfase, 43.8 mg sodium chloride, 6.20 mg sodium phosphate monobasic monohydrate, 1.34 mg sodium
215 phosphate dibasic heptahydrate, and 0.25 mg polysorbate 80 in a 5 mL extractable solution with pH of
216 approximately 5.8. NAGLAZYME does not contain preservatives. Each vial is for single use only.

217 12 CLINICAL PHARMACOLOGY

218 12.1 Mechanism of Action

219 Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for
220 the catabolism of GAG. MPS VI is characterized by the absence or marked reduction in N-acetylgalactosamine
221 4-sulfatase. The sulfatase activity deficiency results in the accumulation of the GAG substrate, dermatan
222 sulfate, throughout the body. This accumulation leads to widespread cellular, tissue, and organ dysfunction.
223 NAGLAZYME is intended to provide an exogenous enzyme that will be taken up into lysosomes and increase
224 the catabolism of GAG. Galsulfase uptake by cells into lysosomes is most likely mediated by the binding of
225 mannose-6-phosphate-terminated oligosaccharide chains of galsulfase to specific mannose-6-phosphate
226 receptors.

227 12.2 Pharmacodynamics

228 The responsiveness of urinary GAG to dosage alterations of NAGLAZYME is unknown, and the relationship of
229 urinary GAG to other measures of clinical response has not been established. No association was observed
230 between antibody development and urinary GAG levels [see *Adverse Reactions* (6.2)].

231 12.3 Pharmacokinetics

232 The pharmacokinetic parameters of galsulfase were evaluated in 13 patients with MPS VI who received 1 mg
233 /kg of NAGLAZYME as a weekly 4-hour infusion for 24 weeks. The pharmacokinetic parameters at Week 1
234 and Week 24 are shown in Table 2.

235 **Table 2: Pharmacokinetic Parameters (Median, Range)**

Pharmacokinetic Parameter	Week 1	Week 24
C _{max} (mcg/mL)	0.8 (0.4 to 1.3)	1.5 (0.2 to 5.5)
AUC _{0-t} (hr•mcg/mL)*	2.3 (1.0 to 3.5)	4.3 (0.3 to 14.2)
V _z (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)

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

236

237 Galsulfase pharmacokinetic parameters listed in Table 2 require cautious interpretation because of large assay
238 variability. Development of anti-galsulfase antibodies appears to affect galsulfase pharmacokinetics, however,
239 the data are limited.

240 **13 NONCLINICAL TOXICOLOGY**

241 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

242 Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have
243 not been performed with galsulfase.

244 Galsulfase at intravenous doses up to 3.0 mg/kg (about 0.5 times the recommended human dose of 1 mg/kg
245 based on body surface area) was found to have no effect on the fertility and reproductive performance of male
246 and female rats.

247 **14 CLINICAL STUDIES**

248 A total of 56 patients with MPS VI, ages 5 years to 29 years, were enrolled in four clinical studies. The majority
249 of patients had severe manifestations of the disease as evidenced by poor performance on a test of physical
250 endurance.

251 In the randomized, double-blind, multicenter, placebo-controlled clinical trial, 38 patients with MPS VI
252 received 1 mg/kg NAGLAZYME or placebo, once-weekly for 24 weeks. The patients' ages ranged from
253 5 to 29 years. Enrollment was restricted to patients with a 12-minute walk distance of 5 to 400 meters. All
254 patients were treated with antihistamines prior to each infusion.

255 The NAGLAZYME-treated group showed greater mean increases in the distance walked in 12 minutes
256 (12-minute walk test, 12-MWT) and in the rate of stair climbing in a 3-minute stair climb test, compared with
257 the placebo group (Table 3).

258 **Table 3: Results from Placebo-Controlled Clinical Study**

	NAGLAZYME			Placebo			NAGLAZYME vs. Placebo
	Baseline	Week 24	Change	Baseline	Week 24	Change	Difference in Changes
N	19	19	19	20	19*	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 [†] 92 ± 40 [‡] (p = 0.025) ^{‡,§}
Median							
Percentiles (25 th , 75 th)	210 90, 330	316 125, 483	48 7, 183	365 256, 560	373 204, 573	34 -3, 89	
Results from 3-Minute Stair Climb Test (Stairs/Minute)							
Mean ± SD	19.4 ± 2.9	26.9 ± 16.8	7.4 ± 9.9	31.0 ± 18.1	32.6 ± 19.6	2.7 ± 6.9	4.7 ± 2.8 [†] 5.7 ± 2.9 [‡] (p = 0.053) ^{‡,§}
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	
* One patient in the placebo group dropped out after 4 weeks of infusion							
† Observed mean of NAGLAZYME - Placebo ± SE							
‡ Model-based mean of NAGLAZYME - Placebo ± SE, adjusted for baseline							
§ p-value based on the model-based mean difference							

259

260 Following the 24-week placebo-controlled study period, 38 patients received open-label NAGLAZYME for
261 72 weeks. Among the 19 patients who were initially randomized to NAGLAZYME and who continued to
262 receive treatment for 72 weeks (total of 96 weeks), increases in the 12-MWT distance and in the rate of stair
263 climbing were observed compared to the start of the open-label period (mean [± SD] change): 72 ± 116 meters
264 and 5.6 ± 10.6 stairs/minute, respectively). Among the 19 patients who were randomized initially to placebo for
265 24 weeks, and then crossed over to treatment with NAGLAZYME, the increases after 72 weeks of
266 NAGLAZYME treatment compared to the start of the open-label period, (mean [± SD] change): were
267 118 ± 127 meters and 11.1 ± 10.0 stairs/minute, for the 12-MWT and the rate of stair climbing, respectively.

268 Bioactivity was evaluated with urinary GAG concentration. Overall, 95% of patients showed at least a 50%
269 reduction in urinary GAG levels after 72 weeks of treatment with NAGLAZYME. No patient receiving
270 NAGLAZYME reached the normal range for urinary GAG levels [see *Clinical Pharmacology* (12.2)].

271 In an additional open-label extension study, patients receiving NAGLAZYME showed maintenance of initial
272 improvement in endurance for approximately 240 weeks.

273 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

277 NDC 68135-020-01, 5 mL vial

278 Store NAGLAZYME under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from
279 light. Do not use NAGLAZYME after the expiration date on the vial. This product contains no preservatives.

280

281 **17 PATIENT COUNSELING INFORMATION**

282 **17.1 Infusion Reactions**

283 Patients and caregivers should be counseled that reactions related to administration and infusion may occur
284 during NAGLAZYME treatment, including life-threatening anaphylaxis. Premedication and reduction of
285 infusion rate may alleviate those reactions associated with the infusion. [*see Warnings and Precautions (5.4)*].

286 Patients should be advised to report any adverse reactions experienced while on NAGLAZYME treatment.

287 **17.2 Clinical Surveillance Program**

288 Patients should be informed that a Clinical Surveillance Program has been established in order to better
289 understand the variability and progression of the disease in the population as a whole, and to monitor and
290 evaluate long-term treatment effects of NAGLAZYME. The Clinical Surveillance Program will also monitor
291 the effect of NAGLAZYME on pregnant women, nursing mothers and their offspring, and determine if
292 NAGLAZYME is excreted in breast milk. Patients should be encouraged to participate and advised that their
293 participation is voluntary and may involve long-term follow-up. For more information call 800-983-4587.

294 NAGLAZYME is manufactured and distributed by:

295 BioMarin Pharmaceutical Inc.

296 105 Digital Drive

297 Novato, CA 94949

298 US License Number 1649

299 1-866-906-6100 (phone)

300 NAGLAZYME[®] is a trademark of BioMarin.