NEW ZEALAND DATA SHEET

1. NAGLAZYME 5 mg/5 mL concentrated solution for injection

NAGLAZYME® galsulfase (rch) 5 mg/mL concentrated solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 1 mg galsulfase (rch). Each vial of 5 mL extractable solution contains 5 mg galsulfase (expressed as protein content).

NAGLAZYME (galsulfase-rch) 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. Galsulfase-rch (glycosaminoglycan N–acetylgalactosamine 4-sulfatase, EC 3.1.6.12) is a lysosomal enzyme 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-rch is a glycoprotein with a molecular weight of approximately 56 kDa. 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 mannose7 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 units per mg of protein content. One activity unit is defined as the amount of enzyme required to convert 1 micromole of 4-methylumbelliferyl sulfate to 4-methylumbelliferone and free sulfate per minute at 37°C.

Excipient(s) with known effect

Each 5 mL vial contains 0.8 mmol (18.5 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for injection is supplied as a sterile, nonpyrogenic, colourless to pale yellow, clear to slightly opalescent solution at a pH of approximately 5.8 that must be diluted in 0.9% Sodium Chloride Injection prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NAGLAZYME (galsulfase-rch) is indicated as long term enzyme replacement therapy in adults and children with Mucopolysaccharidosis VI (MPS VI, N-acetylgalactosamine 4-sulfatase deficiency, Maroteaux-Lamy syndrome).

4.2 Dose and method of administration

NAGLAZYME treatment should be supervised by a physician experienced in the management of patients with MPS VI or other inherited metabolic diseases. Administration of NAGLAZYME should be carried out in an appropriate clinical setting where resuscitation equipment to manage clinical emergencies would be readily available.

Dose

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

Paediatric Population

For patients 20 kg and under or those who are susceptible to fluid volume overload, physicians may consider diluting NAGLAZYME in a volume of 100 mL (See sections 4.4 and 4.8). The infusion rate (mL/h) should be decreased so that the total infusion duration remains no less than 4 hours.

Method of Administration

Each vial of NAGLAZYME provides 5 mg of galsulfase-rch (expressed as 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 injection must be diluted with 0.9% Sodium Chloride Injection, using aseptic techniques.

Pretreatment with antihistamines with or without antipyretics is recommended 30 to 60 minutes prior to the start of the infusion (See section 4.4: Infusion Reactions).

The total volume of the infusion should be delivered over no less than 4 hours. NAGLAZYME should be diluted with 0.9% Sodium Chloride Injection, to a final volume of 250 mL and delivered by controlled IV infusion using an infusion pump. For instructions on dilution of the product before administration, see section 6.6.

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.

4.3 Contraindications

None known.

4.4 Special warnings and precautions for use

Anaphylaxis and Allergic Reactions

Anaphylaxis and severe allergic reactions have been observed in patients during and up to 24 hours after NAGLAZYME infusion. Some of the reactions were life-threatening and included anaphylaxis, shock, respiratory distress, dyspnoea, bronchospasm, laryngeal oedema, and hypotension. If anaphylaxis or other severe allergic reactions occur, NAGLAZYME should be immediately discontinued, and appropriate medical treatment should be initiated. In patients who have experienced anaphylaxis or other severe allergic reactions during infusion with NAGLAZYME, caution should be exercised upon re-challenge; appropriately trained personnel and equipment for emergency resuscitation (including epinephrine) should be available during infusion (See section 4.8).

Immune-mediated Reactions

Type III immune complex-mediated reactions, including membranous glomerulonephritis have been observed with NAGLAZYME, as with other enzyme replacement therapies. If immune-mediated reactions occur, discontinuation of the administration of NAGLAZYME should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering NAGLAZYME following an immune-mediated reaction should be considered. Some patients have successfully been rechallenged and have continued to receive NAGLAZYME under close clinical supervision (See section 4.8).

Risk of Acute Cardiorespiratory Failure

Caution should be exercised when administering NAGLAZYME to patients susceptible to fluid volume overload such as patients weighing 20 kg or less, patients with acute underlying respiratory illness, or patients with compromised cardiac and/or respiratory function, because congestive heart failure may result. Appropriate medical support and monitoring measures should be readily available during NAGLAZYME infusion, and some patients may require prolonged observation times (See section 4.8).

Acute Respiratory Complications Associated with Administration

Sleep apnoea is common in MPS VI patients and antihistamine pretreatment may increase the risk of apnoeic 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 antihistamine use.

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

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 33 of 59 (56%) patients treated with NAGLAZYME. Serious adverse reactions during infusion included laryngeal oedema, apnoea, pyrexia, urticaria, respiratory distress, angioedema and anaphylactoid reaction. Severe adverse reactions included urticaria, chest pain, rash, dyspnoea, apnoea, laryngeal oedema, and conjunctivitis [See section 4.8].

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

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.

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 titre of anti-galsulfase-rch antibodies.

Spinal or Cervical Cord Compression

Spinal/cervical cord compression (SCC) with resultant myelopathy is a known and serious

complication of MPS VI. SCC is expected to occur in the natural history of the disease, including in patients on NAGLAZYME. There have been post-marketing reports of patients treated with NAGLAZYME who experienced the onset or worsening of SCC requiring decompression surgery. Patients with MPS VI should be monitored for signs and symptoms of spinal/cervical cord compression (including back pain, paralysis of limbs below the level of compression, urinary and faecal incontinence) and given appropriate clinical care.

Sodium Restricted Diet

This medicinal product contains 0.8 mmol (18.5 mg) sodium per vial and is administered in sodium chloride 9 mg/ml solution for injection (See section 6.6). To be taken into consideration by patients on a controlled sodium diet.

Use in the Elderly

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.

Paediatric Population

Clinical studies with NAGLAZYME were conducted in 56 patients; ages 5 to 29 years, with the majority of these patients in the paediatric age group (See section 5.1, Clinical efficacy and safety). In addition, an open-label study was conducted in four infants (3 months to 12.7 months) treated with 1 mg/kg (n = 2) or 2 mg/kg (n = 2) of NAGLAZYME. Safety results in infants were consistent with results observed in patients 5 to 29 years old.

Toxicology studies have not been conducted with postnatal or juvenile animals. In pharmacological studies in neonatal and immature cats with similar disease caused by a genetic deficiency, galsulfase-rch produced clinical improvement and did not raise additional safety concerns (See section 4.8).

Effect on Laboratory Tests

No effects on laboratory tests have been identified.

4.5 Interactions with other medicines and other forms of interaction

No formal drug interaction studies have been conducted.

4.6 Fertility, pregnancy, and lactation

Effects on Fertility

There are no data available on the effect of NAGLAZYME enzyme replacement therapy on human fertility.

In male and female rats, intravenous administration of recombinant galsulfase-rch from 4 weeks before mating until late gestation at total weekly doses up to 3 mg/kg/day (about 0.5 times the recommended human dose of 1 mg/kg based on body surface area) was found to have no effect on the fertility or reproductive performance of male and female rats.

Pregnancy

Pregnancy category B3

There are no adequate and well-controlled studies with NAGLAZYME in pregnant women. Placental transfer has not been studied. NAGLAZYME should be used in pregnancy only if maternal benefit

clearly outweighs potential fetal risk.

There was no evidence of teratogenicity following intravenous administration of recombinant galsulfase-rch to male and female rats from 4 weeks before mating until late gestation at total weekly doses up to 3 mg/kg/day (about 0.5 times the recommended human dose of 1 mg/kg based on body surface area) . Intravenous infusions of galsulfase-rch to pregnant rabbits during the period of organogenesis at estimated exposures (plasma AUC) of 3-fold or greater the anticipated clinical exposure was associated with an increased incidence of sternal central fusion in the absence of significant maternal toxicity. The clinical relevance of this finding is uncertain.

Breast-feeding

It is not known whether NAGLAZYME is excreted in human milk and there are no animal studies of postnatal effects. Because many drugs are excreted in human milk, caution should be exercised when NAGLAZYME is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Summary of the Safety Profile

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

Serious adverse reactions experienced in this trial include, apnoea, pyrexia, and, respiratory distress. Severe adverse events include chest pain, dyspnoea, laryngeal oedema, and conjunctivitis. The most common adverse events requiring interventions were infusion reactions.

Tabulated Summary of Adverse Reactions

Table 1 summarises the adverse events that occurred in the placebo-controlled trial in at least 2 patients more in the NAGLAZYME-treated group than in the placebo-treated group.

Table 1: Adverse Events that Occurred in the Placebo-Controlled Trial in at least 2 Patients More in 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
Dyspnoea	4 (21)	2 (10)
Rash	4 (21)	2 (10)
Chills/Rigors	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

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

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

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

Description of selected adverse reactions

Immunogenicity

Ninety-eight percent (53/54) of patients treated with NAGLAZYME and evaluable for the presence of antibodies to galsulfase-rch developed anti-galsulfase-rch IgG antibodies within 4 to 8 weeks of treatment (in four clinical studies). In 19 patients treated with NAGLAZYME from the placebo-controlled study, serum samples were evaluated for a potential relationship of anti-galsulfase-rch

antibody development to clinical outcome measures. Antibodies were assessed for the ability to inhibit enzymatic activity but not cellular uptake. All 19 patients treated with NAGLAZYME developed antibodies specific to galsulfase-rch; however, the analysis revealed no consistent predictive relationship between total antibody titre, neutralizing or IgE antibodies, and infusion reactions, urinary glycosaminoglycan (GAG) levels, or endurance measures. In some patients higher antibody levels were associated with decreases in complement parameters (C3, C4, and CH50). While this association was observed, there was no association with an increase in adverse events or alteration of the safety profile. Higher antibody levels and decreases in complement parameters were not associated with the development of anaphylactoid reactions during infusion. Decreases in complement parameters were observed intermittently, primarily in the first 24 weeks of treatment, in all 3 clinical studies and in all dose groups, including placebo.

The data reflect the percentage of patients whose test results were considered positive for antibodies to galsulfase-rch using specific assays, 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-rch with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

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

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

Additional infusion reactions included pyrexia, erythema, pallor, bradycardia, tachycardia, hypoxia, cyanosis, tachypnoea, and paraesthesia.

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

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

For enquiries about NAGLAZYME, contact medinfoasia@bmrn.com or call BioMarin at New Zealand 0800 882 012

To report adverse events, contact drugsafety@bmrn.com or call BioMarin at 0800 882 012

4.9 Overdose

There is no experience with overdose of NAGLAZYME.

For information on the management of overdose, contact the Poison Information Centre on 0800 764 766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB08

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 characterised 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-rch uptake by cells into lysosomes is most likely mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of galsulfase-rch to specific mannose-6-phosphate receptors.

No association was observed between antibody development and urinary GAG levels (See section 4.8).

Clinical efficacy and safety

The safety and efficacy of NAGLAZYME was assessed in four clinical trials in 56 patients with MPS VI, ages 5 years to 29 years. The majority of patients had severe manifestations of the disease as evidenced by poor performance on a test of physical endurance. A fifth open label study was conducted in four infants.

Study 1 was a Phase 1/2 double-blind, randomised, dose comparison study (0.2 mg/kg vs. 1.0 mg/kg) conducted in seven patients over 24 weeks. After 24-week, six patients continued in an open-label study for a total of 48 weeks. Following 48 weeks, five patients transitioned to 1.0 mg/kg dose. The extension study was completed and efficacy and safety data is reported up to 260 weeks. Patients receiving NAGLAZYME showed maintenance of initial improvement in endurance for approximately 240 weeks.

Study 2 was a Phase 2 open-label, non-randomised study in 10 patients receiving 1.0 mg/kg dose once a week. Efficacy and safety data is reported up to 214 weeks.

Study 3 was a Phase 3, double-blind, randomised, multicentre, placebo-controlled study in 39 patients with MPS VI, ages ranging from 5 to 29. Patients received either 1 mg/kg NAGLAZYME or placebo, once weekly for 24 weeks. The primary efficacy endpoint was the distance walked in a 12-minute walk test (12MWT). One patient in the placebo group discontinued after week 4. Enrolment was restricted to patients with a 12-minute walk distance of 5 to 400 metres. 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 and in the rate of stair climbing in a 3-minute stair climb test, compared with the placebo group (Table 2).

Table 2: 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[a]	19	
Results from the 12-Minute Walk Test (Metres)							
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 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 patient in the placebo group dropped out after 4 weeks of infusion

[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

Study 4 was a Phase 3 open-label extension study following the 24-week placebo-controlled study period in 38 patients for 72 weeks. Among the 19 patients who were initially randomised to NAGLAZYME and who continued to receive treatment for 72 weeks (total of 96 weeks), 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: 72 ± 116 metres and 5.6 ± 10.6 stairs/minute, respectively). Among the 19 patients who were randomised initially to placebo for 24 weeks, and then crossed over to treatment with NAGLAZYME, the increases after 72 weeks of NAGLAZYME treatment compared to the start of the open-label period, (mean [± SD] change): were 118 ± 127 metres and 11.1 ± 10.0 stairs/minute, for the 12-MWT and the rate of stair climbing, respectively.

Bioactivity was evaluated with urinary GAG concentration. Overall, 95% of patients showed at least a 50% reduction in urinary GAG levels after 72 weeks of treatment with NAGLAZYME. No patient receiving NAGLAZYME reached the normal range for urinary GAG levels (See section 5.1, Mechanism of action).

Study 5 was an open-label, randomised study conducted in four infants (3 months to 12.7 months) treated with 1.0 mg/kg (n=2) or 2.0 mg/kg (n=2) of NAGLAZYME. The effects of two doses of NAGLAZYME on development of skeletal dysplasia were assessed. The study was completed and efficacy and safety data was reported up to 104 weeks. Because of the small number of patients studied, no efficacy conclusions can be made regarding comparing the 1.0 mg/kg and 2.0 mg/kg dose groups.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of galsulfase-rch 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 3.

Table 3: 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} (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-rch concentration-time curve (AUC) from start of infusion to 60 minutes post infusion.*

Galsulfase-rch pharmacokinetic parameters listed in Table 3 require cautious interpretation because of large assay variability. Development of anti-galsulfase-rch antibodies appears to affect galsulfase-rch pharmacokinetics, however, the data are limited.

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

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of NAGLAZYME has not been experimentally determined. NAGLAZYME is an enzyme replacement therapy which is unlikely to possess direct genotoxic activity. Studies to evaluate mutagenic potential have not been performed with galsulfase-rch.

Carcinogenicity

The carcinogenic potential of NAGLAZYME has not been determined. NAGLAZYME is an enzyme replacement therapy, which is unlikely to be carcinogenic. However, because galsulfase-rch (the

active constituent of NAGLAZYME) binds to the mannose-6-phosphate receptor found on most cell types and the latter is often associated with the IGF-2 (insulin-like growth factor-2) receptor, there is a theoretical possibility that proliferation pathways may be promoted, facilitating abnormal tissue growth/hyperplasia. Long-term studies in animals to evaluate carcinogenic potential have not been performed with galsulfase-rch.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium chloride
monobasic sodium phosphate monohydrate
dibasic sodium phosphate heptahydrate
polysorbate 80
water for injections

6.2 Incompatibilities

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.

Administer the diluted NAGLAZYME solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter. There is no information on the compatibility of diluted NAGLAZYME with glass containers.

6.3 Shelf Life

3 years

NAGLAZYME does not contain preservatives; therefore, from a microbiological point of view, after dilution with saline the infusion bags should be used immediately. If immediate use is not possible, the diluted solution must be stored refrigerated at 2°C to 8°C and administered within 48 hours from the time of dilution to completion of administration. Other than during infusion, do not store the diluted NAGLAZYME solution at room temperature.

6.4 Special precautions for storage

Store NAGLAZYME under refrigeration at 2°C to 8°C. DO NOT FREEZE OR SHAKE. Protect from light. DO NOT USE NAGLAZYME after the expiration date on the vial.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

5 mL solution in a clear Type I glass vial with a siliconised chlorobutyl rubber stopper and an aluminium seal with a plastic flip-off cap. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The concentrated solution for injection must be diluted with 0.9% Sodium Chloride Injection, using aseptic techniques.

Instructions for Use

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

1. Determine the number of vials to be used based on the patient's weight and the recommended

dose of 1 mg per kg:

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

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

Round up to the next 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 solution 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, withdraw and discard a volume equal to the volume of NAGLAZYME solution to be added. If using a 100 mL infusion bag, this step 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, 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.
7. Administer the diluted NAGLAZYME solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

The product is for single use in one patient only. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Naglazyme is supplied in New Zealand by:

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
AUCKLAND
(09) 918 5100

For enquiries about NAGLAZYME, contact medinfoasia@bmrn.com or call BioMarin at New Zealand 0800 882 012

To report adverse events, contact drugsafety@bmrn.com or call BioMarin at 0800 882 012

9. DATE OF FIRST APPROVAL

24 March 2016

10. DATE OF REVISION OF TEXT

19 June 2018

Naglazyme® is a trademark of BioMarin.

Summary table of changes

Section changes	Summary of new information
All	Adoption of the SmPC format, editorial changes
1, 3, 4.2, 4.4 6.6	Correction to dose form (concentrated solution for injection)