ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Naglazyme 1 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg galsulfase. One vial of 5 ml contains 5 mg galsulfase.

Galsulfase is a recombinant form of human N-acetylgalactosamine 4-sulfatase and is produced by recombinant DNA technology using mammalian Chinese Hamster Ovary (CHO) cell culture.

Excipients

Each 5 ml vial contains 0.8 mmol (18.4 mg) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
A clear to slightly opalescent, and colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Naglazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome) (see section 5.1).

A key issue is to treat children aged <5 years suffering from a severe form of the disease, even though children <5 years were not included in the pivotal phase 3 study. Limited data are available in patients < 1 year of age (see section 5.1).

4.2 Posology and method of administration

As for all lysosomal genetic disorders, it is of primary importance, especially in severe forms, to initiate treatment as early as possible, before appearance of non-reversible clinical manifestations of the disease.

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 medical emergencies would be readily available.

Posology

The recommended dose regimen for galsulfase is 1 mg/kg body weight administered once every week as an intravenous infusion over 4 hours.

Special populations

Elderly
The safety and efficacy of Naglazyme in patients older than 65 years has not been established, and no alternative dose regimen can be recommended in these patients.

Renal and hepatic impairment
The safety and efficacy of Naglazyme in patients with renal or hepatic insufficiency have not been evaluated (see section 5.2) and no alternative dose regimen can be recommended in these patients.

Paediatric population
There is no evidence for special considerations when Naglazyme is administered to the paediatric population. Currently available data are described in section 5.1.

Method of administration

The initial infusion rate is adjusted so that approximately 2.5% of the total solution is infused during the first hour, with infusion of the remaining volume (approximately 97.5%) over the next 3 hours.

100 ml infusion bags should be considered for patients who are susceptible to fluid volume overload and weigh less than 20 kg; in this case the infusion rate (ml/min) should be decreased so that the total duration remains no less than 4 hours.

For information on pre-treatment see section 4.4 and for further instructions see section 6.6.

4.3 Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable.

4.4 Special warnings and precautions for use

Management of compromised airways

Caution must be exercised in the management and treatment of patients with compromised airways by limitation or careful monitoring of antihistamine and other sedative medicinal product use. Institution of positive–airway pressure during sleep as well as potential tracheostomy in clinically appropriate situations should also be considered.

Patients who present with an acute febrile or respiratory illness may need to have their Naglazyme infusions delayed.

Management of infusion-associated reactions

Patients treated with Naglazyme have developed infusion-associated reactions (IARs), defined as any adverse reactions occurring during the infusion or until the end of the infusion day (see section 4.8).

Based on data obtained during Naglazyme clinical trials, the majority of patients are expected to develop IgG antibodies to galsulfase within 4-8 weeks of treatment initiation.

In the Naglazyme clinical trials, IARs were usually manageable by interrupting or slowing the rate of infusion and by (pre-) treating the patient with antihistamines and/or antipyretics (paracetamol), thus enabling the patient to continue treatment.

As there is little experience on resumption of treatment following prolonged interruption, caution is to be used due to the theoretical increased risk of hypersensitivity reaction.

With administration of Naglazyme it is recommended that patients be administered pre-treatment medicinal products (antihistamines with or without antipyretics) approximately 30-60 minutes prior to the start of the infusion, to minimise the potential occurrence of IARs.

In case of a mild or moderate IAR, treatment with antihistamines and paracetamol should be considered and/or a reduction in the infusion rate to half the rate at which the reaction occurred.

In case of a single severe IAR, the infusion should be stopped until the symptoms are resolved and treatment with antihistamines and paracetamol should be considered. The infusion can be restarted with a reduction of the infusion rate to 50% – 25% of the rate at which the reaction occurred.

In case of a recurrent moderate IAR or re-challenge after a single severe IAR, pre-treatment should be considered (antihistamines and paracetamol and/or corticosteroids) and a reduction of the infusion rate to 50% – 25% of the rate at which the previous reaction occurred.

As with any intravenous protein medicinal product, severe allergic-type hypersensitivity reactions are possible. If these reactions occur, immediate discontinuation of Naglazyme is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed. In patients who have experienced 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. Severe, or potentially life-threatening hypersensitivity is a contraindication to rechallenge, if hypersensitivity is not controllable. See also section 4.3.

This medicinal product contains 0.8 mmol (18.4 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.

Spinal or cervical cord compression

Spinal/cervical cord compression (SCC) with resultant myelopathy is a known and serious complication that can be due to MPS VI. There have been post-marketing reports of patients treated with Naglazyme who experienced the onset or worsening of SCC requiring decompression surgery. Patients 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

For Naglazyme, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy or embryo-foetal development (see section 5.3). Naglazyme should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether galsulfase is excreted in milk, therefore breast-feeding should be stopped during Naglazyme treatment.

Fertility

Reproduction studies have been performed in rats and rabbits at doses up to 3 mg/kg/day and have revealed no evidence of impaired fertility or harm to the embryo or foetus due to Naglazyme.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Due to the low number of patients in clinical trials, adverse event (AE) data from all Naglazyme studies have been pooled and reviewed in a single, clinical trial safety analysis.

All patients treated with NAGLAZYME (59/59) reported at least one AE. The majority (42/59; 71%) of patients experienced at least one Adverse Drug Reaction. The most common adverse reactions were pyrexia, rash, pruritus, urticaria, chills/rigors, nausea, headache, abdominal pain, vomiting and dypsnoea. Serious adverse reactions included laryngeal edema, apnoea, pyrexia, urticaria, respiratory distress, angioedema, asthma and anaphylactoid reaction.

Infusion reactions, defined as adverse reactions occurring during Naglazyme infusions or until the end of the infusion day, were observed in 33 (56%) of the 59 patients treated with Naglazyme across five clinical studies. Infusion reactions began as early as Week 1 and as late as Week 146 of Naglazyme treatment, and occurred during multiple infusions though not always in consecutive weeks. Very common symptoms of these infusion reactions were pyrexia, chills/rigors, rash, urticaria and dyspnoea. Common symptoms of infusion reactions were pruritus, vomiting, abdominal pain, nausea, hypertension, headache, chest pain, erythema, cough, hypotension, angioedema, respiratory distress, tremor, conjunctivitis, malaise, bronchospasm and arthralgia.

Adverse reactions are listed in Table 1 by System Organ Class.

The reactions are listed following the MedDRA frequency convention. Very common adverse reactions are those with a frequency of ≥1/10. Common reactions have a frequency of ≥1/100 to <1/10. Due to the small patient population, an adverse reaction in a single patient is classified as common.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions reported during the Post Marketing period are included at a frequency category of "unknown".

Overall, one case of sleep apnoea was experienced from all clinical studies.

Table 1: Frequency of adverse drug reactions with Naglazyme

MedDRA System Organ Class	**MedDRA Preferred Term**	**Frequency**
Immune system disorders	Anaphylaxis, shock	Unknown
Infections and infestations	Pharyngitis[1], gastroenteritis[1]	Very common
Nervous system disorders	Areflexia[1], headache	Very common
	Tremor	Common
	Paresthesia	Unknown
Eye disorders	Conjunctivitis[1], corneal opacity[1]	Very common
Cardiac disorders	Bradycardia, tachycardia, cyanosis	Unknown
Ear and labyrinth disorders	Ear pain[1], hearing impaired[1]	Very common
Vascular disorders	Hypertension[1]	Very common

	Hypotension	Common
	Pallor	Unknown
Respiratory, thoracic, and mediastinal disorders	Dyspnoea[1], nasal congestion[1]	Very common
	Apnoea[1], cough, respiratory distress, asthma, bronchospasm	Common
	Laryngeal oedema, hypoxia, tachypnoea	Unknown
Gastrointestinal disorders	Abdominal pain[1], umbilical hernia[1], vomiting, nausea	Very common
Skin and subcutaneous tissue disorders	Angioeodema[1], rash[1], urticaria, pruritus	Very Common
	Erythema	Common
General disorders and administration site conditions	Pain[1], chest pain[1], rigors[1], malaise[1], pyrexia	Very Common
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Very common

[1]Reactions reported more frequently in the active arm of the placebo-controlled study than the placebo arm; frequency determined from 39 patients of the blinded Phase 3 study.
Other reactions with known frequency were reported from 59 patients treated with Naglazyme from all five clinical trials.
Reactions of unknown frequency were reported post-marketing.

In four patients <1 year of age, the overall safety profile of a higher dose (2 mg/kg/week) did not differ in a clinically meaningful manner from that of the recommended 1 mg/kg/week dose, and was consistent with the safety profile of Naglazyme in older children.

Immunogenicity

Out of the 59 patients treated with Naglazyme in the clinical studies, 54 were tested for IgG antibodies. 53/54 patients (98%) were positive for IgG antibodies to galsulfase.

A comprehensive antibody analysis based on data from three clinical studies has been carried out in 48 patients.

Although a larger proportion of subjects with high total antibody titres experienced recurrent infusion reactions, neither frequency nor severity could be predicted based on the anti-galsulfase antibody titre. Likewise, antibody development is not predictive of decreased efficacy although subjects with limited response in endurance parameters or urinary glycosaminoglycans (GAGs) tended to have higher peak anti-galsulfase titres than those with good response.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Several patients have received their total dose of Naglazyme at approximately twice the recommended infusion rate without apparent adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAGs). MPS VI is a heterogeneous and multisystemic disorder characterized by the deficiency of N-acetylgalactoasamine 4-sulfatase, a lysosomal hydrolase which catalyses the hydrolysis of sulfate moiety of the glycosaminoglycan, dermatan sulfate. Reduced or absent N-acetylgalactosamine 4-sulfatase activity results in the accumulation of dermatan sulfate in many cell types and tissues.

The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyze the accumulated substrate and to prevent further accumulation.

Purified galsulfase, a recombinant form of human N-acetylgalactosamine 4-sulfatase, is a glycoprotein with a molecular weight of approximately 56 kD. Galsulfase is comprised of 495 amino acids after cleavage of the N-terminus. The molecule contains 6 N-linked oligosaccharide modification sites. After intravenous infusion, galsulfase is rapidly removed from the circulation and taken up by cells into lysosomes, most likely via mannose-6 phosphate receptors.

The three clinical studies performed with Naglazyme focused on assessing the systemic manifestations of MPS VI such as endurance, joint mobility, joint pain and stiffness, upper airway obstruction, manual dexterity and visual acuity.

The safety and efficacy of Naglazyme was assessed in a randomised, double blind, placebo controlled, Phase 3 study of 39 MPS VI patients, ranging in age from 5 to 29 years. The majority of the patients presented with short stature, impaired endurance, and musculoskeletal symptoms. Patients who could walk more than 5 meters (m) but less than 250 m in 6 minutes of a 12 Minute Walk test or less than 400 m at the 12 minute time point at baseline were enrolled in the study.

Patients received either 1 mg/kg of galsulfase or placebo every week for a total of 24 weeks. The primary efficacy endpoint was the numbers of meters walked in 12 minutes at Week 24 compared to the number of meters walked at baseline. The secondary efficacy endpoints were the rate of stairs climbed in three minutes and the urinary glycosaminoglycan excretion of treated patients compared to placebo at Week 24. Thirty-eight patients subsequently enrolled in an Open Label extension study where they received 1 mg/kg of galsulfase every week.

Following 24 weeks of therapy, Naglazyme-treated patients experienced a 92 ± 40 m improvement in the distance walked in 12 minutes relative to placebo-treated patients ($p = 0.025$). Treated patients experienced a 5.7 stair per minute improvement in the 3 Minute Stair Climb relative to placebo-treated patients. Treated patients also experienced a mean decrease in urinary glycosaminoglycan excretion of 238 ± 17.8 μg/mg creatinine (± Standard Error [SE]) following 24 weeks of treatment relative to placebo-treated patients. GAG results approached the normal range for age in the Naglazyme treatment group.

In an additional Phase 4, randomised, two-dose level study, four MPS VI patients <1 year of age were treated at 1 or 2 mg/kg/week for 53 to 153 weeks.

Although limited by the very small number of patients that were enrolled, the conclusions that can be drawn from this study are the following:

Treatment with Naglazyme showed improvement, or lack of worsening, of facial dysmorphism. It did not prevent the progression of skeletal dysplasia and development of hernias and did not prevent the progression of corneal clouding. Growth rate remained normal over this limited follow-up period.

Improved hearing was noted in at least one ear for all four subjects. Urinary GAG levels decreased by more than 70%, consistent with results in older patients.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of galsulfase were evaluated in 13 patients with MPS VI who received 1 mg/kg of galsulfase as a 4 hour infusion. After 24 weeks of treatment the mean (± Standard Deviation [SD]) maximum plasma concentration (C_{max}) was 2,357 (± 1,560) ng/ml and the mean (± SD) area under the plasma concentration-time curve (AUC_{0-t}) was 5,860 (± 4,184) h × ng/ml. The mean (± SD) volume of distribution (Vz) was 316 (± 752) ml/kg and the mean (± SD) plasma clearance (CL) was 7.9 (± 14.7) ml/min/kg. The mean (± SD) elimination half-life ($t_{1/2}$) was 22.8 (± 10.7) minutes at Week 24.

Pharmacokinetic parameters in Phase 1 patients have remained stable over the long term (through at least 194 weeks).

Galsulfase is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of galsulfase in a clinically significant way. Renal elimination of galsulfase is considered a minor pathway for clearance (see section 4.2).

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single-dose toxicity, repeated-dose toxicity or on general reproductive performance or embryo-foetal development in rats or rabbits. Peri- and post-natal toxicity has not been investigated. Genotoxic and carcinogenic potential are not expected.

The cause of clinical relevance of the hepatic toxicity (bile duct hyperplasia / periportal inflammation) seen at clinically relevant doses in the repeated dose monkey toxicity study is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 3 years.

Diluted solutions: Chemical and physical in-use stability has been demonstrated for up to 4 days at room temperature (23°C - 27°C).

From a microbiological safety point of view, Naglazyme should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should normally not be longer than 24 hours at 2°C - 8°C followed by up to 24 hours at room temperature (23°C - 27°C) during administration.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (type I glass) with a stopper (siliconized chlorobutyl rubber) and a seal (aluminium) with a flip-off cap (polypropylene).

Pack sizes: 1 and 6 vials.
Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial of Naglazyme is intended for single use only. The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion using aseptic technique. It is recommended that the diluted Naglazyme solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

Any unused product or waste material is to be disposed of in accordance with local requirements.

Preparation of the Naglazyme infusion (aseptic technique is to be used)

The number of vials to be diluted based on the individual patient's weight must be determined and removed from the refrigerator approximately 20 minutes in advance in order to allow them to reach room temperature.

Before dilution, each vial is to be inspected for particulate matter and discolouration. The clear to slightly opalescent and colourless to pale yellow solution must be free of visible particles.

A volume of the sodium chloride 9 mg/ml (0.9%) solution for infusion is to be withdrawn and discarded from a 250 ml infusion bag equal to the total volume of Naglazyme to be added. 100 ml infusion bags should be considered for patients who are susceptible to fluid volume overload and weigh less than 20 kg; in this case the infusion rate (ml/min) should be decreased so that the total duration remains no less than 4 hours. When using 100 ml bags, the volume of Naglazyme may be added directly to the infusion bag.

The volume of Naglazyme is to be slowly added to the sodium chloride 9 mg/ml (0.9%) solution for infusion.

The solution is to be mixed gently before infusion.

The solution is to be visually inspected for particulate matter prior to use. Only clear and colourless solutions without visible particles should be used.

7. MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/324/001
EU/1/05/324/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 January 2006
Date of latest renewal: 26 January 2011

10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

BioMarin Pharmaceutical Inc.
46 Galli Drive, Novato, CA 94949
United States of America

Name and address of the manufacturer responsible for batch release

Catalent UK Packaging Ltd
Wingates Industrial Park,
Westhoughton, Bolton,
Lancs, BL5 3XX
United Kingdom

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management System for medicinal products for human use.

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation , is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 002 of the Risk Management Plan (RMP) presented

in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification,Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Specific Obligations:

Description:	Due Date
Module 5 – Clinical	
SO2 001.3 To evaluate the long-term safety and efficacy data from Naglazyme treatment a Clinical Surveillance Program (CSP) will be conducted. Substudies will be conducted within the CSP that will: 1. Evaluate the effect of Naglazyme on pregnancy and lactation. 2. Evaluate the safety and efficacy of Naglazyme in 10 children less than 5 years of age will be treated with the 1 mg/kg dose for at least one year. Information will also be collected on clinical status, adverse events, assessments of immunogenicity and potential effects on antibody formation. The CSP data will be analysed at yearly intervals and results will be submitted as annual reports. Detailed clinical status information will be collected at study entry and on an annual basis for at least 15 years. Other measures (urinary GAG, antibodies) are assessed more frequently. Severe and serious liver toxicities will be assessed through the PSUR but also through analysis of these events in the CSP database. Subjects enrolled in the program will have urinary glycosaminoglycan and samples for total antibodies routinely collected as specified in the Schedule of Activities. Higher antibody levels (≥65610 Dilution Fraction) will be compared with the subject's urinary GAG values with a view to assess potential impacts on efficacy. Samples from those subjects who have a consistent increase in urinary GAG values together with high antibody levels will have their antibody samples assessed for evidence of neutralizing activities. Samples for total antibody will be collected at specific intervals. If a physician suspects an IgE mediated reaction they have been advised in the protocol to request IgE antibody presence to be conducted by the MAH. The final study report under this CSP will be submitted by 31 July 2020.	Interim results will be provided in the CSP Annual Reports. A brief update will be submitted as part of the Annual Reassessments.
SOB 002 To evaluate the long-term safety and efficacy data from Naglazyme treatment a Clinical Surveillance Program (CSP) will be conducted. Substudies will be conducted within the CSP that will: 1. Evaluate the effect of Naglazyme on pregnancy and lactation. 2. Evaluate the safety and efficacy of Naglazyme in 10 children less than 5 years of age will be treated with the 1 mg/kg dose for at least one year. Information will also be collected on clinical status, adverse events, assessments of immunogenicity and potential effects on antibody formation The CSP data will be analysed at yearly intervals and results will be submitted as annual reports. Detailed clinical status information will be collected at study entry and on an annual basis for at least 15 years. Other measures (urinary GAG, antibodies) are assessed more frequently. Severe and serious liver toxicities will be assessed through the PSUR but also through analysis of these events in the CSP database. Subjects enrolled in the program will have urinary glycosaminoglycan and samples for total antibodies routinely collected as specified in the Schedule of Activities. Higher antibody levels (≥65610 Dilution Fraction) will be compared with the subject's urinary GAG values with a view to assess potential impacts on efficacy. Samples from those subjects who have a consistent increase in urinary GAG values together with high antibody levels will have their antibody samples assessed for evidence of neutralizing	**Final CSP Study Report:** 31 July 2020

activities. Samples for total antibody will be collected at specific intervals. If a physician suspects an IgE mediated reaction they have been advised in the protocol to request IgE antibody presence to be conducted by the MAH. The final study report under this CSP will be submitted by 31 July 2020.	
SO2 003.2 Several measures will be implemented to assess the Naglazyme dose. Data collected in the post-marketing phase will also be examined to determine if a suitable Naglazyme maintenance dose can be recommended relative to the efficacy endpoints used in the clinical studies.	Interim results will be provided in the annual re-assessment reports.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Naglazyme 1 mg/ml concentrate for solution for infusion
Galsulfase

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution contains 1 mg galsulfase. One vial of 5 ml contains 5 mg galsulfase.

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium phosphate monobasic monohydrate
Sodium phosphate dibasic heptahydrate
Polysorbate 80
Water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of concentrate for solution for infusion
6 vials of concentrate for solution for infusion
5 mg/5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only
Any unused solution should be discarded

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/324/001 1 vial
EU/1/05/324/002 6 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Clear type 1, 5 ml VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Naglazyme 1 mg/ml concentrate for solution for infusion
Galsulfase
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg/5 ml

6. OTHER

Store in a refrigerator
Do not freeze

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Naglazyme 1 mg/ml concentrate for solution for infusion
Galsulfase

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

What is in this leaflet:

1. What this medicine is and what it is used for

Naglazyme is used to treat patients with MPS VI disease (Mucopolysaccharidosis VI).

People with MPS VI disease have either a low level, or no level, of an enzyme called N-acetylgalactosamine 4-sulfatase, which breaks down specific substances (glycosaminoglycans) in the body. As a result, these substances do not get broken down and processed by the body as they should. They accumulate in many tissues in the body, which causes the symptoms of MPS VI.

How this medicine works

This medicine contains a recombinant enzyme called galsulfase. This can replace the natural enzyme which is lacking in MPS VI patients. Treatment has been shown to improve walking and stair-climbing ability, and to reduce the levels of glycosaminoglycans in the body. This medicine may improve the symptoms of MPS VI.

2. What you need to know before you are given this medicine

You must not receive this medicine
- If you have experienced severe or life-threatening allergic (hypersensitive) reactions to galsulfase or any of the other ingredients of Naglazyme and re-administration of the medicine was not successful.

Warnings and precautions
- If you are treated with Naglazyme, you may develop infusion-associated reactions. An infusion associated reaction is any side effect occurring during the infusion or until the end of the infusion day (see section 4 “Possible Side Effects”). When you experience such a reaction, **you should immediately contact your doctor.**

- If you have an allergic reaction your doctor may slow down, or stop, your infusion. Your doctor may also give you additional medicines to manage any allergic reactions.
- If you have a fever, or if you are having difficulty breathing before this medicine is given, talk with your doctor about delaying your Naglazyme infusion.
- This medicine has not been tested in patients with kidney or liver problems. Talk to your doctor if you have kidney or liver insufficiency.
- Please talk to your doctor if you experience muscle pain, numbness in your arms or legs, or any bowel or bladder problems as these may be caused by pressure on your spinal cord.

Other medicines and Naglazyme
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Naglazyme should not be given during pregnancy unless clearly necessary. Ask your doctor or pharmacist for advice before taking any medicine. It is not known whether galsulfase is excreted in milk, therefore breast-feeding should be stopped during Naglazyme treatment. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.

This medicine contains Sodium
Each 5 ml vial contains 0.8 mmol (18.4 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet.

3. How this medicine is given

Your doctor or nurse will administer Naglazyme to you.
The dose you receive is based on your body weight. The recommended dose is 1 mg/kg body weight administered once every week through a drip into a vein (by intravenous infusion). Each infusion will take approximately 4 hours. For the first hour the infusion rate will be slow (approximately 2.5% of the total solution), with the remaining volume (approximately 97.5%) being taken over the next 3 hours.

If you are given more Naglazyme than you should
Naglazyme is administered under the supervision of a nurse or doctor, he or she will check that the correct dose has been given and act accordingly if necessary.

If you forget to take this medicine
If you have missed a Naglazyme infusion, please contact your doctor. If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects were mainly seen while patients were being given the medicine or shortly after (“infusion associated reactions”). The most serious side effects were swollen face and fever (very common); longer than normal gaps between breaths, difficulty breathing, asthma and hives (common); and swelling of the tongue and throat, and serious allergic reaction to this medicine (unknown frequency). **If you experience any reaction like this, please tell your doctor immediately**. You may need to be given additional medicines to prevent an allergic reaction (e.g. antihistamines and/or corticosteroids) or to reduce fever (antipyretics).

The most common symptoms of infusion associated reactions include fever, chills, rash, hives and shortness of breath.

Very common side effects (these may affect more than 1 in 10 people):

- Sore throat
- Gastroenteritis
- Poor reflexes
- Headache
- Inflammation of the eye
- Cloudy eyes
- Poor hearing
- High blood pressure
- Nasal congestion
- Bulging belly button
- Vomiting
- Nausea
- Itching
- Pain (including ear, abdominal, joint, chest pain)
- Malaise

Common side effects (these may affect up to 1 in 10 people):

- Tremor
- Low blood pressure
- Cough
- Wheezing
- Skin redness

Other side effects with an unknown frequency:

- Shock
- Tingling
- Decreased heart rate
- Increased heart rate
- Bluish skin
- Skin paleness
- Low blood-oxygen
- Rapid breathing

If you get any of these symptoms, or other symptoms not listed in this leaflet, tell your doctor immediately. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store this medicine

Keep out of the sight and reach of children.

Do not take use this medicine after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

Unopened vials:
Store in a refrigerator (2°C - 8°C).

Do not freeze.

Diluted solutions:
Chemical and physical in-use stability has been demonstrated for up to 4 days at room temperature (23°C - 27°C).

From a microbiological safety point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and must normally not be longer than 24 hours at 2°C - 8°C followed by up to 24 hours at room temperature (23°C - 27°C) during administration.

Do not take Naglazyme if it contains visible particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Naglazyme contains

- The active substance is galsulfase. One ml of Naglazyme contains 1 mg galsulfase. One vial of 5 ml contains 5 mg galsulfase. Galsulfase is recombinant human N-acetylgalactosamine 4-sulfatase produced by genetically engineered Chinese Hamster Ovary (CHO) cells.
- The other ingredients are: sodium chloride, sodium phosphate monobasic, monohydrate, sodium phosphate dibasic, heptahydrate, polysorbate 80, water for injections.

What Naglazyme looks like and contents of the pack

Naglazyme is supplied as a concentrate for solution for infusion. The clear to slightly opalescent and colourless to pale yellow concentrate must be free of visible particles. The solution must be diluted further before it can be infused.

Pack sizes: 1 and 6 vials. Not all package sizes may be marketed.

Marketing Authorization Holder
BioMarin Europe Limited
10 Bloomsbury Way
London, WC1A 2SL
United Kingdom

Manufacturer
Catalent UK Packaging Ltd.
Wingates Industrial Park,
Westhoughton, Bolton,
Lancs, BL5 3XX
United Kingdom

BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

This leaflet was last revised in MM/YYYY

This medicine has been authorised under “exceptional circumstances”.

This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

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The following information is intended for medical or healthcare professionals only:

Naglazyme should not be mixed with other medicinal products in the same infusion, except for those mentioned below.

Each vial of Naglazyme is intended for single use only. The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion using aseptic technique. It is

recommended that the diluted Naglazyme solution be administered to patients using an infusion set equipped with a 0.2 µm in-line filter.

Any unused product or waste material is to be disposed of in accordance with local requirements.

Preparation of the Naglazyme Infusion (Use Aseptic Technique)

The number of vials to be diluted based on the individual patient's weight must be determined and removed from the refrigerator approximately 20 minutes in advance in order to allow them to reach room temperature.

Before dilution, each vial is to be inspected for particulate matter and discolouration. The clear to slightly opalescent and colourless to pale yellow solution must be free of visible particles.

A volume of the sodium chloride 9 mg/ml (0.9%) solution for infusion is to be withdrawn and discarded from a 250 ml infusion bag equal to the total volume of Naglazyme to be added. 100 ml infusion bags should be considered for patients who are susceptible to fluid volume overload and weigh less than 20 kg; in this case the infusion rate (ml/min) should be decreased so that the total duration remains no less than 4 hours. When using 100 ml bags, the volume of Naglazyme may be added directly to the infusion bag.

The volume of Naglazyme is to be slowly added to the sodium chloride 9 mg/ml (0.9%) solution for infusion.

The solution is to be mixed gently for infusion.

The solution is to be visually inspected for particulate matter prior to use. Clear and colourless solutions without visible particles should be used.