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).

4.2 Posology and method of administration

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).

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.

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.

Risk of Acute Cardio-respiratory Failure

Caution should be exercised when administering Naglazyme to patients susceptible to fluid volume overload; such as in 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 occur. Appropriate medical support and monitoring measures should be readily available during Naglazyme infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient (see section 4.2).

Immune-mediated Reactions

Type III immune complex-mediated reactions including membranous glomerulonephritis have been observed with Naglazyme. 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 (see section 4.2).

Sodium restricted diet

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.

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

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

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~~.
The expiry date of the product is indicated on the packaging materials

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 vials.

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. MANUFACTURER

BioMarin Pharmaceutical Inc., Novato, CA, USA

8.License Holder:

Medison Pharma Ltd. POB 7090 Petach Tikva

9. Registration Number

143-48-31767

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