1. NAME OF THE MEDICINAL PRODUCT

Vimizim
concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg elosulfase alfa*. Each vial of 5 ml contains 5 mg elosulfase alfa.

*Elosulfase alfa is a recombinant form of human N-acetylgalactosamine-6-sulfatase (rhGALNS) and is produced in Chinese Hamster Ovary cell culture by recombinant DNA technology.

Excipients with known effect:

Each 5 ml vial contains 8 mg sodium and 100 mg sorbitol (E420).

For the 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

Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages.

4.2 Posology and method of administration

Vimizim treatment should be supervised by a physician experienced in the management of patients with MPS IVA or other inherited metabolic diseases. Administration of Vimizim should be carried out by an appropriately trained healthcare professional with the ability to manage medical emergencies. Home administration under the supervision of an appropriately trained healthcare professional may be considered for patients who are tolerating their infusions well.

Posology

The recommended dose of elosulfase alfa is 2 mg/kg of body weight administered once a week. The total volume of the infusion should be delivered over approximately 4 hours (see Table 1).

Because of the potential for hypersensitivity reactions with elosulfase alfa, patients should receive antihistamines with or without antipyretics 30 to 60 minutes prior to start of infusion (see section 4.4).

Special populations

Elderly patients (≥ 65 years old)
The safety and efficacy of Vimizim in patients older than 65 years has not been established, and no alternative dosage regimen can be recommended in these patients. It is not known whether elderly patients respond differently from younger patients.

Paediatric population
The posology in the paediatric population is the same as in adults. Currently available data are described in section 4.8 and section 5.1.

Method of administration

For intravenous infusion only.

For instructions for dilution of the medicinal product prior to administration, see section 6.6.

Patients weighing less than 25 kg should receive a total volume of 100 ml. When diluted in 100 ml, the initial infusion rate should be 3 ml/hr. The infusion rate may be increased as tolerated, every 15 minutes as follows: first increase the rate to 6 ml/hr, then increase the rate every 15 minutes by 6 ml/hr increments until a maximum rate of 36 ml/hr is reached.

Patients weighing 25 kg or more should receive a total volume of 250 ml. When diluted in 250 ml, the initial infusion rate should be 6 ml/hr. The infusion rate may be increased as tolerated, every 15 minutes as follows: first increase the rate to 12 ml/hr, then increase the rate every 15 minutes by 12 ml/hr increments until a maximum rate of 72 ml/hr is reached.

Table 1: Recommended infusion volumes and rates*

Patient weight (kg)	**Total infusion volume (ml)**	**Step 1 Initial infusion rate 0-15 minutes (ml/hr)**	**Step 2 15-30 minutes (ml/hr)**	**Step 3 30-45 minutes (ml/hr)**	**Step 4 45-60 minutes (ml/hr)**	**Step 5 60-75 minutes (ml/hr)**	**Step 6 75-90 minutes (ml/hr)**	**Step 7 90+ minutes (ml/hr)**
< 25	100	3	6	12	18	24	30	36
≥ 25	250	6	12	24	36	48	60	72

* Infusion rate may be increased as tolerated by patient.

4.3 Contraindications

Life-threatening hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Anaphylaxis and severe allergic reactions

Anaphylaxis and severe allergic reactions have been reported in clinical studies. Therefore, appropriate medical support must be readily available when elosulfase alfa is administered. If these reactions occur, immediately stop the infusion and initiate appropriate medical treatment. The current medical standards for emergency treatment are to be followed. For patients who have experienced allergic reactions during infusion, caution should be exercised upon re-administration.

Infusion reactions

Infusion reactions (IRs) were the most commonly observed adverse reactions in clinical trials. IRs may include allergic reactions. Patients should receive antihistamines with or without antipyretics prior to infusion (see section 4.2). Management of IRs should be based on the severity of the reaction and include slowing or temporary interruption of the infusion and/or administration of additional antihistamines, antipyretics, and/or corticosteroids. If severe IRs occur, immediately stop the infusion and initiate appropriate treatment. Re-administration after a severe reaction should be carried out with caution and close monitoring by the treating physician.

Spinal/Cervical cord compression

In clinical trials, spinal/cervical cord compression (SCC) was observed both in patients receiving Vimizim and patients receiving placebo. Patients should be monitored for signs and symptoms of SCC (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 8 mg sodium per vial and is administered in sodium chloride 9 mg/ml (0.9%) solution for infusion (see section 6.6). This should be taken into consideration for patients on a controlled sodium diet.

Sorbitol

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

There are no data on the use of Vimizim in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy or embryo-foetal development (see section 5.3). These studies however, are of limited relevance. As a precautionary measure, it is preferable to avoid the use of Vimizim during pregnancy, unless clearly necessary.

Breast-feeding

Available reproductive data in animals have shown excretion of elosulfase alfa in milk. It is not known whether elosulfase alfa is excreted in human breast milk, but systemic exposure via breast milk is not expected. Due to lack of human data, Vimizim should only be administered to breast-feeding woman if the potential benefit is considered to outweigh the potential risk to the infant.

Fertility

No impairment of fertility has been observed in nonclinical studies (see section 5.3) with elosulfase alfa.

4.7 Effects on ability to drive and use machines

Vimizim has minor influence on the ability to drive and use machines. Dizziness was reported during Vimizim infusions; if dizziness occurs after the infusion, the ability to drive and use machines may be affected.

4.8 Undesirable effects

Summary of the safety profile

The assessment of adverse reactions is based on the exposure of 176 patients with MPS IVA, ages 5 to 57 years old to 2 mg/kg elosulfase alfa once a week (n=58), 2 mg/kg elosulfase alfa once every other week (n=59), or placebo (n=59) in a randomized, double-blind, placebo-controlled trial.

The majority of adverse reactions in clinical trials were IRs, which are defined as reactions occurring after initiation of infusion until the end of the day following the infusion. Serious IRs were observed in clinical trials and included anaphylaxis, hypersensitivity and vomiting. The most common symptoms of IRs (occurring in ≥ 10% of patients treated with Vimizim and ≥ 5% more when compared to placebo) were headache, nausea, vomiting, pyrexia, chills and abdominal pain. IRs were generally mild or moderate, and the frequency was higher during the first 12 weeks of treatment and tended to occur less frequently with time.

Tabulated list of adverse reactions

The data in Table 2 below describes adverse reactions from clinical trials in patients treated with Vimizim.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with Vimizim

MedDRA System organ class	**MedDRA Preferred term**	**Frequency**
Immune system disorders	Anaphylaxis	Uncommon
	Hypersensitivity	Common
Nervous system disorders	Headache	Very common
	Dizziness	Very common
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Very common
Gastrointestinal disorders	Diarrhoea, vomiting, oropharyngeal pain, upper abdominal pain, abdominal pain, nausea	Very common
Musculoskeletal and connective tissue disorders	Myalgia	Common
	Chills	Very common
General disorders and administration site conditions	Pyrexia	Very common

Paediatric population

In patients < 5 years of age, the overall safety profile of Vimizim at 2 mg/kg/week was consistent with the safety profile of Vimizim observed in older children.

Description of selected adverse reactions

Immunogenicity

All patients developed antibodies to elosulfase alfa in clinical trials. Approximately 80% of patients developed neutralizing antibodies capable of inhibiting the elosulfase alfa from binding to the cation-independent mannose-6-phosphate receptor. Sustained improvements in efficacy measures and reductions in urine keratan sulphate (KS) over time were observed across trials, despite the presence of anti elosulfase alfa antibodies. No correlations were found between higher antibody titres or neutralizing antibody positivity and reductions in efficacy measurements or occurrence of anaphylaxis or other hypersensitivity reactions. IgE antibodies against elosulfase alfa were detected in ≤ 10% of treated patients and have not consistently been related to anaphylaxis or other hypersensitivity reactions and/or treatment withdrawal.

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 (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

In clinical trials, doses of elosulfase alfa were explored up to 4 mg/kg per week and no specific signs or symptoms were identified following the higher doses. No differences in the safety profile were observed. For management of adverse reactions, see sections 4.4 and 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes. ATC code: A16AB12.

Mechanism of action

Mucopolysaccharidoses comprises a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). MPS IVA is characterized by the absence or marked reduction in N-acetylgalactosamine-6-sulfatase activity. The sulfatase activity deficiency results in the accumulation of the GAG substrates, KS and chondroitin 6 sulphate (C6S), in the lysosomal compartment of cells throughout the body. The accumulation leads to widespread cellular, tissue, and organ dysfunction. Elosulfase alfa is intended to provide the exogenous enzyme N-acetylgalactosamine-6-sulfatase that will be taken up into the lysosomes and increase the catabolism of the GAGs KS and C6S. Enzyme uptake by cells into lysosomes is mediated by cation independent mannose-6-phosphate receptors leading to restored GALNS activity and clearance of KS and C6S.

Clinical efficacy and safety

Clinical trials performed with Vimizim assessed the impact of treatment on the systemic manifestations of MPS IVA in various domains including endurance, respiratory function, growth velocity, and mobility, as well as urine KS.

A total of 235 patients with MPS IVA were enrolled and exposed to Vimizim in six clinical trials. The safety and efficacy of Vimizim was assessed in a randomized, double-blind, placebo-controlled, Phase 3 clinical trial of 176 patients with MPS IVA, ranging in age from 5 to 57 years. The majority of the patients presented with short stature, impaired endurance, and musculoskeletal symptoms. Patients who could walk more than 30 meters (m) but less than 325 m in a 6 Minute Walk Test (MWT) at baseline were enrolled in the trial.

Patients received elosulfase alfa 2 mg/kg every week (n=58) or 2 mg/kg every other week (n=59), or placebo (n=59) for a total of 24 weeks. All patients were treated with antihistamines prior to each infusion. The primary endpoint was the change from baseline in the 6 MWT distance compared to placebo at Week 24. The secondary endpoints were the change from baseline in the 3 Minute Stair Climb Test (MSCT) and urine KS levels at Week 24. A total of 173 patients subsequently enrolled in an extension trial in which patients received 2 mg/kg of elosulfase alfa every week or 2 mg/kg every other week, and then all were switched to 2 mg/kg every week upon availability of the Week 24 results.

The primary and secondary endpoints were evaluated at Week 24 (see Table 3). The modeled treatment effect in the distance walked in 6 minutes, compared to placebo, was 22.5 m (CI_{95}, 4.0, 40.9; p=0.0174) for the 2 mg/kg per week regimen. The modeled treatment effect in stairs climbed per minute, compared to placebo, was 1.1 stairs/minute (CI_{95}, -2.1, 4.4; p=0.4935) for the 2 mg/kg per week regimen. The modeled treatment effect for the percent change in urine KS, compared to placebo, was -40.7 % (CI_{95}, -49.0, -32.4; p<0.0001) for the 2 mg/kg per week regimen. The difference was greatest between the placebo group and the weekly treatment group for all endpoints. The results from the every other week regimen in the distance walked in 6 minutes or in stairs climbed per minute were comparable to placebo.

Table 3: Results from placebo-controlled clinical study at 2 mg per kg per week

	Vimizim			**Placebo**			**Vimizim vs. Placebo**
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	
N	58	57*	57	59	59	59	**Difference in changes**
6-Minute walk test (meters)							
Mean ± SD	203.9 ±76.32	243.3 ±83.53	36.5 ±58.49	211.9 ±69.88	225.4 ±83.22	13.5 ±50.63	
					Model-based mean‡ (95%CI) p-value		22.5 (CI_{95}, 4.0, 40.9) (p = 0.0174)
3-Minute stair climb test (stairs/minute)							
Mean ± SD	29.6 ±16.44	34.9 ± 18.39	4.8 ± 8.06	30.0 ± 14.05	33.6 ± 18.36	3.6 ± 8.51	
					Model-based mean‡ (95%CI) p-value		1.1 (CI_{95}, -2.1, 4.4) (p = 0.4935)

* One patient in the Vimizim group dropped out after 1 infusion

‡ Model-based mean of Vimizim versus placebo, adjusted for baseline

In additional extension trials, patients receiving elosulfase alfa 2 mg/kg every week, showed maintenance of initial improvement in endurance and sustained reduction of urinary KS up to 156 weeks.

Paediatric population

It is important to initiate treatment as early as possible.

The majority of patients who received Vimizim during clinical studies were in the paediatric and adolescent age range (5 to 17 years). In an open-label trial, 15 paediatric patients with MPS IVA under the age of 5 years (9 months to <5 years) received 2 mg/kg of Vimizim once a week for 52 weeks. Patients continued a long term follow-up observational study for at least another 52 weeks, for a total of 104 weeks. Safety and pharmacodynamic results in these patients are consistent with results observed in the first 52 weeks (see section 4.8). The baseline mean (±SD) normalized standing height z-score was - 1.6 (±1.61). After the first 52 weeks of treatment the normalised standing height z-score was -1.9 (±1.62). At Week 104 mean (±SD) normalized standing height z-score was -3.1 (± 1.13).

The European Medicines Agency has deferred the obligation to submit the results of studies with Vimizim in one or more subsets of the paediatric population in MPS IVA. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of elosulfase alfa were evaluated in 23 patients with MPS IVA who received weekly intravenous infusions of 2 mg/kg of elosulfase alfa over approximately 4 hours for 22 weeks and the parameters at Week 0 and Week 22 were compared. At Week 22, the mean AUC_{0-t} and C_{max} increased by 181 % and 192 % respectively, when compared to Week 0.

Table 4: Pharmacokinetic properties

Pharmacokinetic parameter	Week 0 Mean (SD)	Week 22 Mean (SD)
AUC_{0-t}, minute • µg/ml*	238 (100)	577 (416)
C_{max}, µg/ml†	1.49 (0.534)	4.04 (3.24)
CL, ml/minute/kg‡	10.0 (3.73)	7.08 (13.0)
$t_{1/2}$, minute§	7.52 (5.48)	35.9 (21.5)
T_{max}, minute¶	172 (75.3)	202 (90.8)

* AUC_{0-t}, area under the plasma concentration-time curve from time zero to the time of last measurable concentration;

† C_{max}, observed maximum plasma concentration;

‡ CL, total clearance of elosulfase alfa after intravenous administration;

§ $t_{1/2}$, elimination half-life;

¶ T_{max}, time from zero to maximum plasma concentration

Biotransformation

Elosulfase alfa 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 elosulfase alfa.

Elimination

Renal elimination of elosulfase alfa is considered a minor pathway for clearance. Mean half life ($t_{1/2}$) increased from 7.52 minutes at Week 0 to 35.9 minutes at Week 22. Male and female patients had comparable elosulfase alfa clearance, and clearance did not trend with age or weight at week 22. Impact of antibodies on elosulfase alfa pharmacokinetics was assessed. No association was apparent

between the total antibody titre and elosulfase clearance. However, patients with positive neutralizing antibodies responses had decreased total clearance (CL) values and prolonged $t_{1/2}$. Despite the alteration of the pharmacokinetics profile, presence of neutralizing antibodies did not affect pharmacodynamics, efficacy, or safety of the patients who were treated with elosulfase alfa. No accumulation of elosulfase alfa in plasma was evident following weekly dosing.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology evaluating central nervous, respiratory and cardiovascular systems, single-dose and repeated-dose toxicity in rats and monkeys or fertility and embryo-foetal development in rats or rabbits. The evaluation of the peri- and postnatal development study in rats is hampered due to subsequent administration of DPH, and therefore of limited relevance.

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with elosulfase alfa. Reproduction studies have been performed in rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or reproductive performance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Monosodium phosphate monohydrate
L-Arginine hydrochloride
Sorbitol
Polysorbate 20
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

The expiry date of the product is indicated on the packaging material

After dilution: Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2°C – 8°C followed by up to 24 hours at 23°C – 27°C.

From a microbiological safety point of view, the diluted solution 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 23°C – 27°C during administration.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

Clear glass vial (Type I) with a butyl rubber stopper and a flip-off crimp seal (aluminium) with a plastic cap.

Pack sizes: 1 vial

6.6 Special precautions for disposal and other handling

Each vial of Vimizim is intended for single use only. Vimizim has to be diluted with sodium chloride 9 mg/ml (0.9 %) solution for infusion using aseptic technique. The diluted solution is administered to patients using an infusion set. An infusion set equipped with an in-line 0.2 µm filter can be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of the Vimizim infusion

Aseptic technique is to be used.

Vimizim must be diluted prior to administration.

The number of vials to be diluted is based on the individual patient's weight. The recommended dose is 2 mg per kg.

1. The number of vials to be diluted based on the individual patient's weight and the recommended dose of 2 mg/kg is determined, using the following calculation:
   - Patient weight (kg) multiplied by 2 (mg/kg) = Patient dose (mg)
   - Patient dose (mg) divided by 1 (mg/ml concentrate of Vimizim) = Total number of ml of Vimizim
   - Total amount (ml) Vimizim divided by 5 ml per vial = Total number of vials
2. The calculated total number of vials is rounded up to the next whole vial. The appropriate number of vials is removed from the refrigerator. Do not heat or microwave vials. Do not shake vials.
3. An infusion bag containing sodium chloride 9 mg/ml (0.9 %) solution for infusion is obtained suitable for intravenous administration. The total volume of the infusion is determined by the patient's body weight.
   - Patients weighing less than 25 kg should receive a total volume of 100 ml.
   - Patients weighing 25 kg or more should receive a total volume of 250 ml.
4. Before withdrawing Vimizim from the vial, each vial is visually inspected for particulate matter and discoloration. Because this is a protein solution, slight flocculation (thin translucent fibers) may occur. The Vimizim solution should be clear to slightly opalescent and colourless to pale yellow. Do not use if the solution is discolored or if there is particulate matter in the solution.
5. A volume of the sodium chloride 9 mg/ml (0.9 %) solution for infusion is to be withdrawn and discarded from the infusion bag, equal to the volume of Vimizim concentrate to be added.
6. The calculated volume of Vimizim from the appropriate number of vials is slowly withdrawn using caution to avoid excessive agitation.
7. Vimizim is slowly added to the infusion bag using care to avoid agitation.
8. The infusion bag is gently rotated to ensure proper distribution of Vimizim. Do not shake the solution.
9. The diluted solution is administered to patients using an infusion set. An infusion set equipped with an in-line 0.2µm filter can be used.

7. MARKETING AUTHORISATION HOLDER

BioMarin International Ltd.
Shanbally, Ringaskiddy,
Co. Cork
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach Street
Petach Tikva
Israel

9. Registration Number 154-1634261-00