NEW ZEALAND DATA SHEET

1. VIMIZIM 1 mg/mL concentrated solution for injection

VIMIZIM® elosulfase alfa (rch) 1 mg/mL concentrated solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 1 mg elosulfase alfa. *Each vial of approximately 5 mL extractable solution contains 5 mg elosulfase alfa.

*Elosulfase alfa is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line.

Human N-acetylgalactosamine-6-sulfatase (EC 3.1.6.4) is a lysosomal enzyme that hydrolyses sulfate from either galactose-6-sulfate or N-acetyl-galactosamine-6-sulfate on the non-reducing ends of the glycosaminoglycans keratan sulfate (KS) and chondroitin sulfate.

Elosulfase alfa is a soluble dimeric protein, and each monomer contains 496 amino acids with an approximate molecular mass of 55 kDa for the peptide chain. The oligosaccharides present at the two consensus N-linked glycosylation sites contain mannose-6-phosphate (M6P). M6P is recognised by a receptor at the cell surface and is crucial for efficient cellular uptake of the protein to the lysosome. Elosulfase alfa has a specific activity of 2.5 to 6.0 units/mg. One activity unit is defined as the amount of the enzyme required to convert 1 micromole of sulfated monosaccharide substrate D-galactopyranoside-6-sulfate (Gal-6S) to de-sulfated-galactose (Gal) and free sulfate per minute at 37°C.

Excipient(s) with known effect

Each 5 mL vial also contains 8 mg sodium and 100 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for injection. A sterile, nonpyrogenic, colourless to pale yellow and clear to slightly opalescent solution with a pH between 5.0 to 5.8 that must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in children and adults of all ages.

4.2 Dose and method of administration

Vimizim treatment should be supervised by a physician or healthcare provider 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 a healthcare professional trained in recognising and medically managing serious infusion related reactions under the direction of a practicing physician may be considered only for patients who are tolerating their infusions well.

Dose

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

Pre-treatment with antihistamines with or without antipyretics is recommended 30-60 minutes prior to start of infusion (see 4.4 Special warnings and precautions for use, Infusion Reactions).

Special Populations

Elderly patients

No alternative dosage regimen can be recommended for elderly patients (see section 4.4 Special warnings and precautions for use, Use in the elderly).

Paediatric population

Dosage and administration are the same as in adults. Currently available data are described in section 4.8 and 5.1.

Method of administration

Vimizim must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, to a final volume of 100 mL or 250 mL based on the patient's weight, prior to infusion, and delivered via intravenous infusion.

The final volume is based on the patient's weight as follows:

- For patients who weigh less than 25 kg, the final volume should be 100 mL;
- For patients who weigh 25 kg or more, the final volume should be 250 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.

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.

For instructions on dilution of the medicine before administration, see section 6.6.

Vimizim does not contain preservatives; therefore, the product should be used immediately after dilution (see 6.6 Special precautions for disposal and other handling).

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

Anaphylaxis and Severe Allergic Reaction

Anaphylaxis and severe allergic reactions have been reported in clinical studies. Therefore, appropriate medical support must be readily available when Vimizim is administered. If these reactions occur, immediately stop the infusion of Vimizim and initiate appropriate medical treatment. The current medical standards for emergency treatment are to be followed. For patients who have experienced severe allergic reactions during infusion with Vimizim, caution should be exercised upon re-challenge. Pretreatment with corticosteroids and/or reduction in the infusion rate in addition to antihistamines and antipyretics should be considered for subsequent infusions.

In clinical trials, anaphylaxis was reported as early as 30 minutes from the start of infusion and up to three hours after infusion. Anaphylaxis occurred as late into treatment as the 47th infusion. The signs and symptoms of anaphylaxis include cough, erythema, throat tightness, urticaria, flushing, cyanosis, hypotension, rash, dyspnoea, chest discomfort, and gastrointestinal symptoms (e.g., nausea, abdominal pain, retching, and vomiting) in conjunction with urticaria (see 4.8 Undesirable effects).

Hypersensitivity reactions reported in clinical trials occurred as early as 30 minutes from the start of infusion but as late as six days after infusion. Frequent symptoms of hypersensitivity reactions (occurring in more than 2 patients) included anaphylactic reactions, urticaria, peripheral oedema, cough, dyspnoea, and flushing (see 4.8 Undesirable effects).

Observe patients closely for an appropriate period of time after administration of Vimizim, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur.

Infusion Reactions

In clinical trials, 96% of patients treated with Vimizim experienced infusion reactions (IRs). IRs may include allergic reactions. In patients who experienced IRs, subsequent infusions were managed with slower infusion rates, treatment with additional prophylactic antihistamines and, in the event of a more severe reaction, treatment with prophylactic corticosteroids. Thirty-five patients (15.2%) discontinued at least one infusion due to an IR. Sixty (0.66%) of the 9,126 infusions administered in the clinical trials were discontinued due to an IR. 17.3% of patients had an infusion reaction requiring medical intervention. In 13 out of 231 patients and less than 1% of the total infusions, the infusion was discontinued and medical intervention was required.

Because of the potential for IRs with Vimizim, patients should receive antihistamines with or without antipyretics prior to infusion. 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 of Vimizim and initiate appropriate treatment. In case of a recurrent IR or re-challenge after a single severe IR, pre-treatment should be considered (antihistamines and antipyretics and/or corticosteroids) and a reduction of the infusion rate to 50% – 25% of the rate at which the previous

reaction occurred. The risks and benefits of re-administering Vimizim following a severe reaction should be considered and patients should be closely monitored by the treating physician (see 4.2 Dose and method of administration).

Spinal/Cervical Cord Compression

Spinal/cervical cord compression (SCC) is a known and serious complication of MPS IVA and may occur as part of the natural history of the disease. In clinical trials, SCC was observed both in patients receiving Vimizim and patients receiving placebo. Patients with MPS IVA should be monitored for signs and symptoms of SCC (including back pain, paralysis of limbs below the level of compression, urinary and fecal incontinence) and given appropriate clinical care.

Acute Respiratory Complications Associated with Administration

Patients with acute febrile or respiratory illness at the time of Vimizim infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of Vimizim and consider delaying the Vimizim infusion.

Sleep apnoea is common in MPS IVA patients. Evaluation of airway patency should be considered prior to initiation of treatment with Vimizim. 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 acute reaction, or extreme drowsiness/sleep induced by antihistamine use.

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 injection (see 4.2 Dose and method of administration). 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.

Use in the elderly

The safety and efficacy of Vimizim in patients older than 65 years have not been established and it is not known whether they respond differently from younger patients.

Paediatric Population

Safety results in patients under the age of 5 years are consistent with results observed in patients 5 to 57 years old (see 4.8 Undesirable effects and 5.1 Pharmacodynamic properties, Clinical efficacy and safety).

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been performed

4.6 Fertility, pregnancy, and lactation

Pregnancy

Pregnancy Category B3

There are no adequate and well-controlled studies in pregnant women receiving Vimizim.

Reproduction studies were performed in rats receiving up to 20 mg/kg/day (AUC exposure ratio around 200) elosulfase alfa with DPH (10 mg/kg, IP) from premating through Gestation Day 20 and rabbits receiving up to 10 mg/kg/day (AUC exposure ratio greater than 30) elosulfase alfa from Gestation Day 7 through Gestation Day 20. There were no elosulfase alfa-related effects on embryo-fetal development, and no increased incidence of fetal gross external, soft tissue or skeletal alterations in rats or rabbits. However, administration of elosulfase alfa to rats at 6 or 20 mg/kg/day (predicted AUC exposure ratios of around 40 and 200, respectively) from Gestation Day 7 through Lactation Day 20, produced significant increases in perinatal pup mortality. As a precautionary measure, it is preferable to avoid the use of Vimizim during pregnancy, unless clearly necessary.

Breast-feeding

Data from rats have shown excretion of Vimizim in milk. It is not known whether Vimizim is excreted in human breast milk, therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Vimizim should be made, taking into account the benefit of breast-feeding to the child and the benefit of Vimizim therapy to the woman.

Effects on Fertility

A combined fertility/embryo-fetal development study was conducted in male and female rats administered intravenous elosulfase alfa up to 20 mg/kg/day with diphenhydramine (DPH) 10 mg/kg intraperitoneal (IP), prior to mating and during the cohabitation period. Dosing of females continued through Gestation Day 20. At systemic exposures, up to around 200-400 times the human value, based on AUC, there was no evidence of impaired fertility or reproductive performance.

4.7 Effects on ability to drive and use machines

No studies of Vimizim effects on the ability to drive and use machines have been performed. 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 Vimizim once a week (n=58, mean duration 23.6 ± 3.03 weeks), 2 mg/kg Vimizim once every other week (n=59, mean duration 24.0 ± 0.19 weeks), or placebo (n=59) in a randomised, double-blind, placebo-controlled trial (MOR-004).

The majority of related adverse events in clinical trials were IRs (reported in 96% of patients treated with Vimizim), 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 (see 4.4 Special warnings and precautions for use, Anaphylaxis and Severe Allergic Reaction). Forty-four of 235 (18.7%) patients experienced hypersensitivity reactions, and 18 of 235 (7.7%) patients treated with Vimizim experienced signs and symptoms consistent with a clinical diagnosis of anaphylaxis based on USA National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria. These 18 patients experienced 26 anaphylactic reactions out of >11,000 infusions (0.24%) (see 4.4 Special warnings and precautions for use, Anaphylaxis and Severe Allergic Reaction).

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 most common adverse events reported in the pivotal trial with an incidence of ≥5% more in patients treated with Vimizim (2 mg/kg per week) than in placebo treated patients, regardless of causality, are listed in Table 2.

Table 2: Adverse events with incidence ≥ 5% more in patients treated with Vimizim weekly than in placebo treated patients

MedDRA System Organ Class/Preferred Term n (%)	Placebo N= 59 (%)	Vimizim 2 mg/kg/week N= 58 (%)
Infections and infestations		
Gastroenteritis	4 (6.8%)	7 (12.1%)
Otitis media	4 (6.8%)	9 (15.5%)
Ear infection	1 (1.7%)	5 (8.6%)
Psychiatric disorders		
Agitation	0	3 (5.2%)
Nervous system disorders		
Headache[#]	21 (35.6%)	24 (41.4%)
Dizziness[#]	3 (5.1%)	7 (12.1%)
Paraesthesia	0	3 (5.2%)
Somnolence	0	3 (5.2%)
Eye disorders		
Corneal opacity	1 (1.7%)	5 (8.6%)
Vascular disorders		
Flushing	0	5 (8.6%)
Respiratory, thoracic, and mediastinal disorders		
Oropharyngeal pain[#]	7 (11.9%)	12 (20.7%)
Dyspnoea[#]	3 (5.1%)	7 (12.1%)
Throat irritation	0	3 (5.2%)
Gastrointestinal disorders		
Vomiting[#]	21 (35.6%)	26 (44.8%)
Nausea[#]	12 (20.3%)	18 (31.0%)
Diarrhoea[#]	7 (11.9%)	12 (20.7%)
Abdominal pain[#]	5 (8.5%)	14 (24.1%)
Abdominal pain upper[#]	5 (8.5%)	9 (15.5%)
Skin and subcutaneous tissue disorders		
Urticaria	0	4 (6.9%)
Musculoskeletal and connective tissue		
Neck pain	0	5 (8.6%)
Myalgia[#]	0	3 (5.2%)

General disorders and administration site conditions		
Pyrexia[#]	17 (28.8%)	25 (43.1%)
Chills[#]	1 (1.7%)	6 (10.3%)
Infusion site pain	0	4 (6.9%)
Chest discomfort	0	3 (5.2%)

[#] Adverse events that are also adverse reactions

Serious adverse events occurred more frequently in patients receiving Vimizim every week (15.5%) than in placebo treated patients (3.4%), regardless of causality.

Other Adverse Reactions Not Listed in the Table

In the placebo controlled study, hypersensitivity was reported in 7 (5.9%) patients receiving Vimizim in both 2 mg/kg per week and 2 mg/kg every other week groups compared to 1 (1.7%) patient in the placebo group. Severe hypersensitivity was reported in one of these patients in the 2 mg/kg Vimizim per week group. Anaphylactic reaction was also reported in one patient in the 2 mg/kg Vimizim every other week group 6 weeks after initiating study medication (see 4.4 Special warnings and precautions for use, Anaphylaxis and Severe Allergic Reaction).

The nature and severity of adverse reactions observed in other clinical trials were similar to the adverse reactions observed in the pivotal trial. One patient discontinued during open-label treatment with Vimizim due to an adverse event.

Description of Adverse Reactions

Immunogenicity

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

Paediatric Population

Adverse Reactions Observed in Paediatric Patients <5 Years of Age

In the MOR-007 clinical trial, 15 paediatric patients <5 years of age (range 9 months to 4.9 years) were treated with Vimizim 2 mg/kg once per week over 52 weeks. The most commonly reported adverse reactions were pyrexia (100%) and vomiting (80%). Other adverse reactions occurring in 2 or more patients were diarrhoea, abdominal pain, abdominal pain upper, oropharyngeal pain, headache, hypersensitivity, and nausea. One serious adverse reaction of hypersensitivity was reported during this period.

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/

4.9 Overdose

There is no experience of overdose in clinical trials.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: A16AB12

Mechanism of Action

Mucopolysaccharidoses (MPS) comprise a group of lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). MPS IVA is characterised 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 sulfate (C6S), in the lysosomal compartment of cells throughout the body. The accumulation leads to widespread cellular, tissue, and organ dysfunction. Vimizim 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. Cell uptake of Vimizim into lysosomes is through cation independent mannose-6-phosphate receptors mediated internalisation leading to restored GALNS activity and clearance of KS. Extracellular KS was not affected by Vimizim treatment, verifying that Vimizim activity was restricted to the lysosome.

Pharmacodynamic effects

The pharmacodynamic effect of Vimizim was assessed by reductions in urinary KS levels. The relationship of urinary KS to other measures of clinical response has not been established (see 5.1 Pharmacodynamic properties, Clinical efficacy and safety). No association was observed between antibody development and urinary KS levels.

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 244 patients with MPS IVA were enrolled and exposed to Vimizim in six clinical trials.

The safety and efficacy of Vimizim was assessed in a randomised, double-blind, placebo-controlled, Phase 3 clinical trial (MOR-004) of 176 patients with MPS IVA, ranging in age from 5 to 57 years. The majority of the patients (82%) presented with a medical history of musculoskeletal conditions, which includes knee deformity (52%), kyphosis (31%), hip dysplasia (22%), prior spinal fusion surgery (22%) and arthralgia (20%). Patients also presented with short stature and impaired endurance. Patients who could walk more than 30 metres (m) but less than 325 m in a 6 Minute Walk Test (MWT) at baseline were enrolled in the trial.

Patients received Vimizim 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 (MOR-005) in which patients received 2 mg/kg of Vimizim 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, using an ANCOVA model with treatment, age stratification (5–11, 12–18, ≥ 19 years), and baseline 6-MWT stratification (≤ 200 metres and > 200 metres) as factors. In the intent-to-treat population, the modelled 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/wk regimen. There was no difference in the rate of stair climbing between patients who received Vimizim 2 mg/kg once per week and those who received placebo. Patients who received Vimizim 2 mg/kg once every other week performed similarly in the 6-MWT and 3-MSCT as those who received placebo. The reduction in urinary KS levels from baseline, a measure of pharmacodynamic effect, was greater in the Vimizim treatment groups compared to placebo. The relationship between urinary KS and other measures of clinical response has not been established. The difference was greatest between the placebo group and the weekly treatment group for all endpoints.

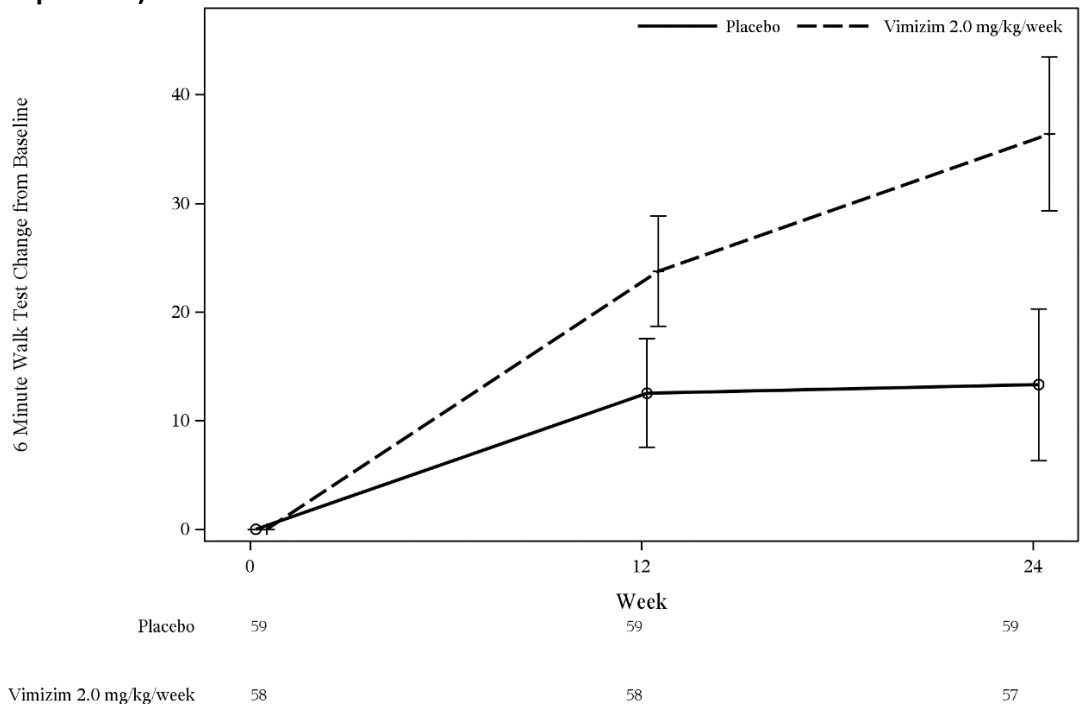
Table 3: Results from Placebo-Controlled Clinical Study at 2 mg per kg per week (Intent-to Treat Population)

	Vimizim			**Placebo**			**Vimizim vs. Placebo**
	Baseline	**Week 24**	**Change**	**Baseline**	**Week 24**	**Change**	**Difference in Changes**
N	58	57[¥]	57	59	59	59	
6-Minute Walk Test (Metres)							
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	23.0[†] (CI_{95}, 2.9, 43.1)
Median Min, Max	216.5 42.4, 321.5	251.0 52.0, 399.9	20.0 -57.8, 228.7	228.9 36.2, 312.2	229.4 50.6, 501.0	9.9 -99.2, 220.5	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	1.1[†] (CI_{95}, -1.9, 4.2)
Median Min, Max	30.5 0.0, 71.9	34.7 0.0, 82.3	4.3 -12.4, 20.5	30.8 0.0, 59.0	32.0 0.0, 79.3	0.9 -13.0, 32.4	1.1[‡] (CI_{95}, -2.1, 4.4) (p = 0.4935)[‡,§]

[¥] One patient in the Vimizim group dropped out after 1 infusion
[†] Observed mean of Vimizim - Placebo
[‡] Model-based mean of Vimizim - Placebo, adjusted for baseline
[§] p-value based on the model-based mean difference

Figure 1: Repeated Measures ANCOVA Mean Change in 6-Minute Walk Test (Intent-To-Treat Population)



Error bars represent standard error of least squares mean change from baseline.

Patients who participated in the placebo-controlled trial were eligible to continue treatment in an open-label extension trial (MOR-005). One hundred seventy-three of 176 patients enrolled in the extension trial in which patients received Vimizim 2 mg/kg once per week (n=86) or Vimizim 2 mg/kg once every other week (n=87). Patients who continued to receive Vimizim 2 mg/kg once per week for another 48 weeks (for a total of 72-week exposure) showed maintenance of the initial improvement in endurance and sustained urinary KS reduction with no further improvement in walking ability beyond the first 24 weeks.

Paediatric population

As for all lysosomal genetic disorders, it is important to initiate treatment as early as possible, before appearance of non-reversible clinical manifestations of the disease.

The majority of patients treated with Vimizim in clinical trials were in the paediatric age range (53% aged 5 to 11 years, 27% aged 12-17 years). Patients <5 years of age were not included in the pivotal study (MOR-004). In an open-label trial (MOR-007), 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. The mean duration of dosing was 125.3 weeks and ranged from 53.0 to 200.9 weeks. Efficacy assessment by a 6 minute walk test was not conducted due to the young age of these patients However, in the MOR-007 study, patients showed a reduction in urinary KS.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of Vimizim were evaluated in 23 patients with MPS IVA ranging in age from 5 to 42 years, who received weekly intravenous infusions of 2 mg/kg of Vimizim over approximately 4 hours for 22 weeks and the parameters at Week 0 and Week 22 were compared (see Table 4). At Week 22, the mean $AUC_{0\text{-}t}$ 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)
$AUC_{0\text{-}t}$, min x µg/mL[¥]	238 (100)	577 (416)
C_{max}, µg/mL[†]	1.49 (0.534)	4.04 (3.24)
CL, mL/min/kg[‡]	10.0 (3.73)	7.08 (13.0)
$t_{1/2}$, min[#]	7.52 (5.48)	35.9 (21.5)
T_{max}, min[Þ]	172 (75.3)	202 (90.8)
V_{dss}, mL/kg[§]	396 (316)	650 (1842)

[¥] $AUC_{0\text{-}t}$, 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 drug after intravenous administration
[#] $t_{1/2}$, elimination half-life
[Þ] $T_{max,}$ time from zero to maximum plasma concentration Min, minutes
[§] V_{dss}, apparent volume of distribution at steady-state

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 Vimizim clearance, and clearance did not trend with age or weight at Week 22.

The impact of antibodies on Vimizim pharmacokinetics was assessed. No association was apparent between the total antibody titre and Vimizim clearance. However, patients with positive neutralising

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

5.3 Preclinical safety data

Carcinogenicity

Long-term studies in animals to evaluate carcinogenic potential have not been performed with Vimizim.

Genotoxicity

Studies to evaluate mutagenic potential have not been performed with Vimizim.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium acetate trihydrate
monobasic sodium phosphate monohydrate
arginine hydrochloride
sorbitol E420
polysorbate 20 E432
water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6

6.3 Shelf Life

3 years

Diluted solutions: Chemical and physical in-use stability has been demonstrated for up to 24 hours refrigerated (2°C - 8°C) followed by up to 24 hours at room temperature (23°C - 27°C).

From a microbiological safety point of view, Vimizim should be used immediately. To reduce microbiological hazard, use as soon as possible after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Keep the vial in its carton in order to protect from light.

For storage conditions after dilution, see section 6.3

6.5 Nature and contents of container

Clear Type I glass vial with a butyl rubber stopper and an aluminium flip-off crimp seal with a plastic cap. Pack-size of 1 vial.

6.6 Special precautions for disposal and other handling

Vimizim must be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection for infusion using aseptic technique. The diluted Vimizim solution is to be administered to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

Vimizim does not contain preservatives. Each vial is for use in one patient on one occasion only. Discard any residue. 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)

1. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 2 mg/kg, using the following calculation:
   - Patient weight (kg) multiplied by 2 mg per 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. Round up to the next whole vial. Remove the appropriate number of vials from the refrigerator. Do not heat or microwave vials. Do not shake vials.
3. Obtain an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection 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, visually inspect each vial for particulate matter and discolouration. Because this is a protein solution, slight flocculation (thin translucent fibres) may occur. The Vimizim solution should be clear to slightly opalescent and colourless to pale yellow. Do not use if the solution is discoloured or if there is particulate matter in the solution.
5. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution for injection from the infusion bag, equal to the volume of Vimizim concentrate to be added.
6. Slowly withdraw the calculated volume of Vimizim from the appropriate number of vials using caution to avoid excessive agitation.
7. Slowly add Vimizim to the infusion bag using care to avoid agitation.
8. Gently rotate the infusion bag to ensure proper distribution of Vimizim. Do not shake the solution.
9. Administer the diluted Vimizim solution to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2 µm in-line filter.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks 2022
Auckland
(09) 918 5100

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

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

9. DATE OF FIRST APPROVAL

20 August 2015

DATE OF REVISION OF THE TEXT

2 May 2019

Vimizim® is a trademark of BioMarin.

Summary table of changes

Section changes	Summary of new information
4.2, 4.4	Text was relocated from Section 4.2 “Special Populations, Elderly patients” to Section 4.4 “Use in elderly” section.
4.4	Sentence was removed, as section 5.1 was revised to include long-term safety data for children under age 5 years.
5.1	Section was added regarding the mean duration of dosing was 125.3 weeks and ranged from 53.0 to 200.9 weeks.
5.2	Editorial changes.