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

Vimizim 1 mg/ml 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
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

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
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

3 years

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/914/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2014

10. DATE OF REVISION OF THE TEXT

MM/YYYY
Detailed information on this medicinal 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 MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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

Name and address of the manufacturer of the biological active substance

BioMarin Pharmaceutical, Inc.
Galli Drive Facility
46 Galli Drive
Novato, CA 94949
USA

BioMarin International Limited
Shanbally, Ringaskiddy, Co.
Cork Ireland
P43 X336

Name and address of the manufacturer responsible for batch release

BioMarin International Limited Shanbally,
Ringaskiddy, Co. Cork Ireland
P43 X336

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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Vimizim are provided with an Educational pack.
The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The educational material for Healthcare Professionals should be a step by step dosing and administration guide that includes information on the following key elements:

- the calculation of the dose and of the volume of infusion
- the calculation of the infusion rate
- the risk of anaphylaxis and of severe allergic reactions and the measures necessary to minimise it:
    - all patients should receive antihistamines with or without antipyretics 30–60 minutes prior to the start of infusion
    - appropriate medical support should be readily available when VIMIZIM® is administered
    - the need to immediately stop the infusion and initiate appropriate medical treatment if these reactions occurred

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Set up a MPS IVA disease Registry to assess the long term safety and efficacy of elosulfase alfa.	Submission of final study report: March 2025

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vimizim 1 mg/ml concentrate for solution for infusion
elosulfase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg elosulfase alfa in 5 ml of solution (1 mg/ml).

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate;
Monosodium phosphate monohydrate;
Arginine hydrochloride;
Sorbitol;
Polysorbate 20;
Water for injections
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
1 vial
5 mg/5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Read the package leaflet before use.
Intravenous use after dilution

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

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

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/1/14/914/001

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

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

5 ml VIAL

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

Vimizim 1 mg/ml sterile concentrate
elosulfase alfa
IV use after dilution

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Vimizim 1 mg/ml concentrate for solution for infusion
elosulfase alfa

▼ 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 you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vimizim is and what it is used for

Vimizim contains an enzyme called elosulfase alfa, which belongs to a group of medicines known as enzyme replacement therapies. It is used to treat adults and children with mucopolysaccharidosis type IVA (MPS IVA disease, also known as Morquio A Syndrome).

People with MPS IVA disease either lack completely or do not have enough N-acetylgalactosamine-6-sulfatase, an enzyme which breaks down specific substances in the body such as keratan sulphate, which are found in many tissues of the body, including cartilage and bone. As a result, these substances do not get broken down and processed by the body as they should. They accumulate in the tissues interfering with their normal function and causing the symptoms of MPS IVA, such as difficulty walking, trouble breathing, short height, and hearing loss.

How Vimizim works
This medicine replaces the natural enzyme N-acetylgalactosamine-6-sulfatase which is lacking in MPS IVA patients. Treatment has been shown to improve walking and to reduce the levels of keratan sulphate in the body. This medicine may improve the symptoms of MPS IVA.

2. What you need to know before you are given Vimizim

You must not receive Vimizim
- if you have experienced life-threatening allergic reactions to elosulfase alfa or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
- If you are treated with Vimizim, you may develop infusion reactions. An infusion reaction is any side effect, including an allergic reaction, occurring during the infusion or within a day following

infusion (see section 4 “Possible side effects”). If you experience such a reaction, **you should immediately contact your doctor.**
- If you have an allergic reaction during your infusion your doctor may slow down, or stop your infusion. Your doctor may also give you additional medicines to manage any allergic reactions.
- If you experience back pain, numbness in your arms or legs, or lack of control over passing urine or stools**, you should immediately contact your doctor**. These problems can be a part of the disease and may be caused by pressure on your spinal cord.

Other medicines and Vimizim
Please tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
You should not receive Vimizim during pregnancy unless clearly necessary. It is not known whether Vimizim is excreted in human breast milk. Discuss with your doctor if the benefits of taking Vimizim are greater than the potential risk to your newborn while breast-feeding. It is not known if Vimizim impacts human fertility. No effect on fertility was observed in animals.

Driving and using machines
Dizziness was reported in some patients during the Vimizim infusion. Tell your doctor if you feel dizzy after your infusion, especially before driving or using any machine where dizziness might be dangerous.

Vimizim contains sodium and sorbitol
Each 5 ml vial contains 8 mg sodium. This should be taken into consideration by patients on a controlled sodium diet.

Each vial also contains 100 mg of sorbitol (E420). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How Vimizim is given

Your doctor or nurse will give Vimizim to you by an infusion into a vein.

The medicine has to be diluted before being given. Your doctor or nurse will give you some medicines before your treatment to reduce allergic reactions and you may also be given medicines to help control any fever.

Dose
The dose you receive is based on your body weight. The recommended dose regimen for adults and children is 2 mg/kg body weight given once every week through a drip into a vein (intravenous infusion). Each infusion will be given over approximately 4 hours. Vimizim may be started at as young as an age possible and is intended for long term use.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

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 reactions”). The most serious side effects were severe allergic reactions (seen uncommonly – may affect up to 1 in 100 people) and mild to moderate vomiting (seen very commonly – may affect more than 1 in 10 people). Symptoms of severe allergic reaction include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives

on the skin. **If you experience any reaction like this, please tell your doctor immediately**. You will be given additional medicines to reduce the effects of a severe allergic reaction (e.g. antihistamines and/or corticosteroids) or to reduce fever (antipyretics).

Very common side effects include symptoms of infusion reactions such as headache, nausea, fever, chills and stomach ache. Other very common adverse reactions were diarrhoea, mouth and throat pain, dizziness and shortness of breath.

Common side effects (which may affect up to 1 in 10 people) were muscle pain and allergic reactions.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. 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 Vimizim

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and 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.

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

Do not use Vimizim 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 Vimizim contains
- The active substance is elosulfase alfa. Each ml of concentrate contains 1 mg elosulfase alfa. Each vial of 5 ml contains 5 mg elosulfase alfa.
- The other ingredients are: sodium acetate trihydrate, monosodium phosphate monohydrate, arginine hydrochloride, sorbitol, polysorbate 20, and water for injections (see section 2 under ‘Vimizim contains sodium and sorbitol’).

What Vimizim looks like and contents of the pack
Vimizim 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.

Pack sizes: 1 vial of 5 ml

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

Manufacturer
BioMarin International Limited
Shanbally, Ringaskiddy
County Cork
Ireland

This leaflet was last revised in MM/YYYY

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:

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

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. Diluted Vimizim solution is to be administered to patients using an infusion set. An infusion set equipped with an in-line 0.2 µm filter can be used.

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

Preparation of the Vimizim 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 in advance in order to allow them to reach 23°C – 27°C. Do not heat or microwave vials. The recommended dose regimen is 2 mg/kg body weight administered once every week through a drip into a vein (by intravenous infusion). Each infusion will take approximately 4 hours.

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. Do not shake vials.

A volume of the sodium chloride 9 mg/ml (0.9 %) solution for infusion is to be withdrawn and discarded from a 100 ml or 250 ml infusion bag equal to the total volume of Vimizim to be added. Preparation of Vimizim for patient’s weighing less than 25 kg, should not be diluted in sodium chloride 9 mg/ml (0.9 %) solution for infusion bags larger than 100 ml.

When diluted with 100 ml sodium chloride 9 mg/ml (0.9 %) solution for infusion, the initial rate will be 3 ml/hr. The infusion rate will be increased 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 with 250 ml sodium chloride 9 mg/ml (0.9 %) solution for infusion, the initial rate will be 6 ml/hr. The infusion rate will be increased 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.

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.

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

The diluted solution is to be mixed gently prior to infusion.

The diluted solution is to be visually inspected for particulate matter prior to use. Do not use if the solution is discoloured or if there is particulate matter in the solution

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.