



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Elosulfase alfa (rch)

Proprietary Product Name: Vimizim

Sponsor: BioMarin Pharmaceutical Australia Pty
Ltd

April 2015

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2015

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

List of the most common abbreviations used in this AusPAR	5
I. Introduction to product submission	9
Submission details	9
Product background	9
Regulatory status	11
Product Information	11
II. Quality findings	12
Drug substance (active ingredient)	12
Drug product	13
Biopharmaceutics	14
Quality summary and conclusions	14
III. Nonclinical findings	15
Introduction	15
Pharmacology	15
Pharmacokinetics	16
Toxicology	17
Nonclinical summary	21
Nonclinical conclusions	22
IV. Clinical findings	22
Introduction	22
Pharmacokinetics	24
Pharmacodynamics	25
Dosage selection for the pivotal studies	25
Efficacy	26
Safety	28
First round benefit-risk assessment	30
First round recommendation regarding authorisation	31
Clinical questions	31
Pharmacokinetics	31
Pharmacodynamics	33
Efficacy	33
Safety	33
Second round evaluation of clinical data submitted in response to questions	33
Second round benefit-risk assessment	38
Second round recommendation regarding authorisation	39

V. Pharmacovigilance findings	40
Risk management plan	40
VI. Overall conclusion and risk/benefit assessment	47
Quality	47
Nonclinical	47
Clinical	48
Risk management plan	54
Risk-benefit analysis	54
Outcome	67
Attachment 1. Product Information	68
Attachment 2. Extract from the Clinical Evaluation Report	68

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
3MSCT	3-minute stair-climb test
6MWT	6-minute walk test
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARRB	Allergic Reaction Review Board
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity
AUC _{0-t}	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BMN	BioMarin Pharmaceutical Inc.
BMN 110	recombinant human N-acetylgalactosamine-6-sulfatase
BMN 110 2.0 mg/kg/qow	every other week cohort
BMN 110 2.0 mg/kg/week	weekly cohort
°C	degree Celsius
C4	complement component 4
CI-M6PR	cation-independent mannose-6-phosphate receptor
C _{max}	observed maximum plasma concentration
CL	total clearance of drug after intravenous administration
CRF	case report form
CSR	Clinical Study Report
CTX1	type I collagen C-terminal crosslinked C-telopeptide
DMC	Data Monitoring Committee

Abbreviation	Meaning
ECG	electrocardiogram
ECHO	echocardiogram
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
FET	forced expiratory time
FEV1	forced expiratory volume in 1 second
FIVC	forced inspiratory vital capacity
FVC	forced vital capacity
GAG	glycosaminoglycan
GALNS	N-acetylgalactosamine-6-sulfatase
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
IAR	Infusion associated reaction
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
KS	keratan sulfate

Abbreviation	Meaning
K_{uptake}	the concentration of enzyme/ligand that yields half the maximal uptake value
LOCF	last observation carried forward
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MPS	mucopolysaccharidosis
MPS HAQ	MPS health assessment questionnaire
MPS IVA	MPS IV type A; Morquio A Syndrome
MVV	maximum voluntary ventilation
NAb	BMN 110-specific neutralizing antibodies (that inhibit cellular receptor binding)
PIIANP	type IIA collagen N-propeptide
PD	pharmacodynamics
PK	pharmacokinetics
PP	per-protocol
qow	every other week
REB	Research Ethics Board
RFTs	respiratory function tests
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQ	Standardised MedDRA Query
SOC	system organ class
$t_{1/2}$	elimination half-life
T_{max}	time to reach C_{max}
TAb	total antibody
urine KS	urine keratan sulfate

Abbreviation	Meaning
US	United States
Vd_z	apparent volume of distribution based upon the terminal phase
Vd_{ss}	apparent volume of distribution at steady state
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	2 December 2014
<i>Active ingredient:</i>	Elosulfase alfa (rch)
<i>Product name:</i>	Vimizim
<i>Sponsor's name and address:</i>	BioMarin Pharmaceutical Australia Pty Ltd 119 Willoughby Rd Crows Nest NSW 2065
<i>Dose form:</i>	Concentrate for solution for Infusion
<i>Strength:</i>	1 mg/mL
<i>Container:</i>	Vial
<i>Pack size:</i>	One
<i>Approved therapeutic use:</i>	<i>Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)</i>
<i>Route of administration:</i>	Intravenous (IV) Infusion
<i>Dosage:</i>	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).
<i>ARTG number:</i>	215523

Product background

This AusPAR describes the application by the sponsor to register Vimizim, Elosulfase alfa (rch) concentrated solution for infusion, for the following indication

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

Mucopolysaccharidoses (MPS) are inherited disorders of the lysosomal enzymes responsible for the stepwise breakdown of glycosaminoglycans (GAGs).

Elosulfase alfa is a recombinant human N-acetylgalactosamine-6-phosphatase intended to supplement the deficient enzyme N-acetylgalactosamine-6-phosphatase with the purpose of disease modification.

GAGs are large polymers comprising repeated sulfated acidic and amino sugar disaccharide units attached to a protein core. They are the components of the ground glass

substance of bone and cartilage, lubricant in synovial fluid and the surface coating that initially binds growth factors to cells. The metabolic recycling of GAGs requires the stepwise degradation of the terminal sulfate, acidic and amino sugar residues by a series of lysosomal enzymes. The deficiency of one of these enzymes blocks degradation of the substrate. The partially degraded GAGs that result from an enzyme deficiency accumulate in the lysosomes of cells, resulting in cellular dysfunction and a specific disorder. The clinical phenotype of the disorder depends upon the distribution and turnover of the substrate affected by the deficiency, rather than the distribution of the enzyme.¹ There are four broad clinical groups:

- Soft tissue storage and skeletal disease with or without brain damage (MPS I, II, VII)
- Soft tissue and skeletal disease (MPS VI)
- Primary skeletal disorders (MPS IVA and IVB)
- Primary central nervous system disorders (MPS III A-D).

Morquio syndrome A (MPS IVA) is an autosomal recessive disorder caused by mutations in the gene encoding galactosamine-6-sulphatase.

N-acetylgalactosamine-6-phosphatase is a lysosomal enzyme that catalyses the hydrolysis of sulphate groups attached to the N-acetyl-D-galactosamine and D-galactose units of chondroitin sulphate and keratan sulphate.

A deficiency of this enzyme results in an accumulation of keratan sulphate and chondroitin-6 sulphate. The incidence is estimated to be 1:201,000 births and an estimated 49 Australians are affected. The key features are progressive skeletal deformities affecting synovial joints and the spine, and respiratory disorders secondary to restrictive lung disease and spinal cord compression. Corneal opacities, cataracts, tooth enamel hypoplasia, hepatosplenomegaly and valvular heart disease can also occur. Life expectancy and disability vary according to the residual enzyme activity.

It has mild to severe forms depending on the residual enzyme activity. Severe forms present in the first one to three years of life. In the severe forms linear growth is minimal after six or seven years of age and death usually occurs in the third or fourth decade from cardiorespiratory failure. Milder forms can appear later in childhood or adolescence and these patients may live into their seventh decade. The clinical features result in diminished functional capacity with significant limitations in mobility and breathing, high care-giver burden, and impaired quality of life from the functional limitations and the requirement for frequent surgical procedures to address the musculoskeletal and/or respiratory dysfunction.

No specific therapy for Morquio A syndrome is currently registered in Australia and Elosulfase alpha has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM).

- There are no specific EU guidelines adopted by the TGA relevant to therapies for mucopolysaccharidoses; however the following guidelines are applicable:
- Clinical investigation of medicinal products for long-term use (Directive 75/318/EEC)
- Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population (CPMP/ICH/2711/99)

¹ UpToDate Mucopolysaccharidoses: Clinical features and diagnosis
<<http://www.uptodate.com/contents/mucopolysaccharidoses-clinical-features-and-diagnosis?source=machineLearning&search=mucopolysaccharidoses&selectedTitle=1%7E46§ionRank=1&anchor=H3#H3>> accessed 15/8/2014

- Reflection paper: formulations of choice for the paediatric population (CPMP/ICH/2711/99).

Regulatory status

The product is considered a new chemical entity for Australian regulatory purposes.

Elosulfase alfa was designated an orphan drug in Australia in July 2013.

Elosulfase was approved in the US in February 2014 and is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) (see Table 1 below). Also in February 2014, it received a positive opinion from the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) and was approved 28 April 2014.

It was approved in Canada in July 2014. An application was under consideration in Switzerland.

Table 1. Overseas regulatory status

Country	Approval date	Approved indications
European Union Centralised Procedure (Rapporteur Netherlands and Co-rapporteur Germany)	28 April 2014	<i>Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages</i>
USA	14 February 2014	<i>Vimizim (elosulfase alfa) is indicated for patients with mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome)</i>
Canada	2 July 2014	<i>Vimizim (elosulfase alfa) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis type IVA (Morquio A Syndrome, or MPS IVA)</i>

Product Information

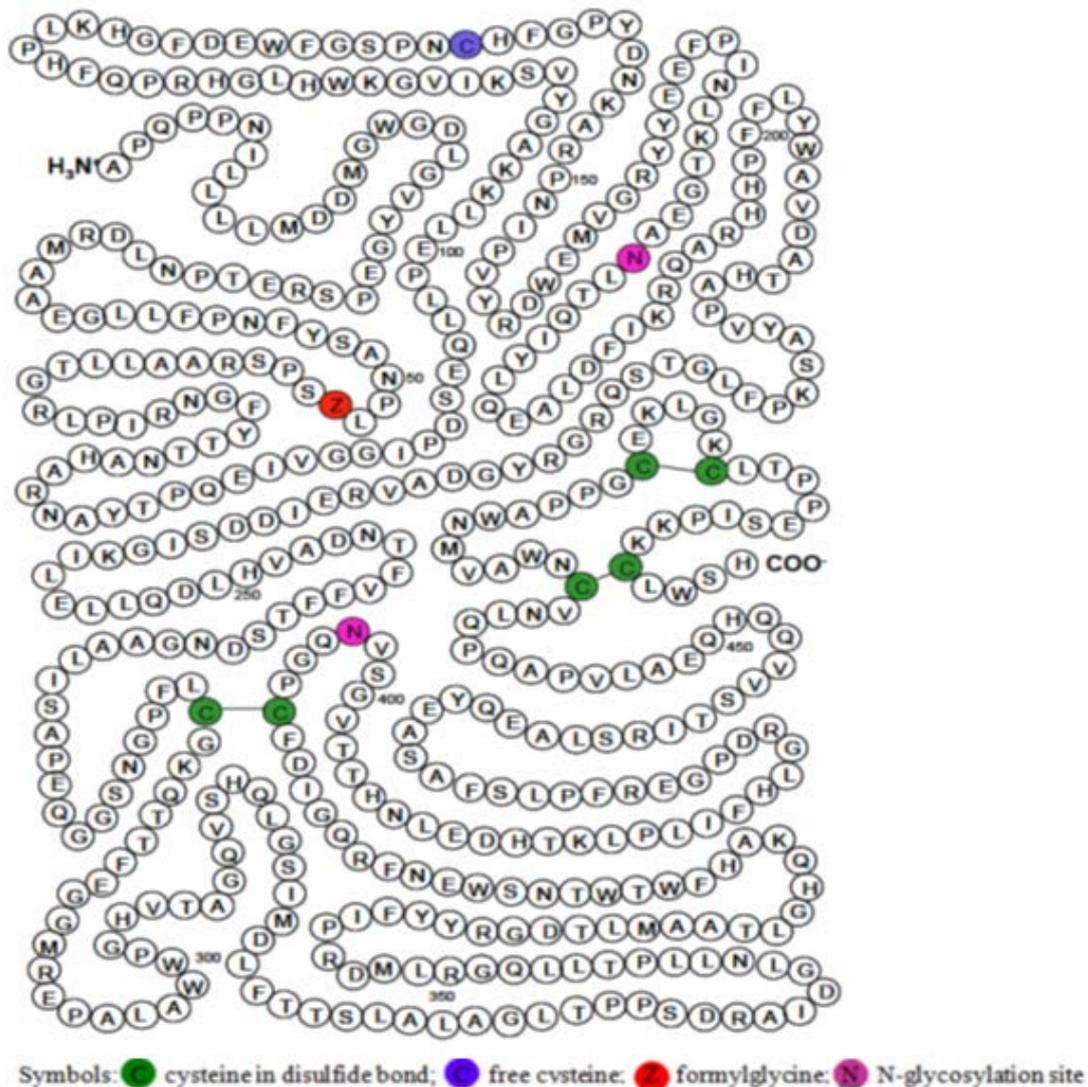
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

The mature recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS, elosulfase alfa) protein contains 496 amino acids. The amino acid sequence of elosulfase alfa is identical to the endogenous lysosomal enzyme, human GALNS. The calculated isotope average molecular mass of the peptide chain is 55412.9 Daltons (Da). Elosulfase alfa contains 8 cysteine residues, 6 of which are involved in intramolecular disulfide bridges (Figure 1). One cysteine residue is unpaired and one cysteine residue in the active site (C53) is enzymatically converted by the production cell into formylglycine (FGly, 2-amino-3-oxopropanoic acid; oxo-alanine). This modification is required for enzyme activity and is conserved in all members of the sulfatase enzyme family.

Figure 1: Schematic Diagram of N-acetylgalactosamine-6-sulfatase Primary Sequence and Amino Acid Residues of Interest



Manufacture

Elosulfase alfa is produced by Chinese Hamster Ovary (CHO) cells that over-express the elosulfase alfa transgene. The Elosulfase alfa formulated bulk active substance (FBDS) is manufactured at BioMarin's commercial manufacturing facility in compliance with current good manufacturing practice (cGMP) regulations.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Elosulfase alfa is a single-chain glycosylated enzyme involved in the lysosomal degradation of the glycosaminoglycans (GAGs) keratan sulfate (KS) and chondroitin sulphate (CS). The glycosylation of elosulfase alfa contains high mannose and phosphorylated high mannose oligosaccharide structures.

The protein and carbohydrate structure, potency, strength and purity of clinical and commercial lots of elosulfase alfa have been characterised and these data are presented to demonstrate comparability of elosulfase alfa produced using the clinical and commercial processes. During clinical development BioMarin performed several comparability studies to support changes in the manufacturing process of elosulfase alfa. The comparability of elosulfase alfa bulk drug substance (BDS) and formulated bulk drug substance (FBDS) lots produced by the Phase I/II, Phase III and the commercial manufacturing processes was evaluated by the combination of release tests and additional characterization methods.

Phase III clinical FBDS lots and reference material BMN 110-0110-001 were also included in this study in order to evaluate the comparability of clinical and commercial materials.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use were submitted. Appropriate validation data have been submitted in support of the test procedures.

Drug product**Formulation**

Vimizim is a sterile solution for infusion, packaged in a container closure system consisting of a Type 1 borosilicate glass tubing vial, butyl rubber stopper and aluminium seal with flip off cap. Each vial is filled to a target volume of 5.3 mL of solution, which allows the withdrawal of 5.0 mL deliverable volume. Vimizim is formulated with a target pH of 5.4.

The visual appearance of the drug product is clear to slightly opalescent, and colourless to pale yellow.

For administration to patients, Vimizim is diluted with 9 mg/mL (0.9%) sodium chloride solution.

Manufacture

The manufacturing process of Vimizim drug product uses conventional recombination, filtration, filling, capping, and inspection equipment commonly used for this type of dosage

form. Manufacturing is performed in a fill suite in accordance with current Good Manufacturing Practices (cGMPs) and takes place in a production area which is specifically designed for aseptic processing.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were submitted.

Stability

Stability data have been generated under real time, accelerated, and stressed conditions to characterise the stability profile of the product. No photostability studies were done for the final product. However, they were done for the FBDS and found to be 'Comparable to Reference'. The vials of drug product are packed in an outer carton and the storage conditions include the recommendation to 'Keep the vial in its carton in order to protect from light.'

The proposed shelf life is 3 years when stored at 2°C to 8°C.

Compatibility studies have been performed to assure that Vimizim is compatible with the infusion solutions and bags used in the clinical studies. This includes stability of diluted solutions. The results demonstrated that Vimizim infusion solutions are stable when stored at 5±3°C for at least 24 hours followed by an additional 24 hours of storage at 25±2°C/60±-5% relative humidity (RH) environmental chamber, at the dilutions evaluated in this study (0.1 mg/mL and 0.5 mg/mL).

Concentrations of Phase I/II rhGALNS diluted in 0.9% saline were studied to levels of 0.04 mg/mL in the polyolefin/polyamide bag, and compatibility was also demonstrated with very low concentrations of rhGALNS. These are stable when stored under refrigerated conditions for 24 hours followed by storage at controlled room temperature for an additional 24 hours.

The above two studies support the following statement in the proposed PI:

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

No temperature excursion data have been provided for the final product. The applicant has been advised that all batches of Vimizim final product shipped to Australia must be equipped with temperature monitors. The sponsor has agreed to this.

Biopharmaceutics

No bioavailability studies were conducted. This is in line with Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), Section 2, bullet point 3 'simple aqueous solutions intended for intravenous injection or infusion'.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The Quality evaluator(s) recommend that Vimizim elosulfase alfa (rch) 1 mg/mL solution for injection vial should be approved.

Should the product be approved, the following conditions of registration should be applied.

Conditions of registration: batch release testing

It is a condition of registration that, as a minimum, the first five independent batches of Vimizim elosulfase alfa (rch) 1 mg/mL solution for injection vial AUST R 215523 imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

III. Nonclinical findings

Introduction

The nonclinical data submitted in support of the efficacy and safety of elosulfase alfa was of high quality. The pivotal, nonclinical safety studies were performed by reputable laboratories in accordance with Good Laboratory Practice (GLP) standards.

Pharmacology

Primary pharmacology

N-acetylgalactosamine-6-sulfatase is a lysosomal enzyme that catalyses the hydrolysis of sulfate groups attached to the *N*-acetyl-D-galactosamine and D-galactose units of chondroitin sulfate and keratan sulfate. The removal of the sulfate groups is a necessary first step in the degradation of these glycosaminoglycans. MPS IVA patients show deficient *N*-acetylgalactosamine-6-sulfatase activity that can lead to progressive accumulation of chondroitin sulfate and keratan sulfate in lysosomes in different tissues. This can result in various abnormalities, particularly of the skeleton.

The normal intracellular localisation of *N*-acetylgalactosamine-6-sulfatase to lysosomes is dependent on the presence of mannose-6-phosphate (M6P)-terminated oligosaccharide chains on the protein. This facilitates binding by M6P receptors in the Golgi apparatus and transport to an acidic pre-lysosomal compartment where the low pH mediates the dissociation of the complex. One of the intracellular receptors for M6P-terminated oligosaccharide chains, insulin-like growth factor II/cation-independent M6P receptor, is also present on the cell membranes of various cell types. This potentially allows the binding of exogenously supplied *N*-acetylgalactosamine-6-sulfatase to the receptor, followed by endocytosis and incorporation into lysosomes.

In vitro studies examined the cellular uptake, localisation and intracellular activity of elosulfase alfa. Elosulfase alfa showed high efficiency uptake by MPS IVA fibroblasts (K_{uptake} values approximately 3 nM), which was blocked at low affinity by M6P and at much higher affinity by another lysosomal enzyme (this is because high affinity inhibition requires an oligosaccharide with two M6P residues). Such uptake of enzyme by MPS IVA chondrocytes was shown by fluorescence microscopy to co-localise with a lysosomal marker. An *in vivo* study, examining uptake of fluorescent elosulfase alfa by mouse heart, also demonstrated co-localisation of elosulfase alfa with a lysosomal marker. Long-term (to 9 weeks) continuous treatment of MPS IVA chondrocytes with elosulfase alfa produced a dose and time dependent decrease in keratan sulfate immunofluorescence in the lysosomal

compartment (but not in the extracellular matrix). The half-life of exogenously supplied *N*-acetylgalactosamine-6-sulfatase in MPS IVA fibroblasts was approximately 6 days.

In vivo nonclinical studies examining the efficacy of elosulfase alfa were not performed. This is reasonable given that mice lacking *N*-acetylgalactosamine-6-sulfatase activity show a normal phenotype and lack the skeletal abnormalities that characterise severely affected MPS IVA patients.

The sponsor's studies support the proposed mechanism of action and indication for elosulfase alfa.

Secondary pharmacodynamics and safety pharmacology

As elosulfase alfa is a large protein that targets a specific receptor on cells and catalyses a specific reaction only in the low-pH environment of the lysosome, it appears unlikely that it would interfere with other cellular processes. It should be noted that insulin-like growth factor-II and M6P-terminated oligosaccharide chains have separate binding sites on insulin-like growth factor II/cation-independent M6P receptor and that the receptor lacks signal transduction capacity. Moreover, no off-target findings were noted in the chronic repeat dose toxicity studies in the rat and monkey (see below). Hence, the lack of secondary pharmacodynamics studies is acceptable.

Safety pharmacology studies examined possible elosulfase alfa effects on the central nervous system (CNS), cardiovascular and respiratory systems. Rats (both sexes), given a single intravenous (IV) dose of elosulfase alfa at up to 20 mg/kg (area under the concentration versus time curve (AUC) exposure ratio of approximately 16) and then monitored for 14 days, showed no changes in neurobehavioural parameters. Similarly, male rats given a single IV dose of elosulfase alfa at up to 20 mg/kg showed no changes in respiratory parameters. Cynomolgus monkeys (males, approximately 4 to 5 years of age), given IV infusions of elosulfase alfa at up to 20 mg/kg (AUC exposure ratio approximately 20, see table below), showed no test article-related effects on haemodynamic or electrocardiogram (ECG) parameters.

Pharmacokinetics

Plasma toxicokinetics (TK): After the first dose of elosulfase alfa in both rats and cynomolgus monkeys, increases in peak plasma concentration (C_{max}) and AUC from time zero to infinity ($AUC_{0-\infty}$) for both sexes were roughly proportional to dose between 1 and 6 mg/kg, but were greater than proportional at 20 mg/kg. Elosulfase alfa showed short half-life ($t_{1/2}$) values in both rats and cynomolgus monkeys. Values in rats were dose dependent (increased from approximately 2 to 10 min. over the range 1 to 20 mg/kg) and increased during the dosing period (from approximately 10 minutes after the first dose at 20 mg/kg to approximately 25 minutes after 26 doses). Dose had little effect on $t_{1/2}$ values in cynomolgus monkeys, although after 52 weeks of dosing at 20 mg/kg, $t_{1/2}$ had increased to approximately 100 minutes compared to approximately 10 minutes after the first dose. Humans also showed an increase in $t_{1/2}$ values during dosing at 2 mg/kg, with a $t_{1/2}$ of 7.5 minutes after the first dose compared to 36 minutes after the twenty-second dose (Study MOR-004). Exposure to elosulfase alfa trended higher in male compared to female cynomolgus monkeys at all dose levels, and was higher in male cf. female rats at 20 mg/kg but not at lower doses. The basis for the effects of dosing period and dose size on plasma TK was not explored but is likely to include changes in the rate and/or mode of degradation induced by binding to anti-drug antibodies.² Such antibodies were detected in rats and monkeys given multiple doses of elosulfase alfa (see below). Anti-drug antibodies

² Vugmeyster Y., Xu X., Theil F.-P., Khawli L.A. and Leach M.W. (2012) Pharmacokinetics and toxicology of therapeutic proteins: advances and challenges. *World Journal of Biological Chemistry*, **3**: 73–92.

were also induced in all patients treated with elosulfase alfa, with approximately 80% of patients developing antibodies capable of inhibiting drug binding to cation-independent M6P receptor *in vitro*.

Distribution: Analysis of femurs and tibias from mice given IV doses of fluorescent elosulfase alfa showed uptake by epiphysis, marrow and growth plate. (Growth plate cartilage, as well as resting cartilage, is major sites of keratan sulfate accumulation that lead to skeletal dysplasia in MPS IVa patients.) The level of test article in chondrocytes appeared to reflect proximity to vasculature. Analysis of mouse heart showed uptake by septum, atrium, and heart valve (major location of morbidity in MPS IVa patients). In mouse liver, elosulfase alfa was taken up by sinusoidal endothelial and Kupffer cells but not by hepatocytes. (Morbidity in some MPS IVa patients is due to liver dysfunction deriving from keratan sulfate accumulation in Kupffer cells and resulting hepatomegaly).

Metabolism and excretion: No studies were performed in these areas. This is reasonable as elosulfase alfa would be expected to undergo proteolysis to amino acids, which are an intrinsic cellular component.

Conclusion: As noted above, the pharmacokinetics of elosulfase alfa in rats and monkeys showed similarities with human results. Hence, these laboratory animal species would appear to be reasonable models for the assessment of elosulfase alfa toxicity in humans.

Pharmacokinetic drug interactions

No studies were performed in this area. Elosulfase alfa showed rapid clearance from the plasma of rats and cynomolgus monkeys (see above). Such clearance might involve various mechanisms, such as binding by insulin-like growth factor II/cation-independent M6P receptors on various cell types, followed by endocytosis and proteolysis. Although drugs that interfere with such processes have been identified, it appears unlikely that they would be used to treat MPS IVA patients. Accordingly, the lack of drug interaction studies is acceptable.

Toxicology

Acute toxicity

Single-dose studies in rats showed no toxicity effects at IV doses up to 20 mg/kg (see above).

Repeat-dose toxicity

Studies were performed with rats (both sexes) and juvenile cynomolgus monkeys (both sexes, approximately 2 to 3 years of age) at durations of up to 6 months and 1 year, respectively. Animals received a once weekly IV infusion of test article, which is consistent with the mode and frequency of clinical dosing. The design of the studies was consistent with the relevant EMA guideline.³

Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC_{0-∞} values (Table 2). Human reference values are from Week 22 of the clinical pharmacology Study MOR-004. Relative exposure values at No Observable Adverse Effect Level (NOAEL), for both rat and monkey, are high (see Table 2).

³ CPMP/SWP/1042/99 Rev 1: Guideline on repeated dose toxicity

Table 2: Relative exposure in repeat-dose toxicity studies^a

Species	Study number	Study duration (day of TK sampling)	Dose (mg/kg) ^b	Sex	AUC _{0-∞} (µg.h/mL)	Exposure ratio ^c
Rat (SD)	0110-08-020	6 months (Week 26)	6, <u>20</u> ^{d, e}	♂	7.0, <u>513.9</u>	0.7, <u>50</u>
				♀	25.3, <u>337.7</u>	2.5, <u>33</u>
Monkey cynomolgus	BMN110-10-100	1 month (Week 4)	<u>20</u> (lot 1), <u>20</u> (lot 2), <u>20</u> (lot 3)	♂	<u>171.5</u> , <u>208.1</u> , <u>250.9</u>	<u>17</u> , <u>20</u> , <u>24</u>
				♀	<u>89.0</u> , <u>121.7</u> , <u>131.6</u>	<u>8.6</u> , <u>12</u> , <u>13</u>
	0110-08-018	1 year (Week 52)	1, 6, <u>20</u>	♂	1.57, 20.9, <u>711.8</u>	0.2, 2.0, <u>69</u>
				♀	0.76, 18.1, <u>496.5</u>	0.1, 1.8, <u>48</u>
Human (MPS IVA patients, ≥ 5 years of age, n = 22)	MOR-004	(Week 22)	2	♂ + ♀	10.3	–

^a All listed studies are GLP compliant; ^b once weekly dose given as IV infusion (over 1 to 2 minutes for rats and over approximately 4 h for monkeys and humans); ^c animal: human plasma AUC_{0-∞}; ^d values at NOAEL dose are bolded and underlined; ^e includes pre-treatment with the antihistamine diphenhydramine at 2 mg/kg.

Major toxicities

No targets for toxic effects were identified in either rats or monkeys. Anaphylactic-type reactions, leading in some cases to death, were seen after the Week 3 dose administration in all rat groups given test article. This response was subsequently controlled by oral pre-treatment with the antihistamine diphenhydramine. Both rats and monkeys showed dose and time dependent induction of anti-drug antibodies, although monkeys did not show anaphylactic-type reactions. Neutralising antibodies (blocking binding to cation-independent M6P receptor) were commonly present in serum from both species.

Control and high-dose monkeys were tested during Week 13 of the 1 year study for plasma levels of keratan sulfate-derived disaccharides and for the terminal crosslink peptide of collagen type 1A1 chains (released during osteoclastic bone resorption). Neither marker showed a test article-related change in concentration. This suggests that elosulfase alfa is not inducing an exaggerated pharmacology in cartilage and bone.

The validity of the pharmacology and toxicology studies, as a guide to possible human effects, is based in part on the assumptions that human *N*-acetylgalactosamine-6-sulfatase (that is elosulfase alfa) binds to the cation-independent M6P receptor and is effectively transferred to and functions within the lysosomes of the test animals. These assumptions are probably reasonable given that mouse, rat, rabbit, and cynomolgus monkey *N*-acetylgalactosamine-6-sulfatase show 84, 84, 85 and 97% amino acid sequence homology, respectively, with the human enzyme. Similarly, mouse, rat, rabbit and cynomolgus

monkey cation-independent M6P receptor showed 81, 80, 79 and 94% amino acid sequence homology, respectively, with the human protein.⁴

Genotoxicity and carcinogenicity

The range and type of genotoxicity and carcinogenicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology derived pharmaceuticals and therefore are not needed⁵. Accordingly, possible genotoxic or carcinogenic action by elosulfase alfa was not examined. It is not expected that these substances would interact directly with deoxyribonucleic acid (DNA) or other chromosomal material. Based on the nature of the test article (recombinant human glycoprotein), its impurity profile (see below), its enzymic action (N-acetylgalactosamine-6-sulfatase), and the products it generates, it appears unlikely that elosulfase alfa would have genotoxic or carcinogenic activity.

Reproductive toxicity

Elosulfase alfa was assessed for effects on fertility (both sexes) and embryofetal and pre/postnatal development in Sprague Dawley (SD) rats, and for effects on embryofetal development in rabbits. Due to the more limited time frame for such studies, all reproductive toxicity studies involved once daily IV administration of elosulfase alfa. High relative exposures were achieved at the high dose (HD) for both species (see table). The scope and design of the studies were appropriate and consistent with the relevant EMA guideline.⁶ The pivotal studies were performed to GLP standards.

Relative exposure

Table 3 shows the relative animal: human exposure ratios.

Table 3: Relative exposure in the reproductive toxicity studies

Species (strain) study type (number)	Treatment period (day of sampling)	Sex	Dose (mg/kg/ day) IV	AUC _{0-∞} (µg.h/mL)	Exposure ratio ^a
Rat (SD) Fertility/embryofetal development (BMN110-10-007)	♂ = Day 1– Day 44 (Day 43) ♀ = Day 1– GD20 (GD 19)	♂	1^b, 6, <u>20^b</u>	1.4, 49.8, <u>550.1</u>	1.0, 34, <u>374</u>
		♀	1, 6, <u>20^b</u>	1.1, 53.2, <u>334.7</u>	0.7, 36, <u>227</u>
Rabbit (NZW) Embryofetal development (BMN110-10-008)	GD7–GD20 (GD19)	♀	1, <u>6</u>, 20	≥1.3, <u>42.2</u>, 153.4	≥0.9, <u>29</u>, 104

^a Animal: human plasma AUC_{0-∞} based on human AUC of 10.3 µg.h/mL (clinical Study MOR-004). Animal AUC_{0-∞} value was multiplied by 7 to reflect daily dosing compared to weekly dosing for humans. ^b NOAEL doses for fertility, maternal or paternal toxicity, and embryofetal development are underlined, bolded, and boxed, respectively. NOAEL for rat female toxicity was less than the low dose (LD).

⁴ Coutinho, MF, Lacerda, L, Alves, S. (2012) Glycosaminoglycan storage disorders: a review. *Biochem Res Int*, Article ID 471325.

⁵ Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals, ICH S6(R1)

⁶ CPMP/ICH/386/95: ICH Topic S 5 (R2). Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

Effects of elosulfase alfa on male and female fertility and embryofetal development were investigated using rats given daily IV doses up to 20 mg/kg. There were no effects at the HD (AUC exposure ratio approximately 200 to 400 times that expected in humans) on estrus cycling, mating or fertility. The interpretation of other results from this study was complicated by the necessity of giving animals diphenhydramine prior to elosulfase alfa dosing, in order to mitigate anaphylactoid-type reactions. Increases in fetal resorptions and fetal alterations in diphenhydramine control and diphenhydramine plus test article groups were attributed to diphenhydramine. Effects on males (decreased weight gain in the mid dose (MD) and HD groups) and deaths in the female groups were attributed to elosulfase alfa but may have been due to incomplete suppression of anaphylactoid-type reactions.

Embryofetal development was also examined in rabbits dosed once daily with elosulfase alfa from gestation day (GD) 7 to GD 20 at 0, 1, 3 or 10 mg/kg. At the HD (exposure ratio >30, by comparison with rabbit study shown in table), there was no test article-related increase in fetal variations/malformations. MD and HD dams, however, showed apparently significant increases in the incidences of liver morphology changes (pitted or tan areas).

Mated female rats were IV dosed with elosulfase alfa at 0, 1, 6 or 20 mg/kg/day (following diphenhydramine dosing) from GD7 to lactation day (LD) 20. There were significant reductions in percentages of live-born pups from MD and HD dams (exposure ratios of approximately 35 and 200, respectively, by comparison with fertility study), and a significant increase in postpartum deaths of pups from HD dams. Pup development showed no effects of test article dosing of their dams.

Milk was collected at approximately 0.5 h postdose, on Day 14 postpartum, from rats dosed at 0, 1, 6 or 20 mg/kg. Milk from control or low dose (LD) treated dams was negative for elosulfase alfa, whilst 1 of 5 MD dams and 4 of 5 HD dams produced milk that was positive for elosulfase alfa. Placental transfer of elosulfase alfa was examined at 15 minutes post infusion in fetuses from rabbit dams dosed at 1, 6 or 20 mg/kg. Elosulfase alfa concentrations were below the lower limit of quantification (LLOQ) (75 ng/mL) at 1 and 6 mg/kg, however, a mean plasma level of 94 ng/mL was detected in fetuses from dams dosed at 20 mg/kg.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1: *'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.'* Given the above-noted findings from rats of decreased percentages of live-born pups and increases in post-partum deaths, Pregnancy Category B3⁷ would seem more appropriate.

Local tolerance/immunotoxicity

Injection or infusion site reactions were not observed in animal toxicology studies. See discussion above regarding immunotoxicity.

⁷ Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Impurities

The impurities/degradants in elosulfase alfa are not of toxicological concern.

Paediatric use

Elosulfase alfa is indicated for long-term enzyme replacement therapy of both paediatric and adult patients with MPS IVA. In support of pediatric use, repeat-dose toxicity studies used normal juvenile cynomolgus monkeys (2 to 3 years old). Such monkeys are actively growing, have open bone growth plates and show a similar bone development process to humans.⁸ As noted above, weekly IV dosing of juvenile monkeys with elosulfase alfa for up to a year, at AUC exposure ratios of approximately 50 to 70 times those expected in humans, did not demonstrate target organ toxicity.

Nonclinical summary

- The nonclinical studies submitted covered all relevant areas, were of high quality, and the pivotal toxicological studies were performed to GLP standards.
- Normal intracellular localisation of N-acetylgalactosamine-6-sulfatase to lysosomes is dependent on the presence of mannose-6-phosphate (M6P)-terminated oligosaccharide chains on the protein. In vitro studies using fibroblasts or chondrocytes from MPS IVA patients showed efficient uptake of elosulfase alfa that could be blocked in the presence of M6P, localisation of elosulfase alfa to lysosomes, and a subsequent dose- and time-dependent decrease in lysosomal keratan sulfate levels.
- Rats (both sexes), given elosulfase alfa doses up to an AUC exposure ratio of approximately 16, showed no effects on neurobehavioural or respiratory parameters. Likewise, cynomolgus monkeys (males, approximately 4 to 5 years of age) showed no effect of elosulfase alfa dosing (up to an expected AUC exposure ratio of approximately 20) on haemodynamic or ECG parameters.
- Tissue distribution studies, using mice given IV doses of fluorescent elosulfase alfa, showed uptake by epiphysis, marrow, and growth plate of femurs and tibias. Uptake by chondrocytes appeared to reflect proximity to vasculature. Mouse heart showed uptake by septum, atrium, and heart valve. In mouse liver, elosulfase alfa was taken up by sinusoidal endothelial and Kupffer cells but not by hepatocytes. Growth plate and resting cartilage are major sites of keratan sulfate accumulation that lead to skeletal dysplasia in MPS IVA patients; keratan sulfate accumulation in heart valve and Kupffer cells are causes of morbidity.
- Repeat-dose toxicity studies were performed with rats (both sexes) and juvenile cynomolgus monkeys (both sexes, approximately 2 to 3 years of age) for durations of up to 6 months and 1 year, respectively, and at exposure ratios of up to approximately 50 times those expected in humans. Animals received a once weekly IV infusion of test article, which is consistent with the mode and frequency of clinical dosing. No targets for toxic effects were identified in either species. The lack of effects in juvenile monkeys was taken as support for the use of elosulfase alfa in children. Monkeys given high doses of elosulfase alfa showed no increase (compared to controls) in plasma concentrations of keratan sulfate-derived disaccharides or the terminal crosslink peptide of collagen type 1A1 chains (released during osteoclastic bone resorption). This suggested that elosulfase alfa is not inducing exaggerated pharmacology in

⁸ Zoetis T., Tassinari M.S., Bagi C., Walthall K., and Hurtt M.E. (2003) Species comparison of postnatal bone growth and development. *Birth Defects Research (Part B)*, **68**: 86–110.

cartilage and bone leading to breakdown of extracellular matrix but rather is only active in the acidic environment of the lysosome.

- The absence of genotoxicity or carcinogenicity studies for elosulfase alfa was consistent with currently accepted international guidelines for the nonclinical testing of biotechnology derived products.
- Reproductive toxicity studies, using rats and rabbits, showed no effects of elosulfase alfa on fertility or embryofetal development, although dosing of pregnant rats produced an apparent increase in perinatal pup mortality. Dams given high doses of elosulfase alfa showed transfer of the test article into milk and the fetal circulation.

Nonclinical conclusions

- There were no major deficiencies in the submitted nonclinical dossier.
- Primary pharmacology studies demonstrated localisation of elosulfase alfa to lysosomes and reduction of keratan sulfate levels in this compartment. These findings support elosulfase alfa's use for the treatment of MPS IVA patients.
- Safety pharmacology studies monitoring the CNS, cardiovascular, and respiratory systems did not identify clinically relevant hazards.
- Repeat-dose toxicity studies in rats and juvenile cynomolgus monkeys did not identify any target organs for toxic effects.
- The absence of genotoxicity or carcinogenicity studies for elosulfase alfa was consistent with currently accepted international guidelines for the nonclinical testing of biotechnology derived products.
- Reproductive toxicity studies using elosulfase alfa in pregnant rats showed an increase in perinatal pup mortality. The Pregnancy Category for elosulfase alfa should be changed from B1 to B3.
- There are no nonclinical objections to the registration of elosulfase alfa.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor stated that it is developing elosulfase alfa (BMN 110) as an enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis IV, Type A (Morquio A syndrome, MPS IVA), a severely debilitating and progressive disease which is an unmet medical need.

MPS IVA is a rare, devastating, inherited disorder caused by mutations of the gene that codes for the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S).

With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues. This pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystem clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life and early mortality.

MPS IVA (from UpToDate, accessed 2 January 2014)

MPS type IV (Morquio syndrome) - Mucopolysaccharidosis IV (MPS IV A and B) is also known as Morquio syndrome. This disorder consists of two forms with similar clinical findings and autosomal inheritance. MPS IV A (MIM #253000) results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS), located at 16q24.3. MPS IV B (MIM #253010) is due to beta-galactosidase deficiency. The clinical features result from accumulation of keratan sulfate and chondroitin-6-sulfate.

Morquio syndrome is characterised by skeletal involvement. Patients typically present at approximately one year of age with short stature, primarily due to a shortened neck and trunk and joint laxity. Pectus carinatum (protuberant sternum) and genu valgum (knock-knee deformity) are common. Dysostosis multiplex occurs early. Other complications include spondyloepiphyseal dysplasia and severe flattening of the vertebrae (platyspondyly), odontoid dysplasia with failure to ossify which leads to atlantoaxial instability and C1-C2 subluxation. This can result in the insidious onset of cervical cord compression, beginning with fatigue and progressing to weakness. Acute cord compression and respiratory arrest may occur after minor falls. Patients may be confined to wheelchairs by their second or third decade. Respiratory problems often develop due to cord compression and the restrictive effects of skeletal disease.

Mild corneal opacities, hepatosplenomegaly, and valvular heart disease may occur in Morquio syndrome. Some patients develop progressive hearing loss. Enamel hypoplasia is seen in MPS IV A but not IV B.

Both types of Morquio syndrome can have severe or mild forms, depending upon the amount of residual enzyme activity. In the severe forms, linear growth is minimal after six or seven years of age and death usually occurs in the third or fourth decade from cardiorespiratory failure. Mildly affected patients may survive into the seventh decade.

Guidance

The evaluator was provided with the following European guidance:

- Clinical investigation of medicinal products for long-term Use (Directive 75/318/EEC)
- Guideline on the investigation of medicinal products in the term and preterm neonate (Regulation (EC) 1901/2006)
- Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population (Directive 2001/83/EC)
- Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population (CPMP/ICH/2711/99)
- Reflection paper: formulations of choice for the paediatric population (CPMP/ICH/2711/99).

The submission does incorporate the recommendations of the Guidance documents but the data related to children less than 5 years was incomplete at the time of submission.

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 pivotal efficacy/safety studies, one of which included pharmacokinetic data. Pharmacodynamic data were included as part of the clinical efficacy and safety analysis.
- 4 other efficacy/safety studies, one of which included pharmacokinetic data.

Paediatric data

The submission included paediatric pharmacokinetic, pharmacodynamic, efficacy and safety data as children are expected to benefit from treatment.

Good clinical practice

The dossier stated that all of the included studies complied with Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 shows the studies relating to each pharmacokinetic topic and the location of each study summary. The PK assessment of BMN 110 was planned in the 4 clinical studies. However, PK data from only MOR-002 and MOR-004 were provided in this marketing application because PK data from MOR-005 and MOR-008 were not available as of the data cut-off date for the submission.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in target population [§] (MPS IVA)	PK on Week 0 and Week 24 (2.0 mg/kg/qow; 2.0 mg/kg/week) 65 PK subjects	MOR-004 Phase III	Efficacy/ Safety
	PK – Dose-escalation study (0.1 mg/kg/week; 1.0 mg/kg/week; 2.0 mg/kg/week) 19 PK subjects	MOR-002 Phase I/II	Efficacy/ Safety

* Indicates the primary aim of the study where applicable.

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics (PK)

The sponsor has supplied a minimal clinical PK data set incorporating two clinical studies. The dose finding study, MOR-002, showed a non-linear dose dependent increase in plasma concentrations, in that both AUC and C_{max} increased by up to 93 times when the dose was increased only 20 times. Study MOR-004 also did not demonstrate linear dose dependent changes in plasma concentrations when comparing weekly to second weekly infusions.

This is not surprising given the relatively short plasma half-life of BMN 100; which was approximately 6 minutes with initial dosing increased to approximately 36 minutes at the end of the study; when compared to the dosing interval (weekly or second weekly). There was a time dependent increase in half-life from Week 1 to Week 22 resulting from a decrease in clearance and a concurrent increase in volume of distribution over that time. The studies are adequate to characterise the pharmacokinetics of BMN 110 including the dose proposed for administration in the product information for adults and children greater than 5 years of age. However, the pharmacokinetic data from Study MOR-007, which enrolled children less than 5 years of age was not presented in the dossier. This is a deficiency in the data.

Pharmacodynamics

Studies providing pharmacodynamic (PD) data

All of the presented clinical studies collected pharmacodynamic data related to serum and urine keratan sulfate (KS) as well as immunogenicity. Only Studies MOR-004 and MOR-002 presented PK data and so could explore the PK–PD relationship (Table 5). All of the studies are summarised Attachment 2 to this AusPAR.

Table 5: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology [§]	Effect on: Efficacy (6MWT, 3MSCT, MVV) PD (urine KS reduction)	MOR-004	Efficacy/ Safety
	Effect on: Efficacy (6MWT, 3MSCT) PD (urine KS reduction)	MOR-002	Efficacy/ Safety

* Indicates the primary aim of the study where applicable.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

‡ And adolescents if applicable.

Both pharmacodynamic studies had had some deficiencies but this did not exclude their results from consideration.

Evaluator's conclusions on pharmacodynamics

The studies failed to clearly demonstrate a concentration dependent change in any of the measured pharmacodynamic outcomes. This probably reflects the relatively modest changes effected by the medication in these parameters. The sponsor should incorporate the as yet not presented data from Studies MOR-005, MOR-100, MOR-006, MOR-007, MOR-008 and BMN 110-502. The use of population techniques with the full dataset may allow for a clearer analysis of the combined data including better defining the dose-concentration-pharmacodynamic relationship. A population analysis may also better define any effect of age and gender upon the pharmacodynamics of BMN 110.

Dosage selection for the pivotal studies

Based on the early phase studies, especially Study MOR-002 the sponsor chose 2 mg/kg/week and 2 mg/kg/every other week (QOW) for the pivotal study. This was an

appropriate choice given the preceding data. Specifically Study MOR-002 demonstrated improvements in both exercise tolerance (6-minute walk test (6MWT) and 3-minute stair-climb test (3MSCT)) as well as favourable reductions in urine KS excretion. However, a higher dose of BMN 110 was not explored to investigate whether this would be tolerated. Study MOR-008 (ongoing at the time of the report) is exploring whether a dose of 4 mg/kg/dose weekly is more efficacious in children greater than 7 years. The results of this study have not been reported.

Efficacy

Studies providing efficacy data

A pivotal efficacy Study MOR-004 (Phase III) as well as Study MOR-005 (extension double-blind followed by open-label study), Study MOR-002 (Phase I/II), Study MOR-100 (open label extension study), Study MOR-007 (Phase II open label) and Study MOR-008 (randomised double-blind pilot study) were submitted to support this application.

Evaluator's conclusions on efficacy

The pivotal study showed a modest improvement in exercise capacity in the treated population, that being adults and children greater than or equal to 5 years of age. In the 6 minute walk test, there was up to a 24 percent increase in the distance walked after 24 weeks of weekly therapy corresponding to 36 m in distance (Table 6). The changes in the other main efficacy parameters including stair climbing, respiratory function and health questionnaires were not clinically significantly better in the treatment groups when compared to placebo. There was a significant decrease in urinary keratan sulfate excretion (Table 7) but this did not appear to translate into clinical improvement over the time of the study. The follow-up study and the supportive studies produced a similar range of results. The primary outcome measure, the 6 minute walk test, is an appropriate measure for this population. Other clinical outcome measures included 3 minute stair climb and ventilator capacity.

Table 6: Summary of 6-Minute Walk Test - Intent-To-Treat Population

6-Minute Walk Test (meters)	Placebo (n=59)	BMN 110 2.0 mg/kg/qow ^a (n=59)	BMN 110 2.0 mg/kg/week (n=58)
Baseline			
n	59	59	58
Mean (SD)	211.9 (69.9)	205.7 (81.2)	203.9 (76.3)
Median	228.9	218.0	216.5
Min, Max	36.2, 312.2	47.1, 319.6	42.4, 321.5
Week 12			
n	59	59	58
Mean (SD)	224.6 (78.5)	219.1 (78.4)	227.6 (76.4)
Median	231.3	232.1	237.1
Min, Max	51.5, 431.5	54.7, 377.3	48.6, 350.7
Week 24			
n	59	58	57
Mean (SD)	225.4 (83.2)	220.5 (88.2)	243.3 (83.5)
Median	229.4	238.1	251.0
Min, Max	50.6, 501.0	44.1, 370.4	52.0, 399.9
Week 12 - Change from Baseline			
n	59	59	58
Mean (SD)	12.7 (35.8)	13.5 (38.4)	23.7 (42.2)
Median	11.4	13.6	21.4
Min, Max	-70.9, 137.0	-102.5, 106.8	-86.4, 171.0
Week 24 - Change from Baseline			
n	59	58	57
Mean (SD)	13.5 (50.6)	14.9 (40.8)	36.5 (58.5)
Median	9.9	16.1	20.0
Min, Max	-99.2, 220.5	-105.9, 114.2	-57.8, 228.7
Week 12 - Percent Change from Baseline			
n	59	59	58
Mean (SD)	7.3 (19.1)	13.3 (32.5)	17.2 (33.1)
Median	5.5	6.6	14.2
Min, Max	-48.6, 54.8	-63.4, 139.6	-29.6, 192.9
Week 24 - Percent Change from Baseline			
n	59	58	57
Mean (SD)	8.7 (28.8)	10.6 (26.5)	23.9 (44.8)
Median	3.8	7.1	10.0
Min, Max	-45.6, 105.4	-65.5, 105.9	-38.7, 257.9

^a qow, every other week; SD, standard deviation

Table 7: Primary Analysis of Normalized Urine Keratan Sulfate: Percent Change from Baseline at Week 24 - Intent-To-Treat Population

	BMN 110 2.0 mg/kg/qow ^a vs Placebo	BMN 110 2.0 mg/kg/week vs Placebo
Observed Treatment Effect^b (Observed Case)		
n	57	54
Mean Difference (%)	-30.8	-40.7
95% CI	(-39.8,-21.8)	(-49.7,-31.6)
Observed Treatment Effect^b		
n	59	58
Mean Difference (%)	-31.7	-40.1
95% CI	(-40.6,-22.9)	(-49.3,-30.9)
Modeled^c Treatment Effect^b		
n	59	58
LS Mean Difference (%)	-30.2	-40.7
95% CI	(-38.5, -22.0)	(-49.0, -32.4)
p-value ^d	<.0001	<.0001

^a qow, every other week.

^b Treatment effect defined as: (change from Baseline to week 24, BMN 110) – (change from Baseline to Week 24, Placebo).

^c ANCOVA model, adjusted for baseline covariates: age group, 6MWT category and normalized uKS.

^d P-value determined by t-test from ANCOVA model.

LS Mean, least squares mean.

Overall the clinical gains from weekly treatment of BMN 110 in patients already significantly affected by MPS IVA were small. What is unknown is whether treatment will be more effective in very young children with MPS IVA who are not yet significantly impaired by the disease. The data has not been presented for children less than 5 years of age although Study MOR-007 is ongoing. The sponsor should report of the results of this study to clarify whether BMN 110 can be registered for use in this age group. Otherwise BMN 110 registration should be limited to the treatment of children greater than or equal to 5 years of age.

Safety

Studies providing safety data

The following 6 studies provided evaluable safety data:

- The completed pivotal double-blind, placebo-controlled Phase III study (MOR-004) and its ongoing extension study (MOR-005)
- The completed Phase I/II study (MOR-002) and its ongoing extension study (MOR-100), and 2 ongoing Phase II studies (MOR-007 and MOR-008).

Safety data up to the data cut-off dates for these 6 studies were included. Safety data from the ongoing ancillary Phase II Study MOR-006 were not included in the submission.

The clinical safety summary was based on safety results from these 6 clinical studies in a total of 235 subjects with MPS IVA exposed to BMN 110 for up 169.7 weeks of continuous treatment. The overall mean [±SD] duration of exposure was 50.2 [± 37.03] weeks.

Patient exposure

A total of 86 patients have received at least 48 weeks of therapy with BMN 110. This is less than the 100 patients normally required for registration of a new chemical entity but this is acceptable given it is a rare disease. Table 8 shows the All exposed population by study.

Table 8: All Exposed Population by Study

	Phase 3						Phase 1/2		Ancillary Phase 2			Total (n=235)
	MOR-004 2.0 mg/kg		MOR-005 2.0 mg/kg				MOR-002 ≤ 2.0 mg/kg	MOR-100 2.0 mg/kg	MOR-007 2.0 mg/kg	MOR-008		
	QOW (n=59)	QW (n=58)	FBO-QOW (n=29)	FBO-QW (n=29)	QOW-QOW (n=59)	QW-QW (n=56)	/QW (n=20)	/QW (n=17)	/QW (n=15)	2.0 mg/kg QW (n=15)	4.0 mg/kg QW (n=10)	
Total Study Drug Exposure (weeks)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	24.0 (0.19)	23.6 (3.03)	32.9 (13.17)	31.7 (14.27)	31.6 (13.53)	32.4 (14.95)	69.5 (22.05)	82.9 (3.46)	24.8 (9.12)	11.6 (4.59)	10.0 (3.51)	50.2 (37.03)
Median	24.0	24.0	29.1	29.0	24.0	26.0	78.4	84.0	26.9	10.3	9.3	44.6
Min, Max	23.3, 24.4	1.0, 25.0	19.9, 66.0	11.0, 75.6	11.0, 76.6	1.0, 76.1	9.1, 84.0	74.0, 87.0	8.0, 44.0	6.4, 20.0	6.4, 15.9	1.0, 169.7
Mean Weekly Dose Subject (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	0.99 (0.030)	1.96 (0.073)	1.99 (0.015)	2.00 (0.004)	1.99 (0.034)	1.99 (0.033)	0.91 (0.280)	1.99 (0.067)	1.91 (0.146)	1.95 (0.079)	3.96 (0.167)	1.64 (0.686)
Median	1.00	1.99	2.00	2.00	2.00	2.00	1.00	2.00	1.96	1.99	4.02	1.90
Min, Max	0.88, 1.03	1.68, 2.05	1.93, 2.00	1.98, 2.01	1.75, 2.01	1.83, 2.01	0.09, 1.06	1.87, 2.20	1.50, 2.04	1.73, 2.04	3.72, 4.22	0.09, 4.22

	Phase 3						Phase 1/2		Ancillary Phase 2			Total (n=235)
	MOR-004 2.0 mg/kg		MOR-005 2.0 mg/kg				MOR-002 ≤ 2.0 mg/kg	MOR-100 2.0 mg/kg	MOR-007 2.0 mg/kg	MOR-008		
	QOW (n=59)	QW (n=58)	FBO-QOW (n=29)	FBO-QW (n=29)	QOW-QOW (n=59)	QW-QW (n=56)	/QW (n=20)	/QW (n=17)	/QW (n=15)	2.0 mg/kg QW (n=15)	4.0 mg/kg QW (n=10)	
Total Dose Subject (mg/kg)												
n	59	58	29	29	59	56	20	17	15	15	10	235
Mean (SD)	23.7 (0.70)	46.2 (6.18)	62.2 (25.11)	60.9 (27.60)	60.2 (25.94)	61.0 (27.66)	65.6 (23.74)	147.3 (22.09)	48.0 (18.88)	22.8 (9.29)	39.7 (14.64)	73.2 (54.37)
Median	24.0	48.0	51.9	54.1	44.0	49.1	72.0	152.1	49.9	20.1	36.5	55.0
Min, Max	21.0, 24.3	1.8, 48.1	36.0, 125.3	20.0, 143.9	20.0, 145.2	2.0, 136.0	0.8, 83.9	91.7, 171.4	12.0, 88.1	12.0, 40.1	23.9, 64.4	0.8, 251.7

Study drug exposure (in week) is defined (last infusion date - first infusion date + 7)/7; SD, standard deviation
FBO: placebo; QOW: every other week; QW: every week

Safety issues with the potential for major regulatory impact

No liver, haematological, skin or cardiovascular related safety issues with the potential for major regulatory impact were identified.

Immunological phenomena were commonly reported events in patients receiving BMN 110. These events included Type I sensitivity reactions including anaphylaxis, infusion reactions and antibody development against BMN 110. These potential reactions need to be clearly described in the PI and CMI. Furthermore, specific advice on managing these events needs to be included in the PI.

No particular safety issues in special populations were identified. However, data were limited in children less than 5 years; albeit that these limited data did not reveal any unexpected events.

No significant drug-drug interactions were identified.

Postmarketing data

No postmarketing data were submitted.

Evaluator's conclusions on safety

Overall, the safety of BMN 110 is comparable with other biologics used for enzyme replacement in the mucopolysaccharide storage disorders. The main concerns are the immunological sequelae with the development of antibodies and the risk of local and generalised immune reactions, especially during infusions. There is the acute, life-threatening risk of a severe reaction during the infusion. However, the evaluator notes that there were no deaths reported in the study. There are also the long term implications that a particular patient may be excluded from future treatment if they develop a severe recurrent allergic reaction to therapy with BMN 110. This risk was not apparent in the current dossier. Pre-treatment of patients may be effective in reducing allergic reactions

but practice varied across the studies. No desensitisation protocol was developed for the use of BMN 110 although such protocols are available for other biologics.

There was almost universal development of an antibody to BMN 110 in patients receiving therapy. The implications of antibody development are uncertain however, there was no correlation between antibodies and adverse events or changes in efficacy. There was an increase in the exposure to BMN 110 with ongoing therapy but it is unclear whether this was related to antibody development.

Overall the safety of BMN 110 is comparable to other biological agents used in a range of similar diseases.

First round benefit-risk assessment

First round assessment of benefits

The main efficacy outcomes of the pivotal and supportive studies are appropriate, those being assessments of exercise tolerance. There are limited data on growth and development. Those data do suggest that there may be some improvement in linear growth but the studies were unable to demonstrate clinical or statistical improvement over the duration of the studies. Any significant improvements in linear growth and development would be expected within the first 5 years of life. These data are not currently available. Dosing data are only currently supported by the pharmacokinetic and clinical studies in children over 5 years of age. Exposure data over the longer term is limited with only 86 patients reported to have exposure up to 48 weeks. The benefits of BMN 110 in the proposed usage are:

- A modest improvement in 6 minute walk distance
- A decrease in the excretion of urinary keratan sulfate.

First round assessment of risks

The risks of BMN 110 in the proposed usage are:

- The risk of immunological reactions
- A high general rate of infusion related side-effects
- The universal development of antibodies and the long-term impact upon therapy
- Pharmacokinetic data indicates a non-linear relationship between dose and plasma concentrations. While this does not appear to have a direct impact upon patient safety or efficacy, this needs to be monitored in the ongoing studies
- The Pharmacokinetic, safety and efficacy data do not support the use of BMN 110 in children less than 5 years of age
- Pharmacodynamic data have not demonstrated a relationship between dose, concentration and pharmacodynamic measures.

First round assessment of benefit-risk balance

MPS IVA is a debilitating and relentlessly progressive disease for which there is currently no effective therapy. BMN 110 offers the first specific enzyme replacement which may offer some improvement in the physical limitations imposed by the disease. The current data set has some significant deficiencies in the supportive kinetic and dynamic data. This includes the nonlinearity of the pharmacokinetics and more especially, the inability to demonstrate a relationship between dose, concentration and clinical outcome. However

the modest improvement in the 6 minute walk distance, in adults and children greater than or equal to 5 years of age, as well as the trend to improvement in other physiological outcomes offers some hope to these patients. The safety profile is acceptable given the severity of the disease although the issue around the management of hypersensitivity and antibody development needs to be clarified.

In conclusions, the benefit-risk balance of BMN 110, given the proposed usage, is favourable in adults and children greater than or equal to 5 years of age, given the severity of the underlying disease and the lack of any other effective therapies.

First round recommendation regarding authorisation

The evaluator recommends that Vimizim be approved for the following indication:

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in adults and children greater than or equal to the age of 5 years.

The age range could be extended if the final results of Study MOR-007 and Study BMN 110-502 become available and show adequate efficacy and safety for children less than 5 years of age.

Clinical questions

The demonstrated clinical benefits of BMN 110 are modest.

The sponsor should provide updates from all of the ongoing studies for which there are only interim reports. This should include updates in pharmacokinetic, pharmacodynamic and efficacy parameters as well as safety data. Specifically, the sponsor should submit the as yet not presented data from Studies MOR-005, MOR-100, MOR-006, MOR-007, MOR-008 and BMN 110-502.

Pharmacokinetics

The sponsor should further address the time-dependent kinetics of BMN 110. What are possible mechanisms to explain this? Are there further changes in exposure with even longer periods of exposure? Within this response, the sponsor should address the following observations:

The dose finding study, MOR-002, showed a non-linear dose dependent increase in plasma concentrations, in that both AUC and C_{max} increased by up to 93 times when the dose was increased only 20 times (see Table 9).

In Study MOR-004 there was a time dependent increase in half-life from Week 1 to Week 22 resulting from a decrease in clearance and a concurrent increase in volume of distribution over that time (Table 10).

Table 9: Dose Proportionality for BMN 110 in Study MOR-002

Actual Dose Level Increase	0.1 mg/kg/week in Week 1 ^a		0.1 mg/kg/week in Week 12 ^b	
	C_{max} Dose Ratio	AUC _{0-t} Dose Ratio	C_{max} Dose Ratio	AUC _{0-t} Dose Ratio
1-: 10-: 20- fold	1:15:59	1:16:60	1:20:79	1:25:93

^a C_{max} and AUC_{0-t} were compared among Week 1, 24 and 36.

^b C_{max} and AUC_{0-t} were compared among Week 12, 24 and 36.

Table 10: Summary of Pharmacokinetic Parameters in Study MOR-004

Study Visit Mean (n, SD)	BMN 110 2.0 mg/kg qow	BMN 110 2.0 mg/kg/week	*Ratio of BMN 110 qow/week (%)
Week 0			
n	24	22	
AUC _{0-∞} , min*ng/mL	287597 (14, 96432.1)	231074 (15, 103207.4)	124.5
AUC _{0-t} , min*ng/mL	248720 (24, 97063.7)	237884 (22, 100328.6)	104.6
C _{max} , ng/mL	1438 (24, 435.3)	1494 (22, 534.1)	96.2
CL, mL/min/kg	7.54 (14, 2.002)	10.04 (15, 3.733)	75.1
V _{dis} , mL/kg	219.42 (12, 95.483)	395.74 (14, 315.636)	55.4
V _d , mL/kg	68.79 (14, 34.008)	123.66 (15, 144.115)	55.6
T _{1/2} , min	6.57 (14, 3.110)	7.52 (15, 5.484)	87.4
T _{max} , min	150 (24, 58.1)	172 (22, 75.3)	87.2
Week 22			
n	23	22	
AUC _{0-∞} , min*ng/mL	463460 (19, 491418.9)	619080 (20, 422048.3)	74.9
AUC _{0-t} , min*ng/mL	411687 (23, 420279.7)	577371 (22, 416316.6)	71.3
C _{max} , ng/mL	2616 (23, 2702.1)	4036 (22, 3237.1)	64.8
CL, mL/min/kg	6.50 (19, 2.942)	7.08 (20, 12.997)	91.8
V _{dis} , mL/kg	245.19 (17, 273.145)	649.67 (20, 1841.703)	37.7
V _d , mL/kg	120.11 (19, 71.076)	299.52 (20, 543.309)	40.1
T _{1/2} , min	19.25 (19, 19.217)	35.86 (20, 21.485)	53.7
T _{max} , min	159 (23, 60.6)	202 (22, 90.8)	78.5

Study Visit Mean (n, SD)	BMN 110 2.0 mg/kg/qow	BMN 110 2.0 mg/kg/week	*Ratio of BMN 110 qow/week (%)
Week 22/Week 0^b (%)			
n	23	21	
AUC _{0-∞} , min*ng/mL	179.2	328.6	
AUC _{0-t} , min*ng/mL	176.3	280.6	
C _{max} , ng/mL	183.6	291.6	
CL, mL/min/kg	87.0	46.4	
V _{dis} , mL/kg	127.0	188.9	
V _d , mL/kg	147.0	246.0	
T _{1/2} , min	280.0	696.0	
T _{max} , min	119.8	145.7	

* Ratio is ratio of means.

^b Only subjects with PK data available for both visits are included.

AUC_{0-∞}, area under the plasma concentration-time curve from time zero to infinity; 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 drug after intravenous administration; qow, every other week; SD, standard deviation; V_{dis}, apparent volume of distribution at steady-state; V_d, apparent volume of distribution based upon the terminal phase; t_{1/2}, elimination half-life.

For subjects who have missing values of AUC_{0-∞}, t_{1/2}, CL, V_d and V_{dis}, the parameters could not be estimated due to insufficient data in the terminal phase of the plasma profile. For subjects who have missing values of V_{dis} only, their V_{dis} was not reported due to a negative value. Adjusting for infusion caused a negative MRTinf value. The V_{dis} value was also negative because of the relationship: V_{dis}=MRTinf*CL.

Pharmacodynamics

The sponsor should incorporate the as yet not presented data from Studies MOR-005, MOR-100, MOR-006, MOR-007, MOR-008 and BMN 110-502 in the pharmacodynamic analysis.

The use of population techniques with the full dataset may allow for a clearer analysis of the combined data including better defining the dose-concentration-pharmacodynamic relationship. A population analysis may also better define any effect of age and gender upon the pharmacodynamics of BMN 110.

Efficacy

The data has not been presented for children less than 5 years of age although Study MOR-007 is ongoing. The sponsor should report of the results of this study to clarify whether BMN 110 can be registered for use in this age group. Otherwise BMN 110 registration should be limited to the treatment of children greater than or equal to 5 years of age.

Safety

The sponsor should provide the individual liver function data for two patients with abnormalities in their liver function.

The sponsor should reanalyse their current safety database to develop recommended prophylactic antihistamine and steroid regimens for infusion and hypersensitivity reactions. This should be provided for review in the second round.

Second round evaluation of clinical data submitted in response to questions

The demonstrated clinical benefits of BMN 110 are modest. The sponsor should provide updates from all of the ongoing studies for which there are only interim reports. This should include updates in pharmacokinetic, pharmacodynamic and efficacy parameters as well as safety data. Specifically, the sponsor should submit the as yet not presented data from Studies MOR-005, MOR-100, MOR-006, MOR-007, MOR-008 and BMN 110-502.

Sponsor response

The sponsor submits '*that the mean effect on 6MWT seen in Study MOR-004 translates into extensive clinical benefit to the patients*].'

New data in support of the sponsor's assertion as follows.

Discussion of study design and endpoint considerations

The sponsor reiterated that the rarity of MPS IVA and the severity of the disease make clinically meaningful endpoints difficult to show via large improvements in measures of mobility.

The evaluator accepts that this is the case.

Change in 6MWT - Study MOR-001

The response stated that:

Recently available preliminary longitudinal data from patients who have been enrolled in MOR-001 and completed annual assessments demonstrate the progressive deterioration of this measure over time. Data from Visits 1, 2, and 3 were analysed using a repeated measure regression model. The annualized estimate of change in 6MWT from Visit 1 across all subjects in MOR-001 was -4.9

meters (CI₉₅, -11.3, 1.6). The annualized estimate of change in 6MWT from Visit 1 was -6.8 meters (95% CI, -17.5, 3.9) in the subset of patients selected to match the MOR-004 study population (age ≥ 5 years, 6WMT between 30 and 325 meters at Visit 1 (data on file; publication being drafted). These data confirm and extend our understanding that patients with MPS IVA experience a chronic, progressively debilitating decline in performance as measured by 6MWT. Although these data suggest that there is a large impact of placebo in the course of the randomized clinical trial (patients treated with placebo in MOR-004 showed a mean increase in distance walked of 13.5 meters at Week 24 compared to Baseline), the treatment effect on 6MWT in Study MOR-004 against placebo (22.5 meters at Week 24 compared to Baseline) was statistically significant in patients receiving weekly doses of BMN 110.

The evaluator accepts that the natural history of patients with MPS IVA includes deterioration in 6MWT. However, the improvement in 6MWT of 22.5 metres at Week 24 (compared to Baseline) is hard to characterise as '*translates into extensive clinical benefit*'. This is however statistically significantly different to the placebo improvement of 13.5 metres at Week 24 (compared to Baseline).

Definition of an MCID and responder analyses - Study MOR-004

The sponsor identifies the responder definition thresholds, expressed as the percent change improvement from Baseline after 24 weeks of treatment, were as follows:

- A 15% change for the 6MWT
- A 20% change for the 3MSCT
- A 20% change for maximum voluntary ventilation (MVV).

Responder analyses, based on these thresholds for 6MWT, 3MSCT and MVV showed a higher proportion of responders in the weekly group compared with the placebo group for all three measures (MOR-004 CSR):

- 6MWT (weekly versus Placebo): 45.6% versus 30.5%; P=0.0603
- 3MSCT (weekly versus Placebo): 45.6% versus 25.4%; P=0.0228
- MVV (weekly versus Placebo): 28.6% versus 12.0%; P=0.0576.

The evaluator accepts that there was a trend to improvement in other clinical parameters including 3MSCT and MVV.

Long-term efficacy data - Study MOR-005

The sponsor has provided more long term efficacy data from Study MOR-005. These new data supports ongoing improvement of 6MWT up to 48 weeks in open label follow-up (see Figure 2). Other secondary outcomes showed similar trends to improvements were maintained in the newly provided data. In this extension study, no control group was available for comparative statistical analysis.

6MWT

Using the primary analysis of co-variance (ANCOVA) model in the Intent-to-Treat (ITT) population, the least square mean changes from MOR-004 Baseline for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 22.7 (Confidence Interval_{95%} (CI₉₅), 9.8, 35.5) and 40.9 (CI₉₅, 27.8, 54.0) metres, at Week 48 were 11.0 (CI₉₅, -9.6, 31.7) and 29.1 (CI₉₅, 8.5, 49.7) metres, and at Week 72 were 26.3 (CI₉₅, 9.1, 43.5) and 30.1 (CI₉₅, 12.6, 47.6) metres.

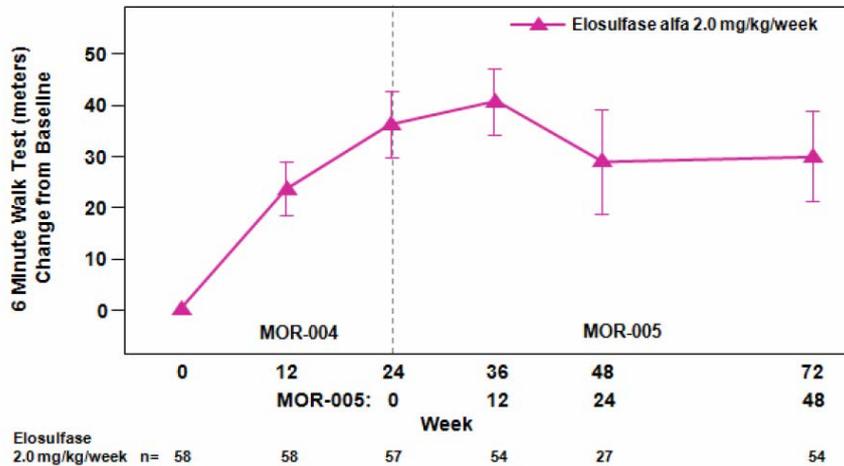
3MSCT

Using the primary analysis ANCOVA model in the ITT population, the least square mean change from MOR-004 Baseline in 3MSCT results for the QOW-QOW and QW-QW cohorts, respectively, at Week 36 were 4.1 stairs/min (CI₉₅, 1.4, 6.8) and 5.8 stairs/min (CI₉₅, 3.0, 8.5), at Week 48 were 2.9 stairs/min (CI₉₅, -0.9, 6.8) and 6.9 stairs/min (CI₉₅, 3.0, 10.8), and at Week 72 were 5.0 stairs/min (CI₉₅, 2.1, 7.9) and 5.3 stairs/min (CI₉₅, 2.3, 8.2).

Urine KS

At Week 24, mean percent changes from MOR-004 Baseline for cohorts QOW-QOW and QW-QW in the ITT population were -34.6% and -45.5%, respectively. Using the primary analysis ANCOVA model in the ITT population, the least square mean percent changes in urine KS levels from MOR-004 Baseline at Week 48 were -45.0% (CI₉₅, -49.0, -41.1) and -51.5% (CI₉₅, -55.7, -47.3) for the QOW-QOW and QW-QW cohorts, respectively. At Week 72, when most subjects were receiving the same weekly regimen (2.0 mg/kg/week), the least square mean percent changes from MOR-004 Baseline were -53.8% (CI₉₅, -57.4, -50.1) and -54.3% (CI₉₅, -58.3, -50.3) for the QOW-QOW and QW-QW cohorts, respectively.

Figure 2: Analysis of 6MWT: Repeated Measures Model Analysis Population: Intent-to-Treat



Additional quality-of-life assessments and clinical improvements - Study MOR-004

The sponsor provided further analysis of the quality of life data for Study MOR-004. The data included that in regard to wheelchair use, there was a net increase of 5 (8.8%) patients in the placebo group using a wheelchair at Week 24 versus 0 (0%) in the BMN 110 weekly dose group as compared to Baseline. Assessments of several other essential daily activities showed similar treatment-associated improvements, with a positive shift at Week 24 in the number of subjects on weekly BMN 110 compared to placebo who were able to perform important activities of daily living, such as transferring to and from the bathtub, toilet, furniture and car, as well as some independent dressing and feeding skills.

Variability of patient response - Study MOR-004

The sponsor noted that there was variability in patient response to treatment with BMN 110; for example a positive response in the 6MWT did not predict a positive response in the 3MSCT or the MVV. Also a positive response in the 3MSCT or the MVV did not appear to be predictive of a positive response in the 6MWT.

The sponsor did not provide any new data from the ongoing clinical studies listed above. A summary of the anticipated completion dates is shown in Table 11.

Table 11: Anticipated Completion Dates for the CSRs of Ongoing Clinical Studies

Study	Status	Anticipated LPO	Interim Analysis	Anticipated CSR Completion
MOR-100 (Phase 1/2 Extension)	Ongoing	Q2/2014	Not Planned	Q4/2014
MOR-005 (Phase 3 Extension)	Ongoing	Q1/2015	Not Planned	Q3/2015
MOR-006 (Non-ambulatory)	Ongoing	Q3/2014	Not Planned	Q2/2015
MOR-007 (Under 5 years old)	Ongoing	Q1-2/2015	Not Planned	Q2/2014 (for the 52-Week Primary Treatment Phase); Q3/2015 (for Extension Phase)
MOR-008 (Cardiopulmonary)	Ongoing	Q3/2014	Not Planned	Q4/2014
110-502	Ongoing	Q4/2015	Not Planned	Q4/2016

The sponsor also provided safety updates for the following studies for the time periods listed below.

- MOR-005: 05 January 2013 – 11 March 2013
- MOR-006: 23 August 2012 – 11 March 2013
- MOR-007: 29 September 2012 – 11 March 2013
- MOR-008: 15 September 2012 – 11 March 2013
- MOR-100: 20 July 2012 – 11 March 2013.

No new safety findings were identified over the period of these reports.

Clinical questions

Pharmacokinetics

The sponsor should further address the time-dependent kinetics of BMN 110. What are possible mechanisms to explain this? Are there further changes in exposure with even longer periods of exposure? Within this response, the sponsor should address the following observations:

The dose finding study, MOR-002, showed a non-linear dose dependent increase in plasma concentrations, in that both AUC and C_{max} increased by up to 93 times when the dose was increased only 20 times (see Table 9).

In Study MOR-004 there was a time dependent increase in half-life from week 1 to week 22 resulting from a decrease in clearance and a concurrent increase in volume of distribution over that time (Table 10).

The sponsor identified that the exact mechanism causing time-dependent kinetics of BMN 110 is unknown but postulated that anti-BMN 110 antibodies were a major factor. The sponsor also failed to identify the mechanism of the non-linear dose dependent increase in plasma concentrations. Furthermore, the sponsor did not address whether there are further changes in exposure with even longer periods of exposure.

Pharmacodynamics

The sponsor should incorporate the as yet unrepresented data from Studies MOR-005, MOR-100, MOR-006, MOR-007, MOR-008 and BMN 110-502 in the pharmacodynamic analysis.

The use of population techniques with the full dataset may allow for a clearer analysis of the combined data including better defining the dose- concentration-pharmacodynamic relationship. A population analysis may also better define any effect of age and gender upon the pharmacodynamics of BMN 110.

The sponsor did present some new pharmacodynamic data including evidence of normalized urine KS levels and a trend towards stabilisation of normalised standing height z-scores. However, the sponsor did not reanalyse the data to better define the dose-concentration-pharmacodynamic relationship.

Efficacy

The data has not been presented for children less than 5 years of age although Study MOR-007 is ongoing. The sponsor should report of the results of this study to clarify whether BMN 110 can be registered for use in this age group. Otherwise BMN 110 registration should be limited to the treatment of children greater than or equal to 5 years of age.

The sponsor did not present any new efficacy data or analysis related to the efficacy of BMN 110 in children less than 5 years. However, the sponsor did present some new pharmacodynamic data including evidence of normalized urine KS levels and a trend towards stabilisation of normalised standing height z-scores.

Urine KS levels

Treatment with BMN 110 led to a decrease in mean normalised urine KS levels within 2 weeks and the decreased levels were maintained over 52 weeks. The mean (\pm SD) percent change from Baseline in urine KS was -30.2% (\pm 12.68; n=15) at 2 weeks, and -39.9% (\pm 24.03; n=15) at 26 weeks, and -43.5% (\pm 22.15; n=10) at 52 weeks.

Normalized growth rate z-scores

The mean normalised growth rate z-scores improved for all subjects (n=15) and for the subgroup of subjects \geq 2 years of age (n=12) indicating a trend towards improved growth rates with long term BMN 110 treatment. The Baseline and Week 52 mean (\pm SD) normalised growth rate z-scores were -0.6 (\pm 0.64) and -0.4 (\pm 0.53), respectively, for all subjects and -0.8 (\pm 0.78) and -0.3 (\pm 0.53), respectively, for subjects \geq 2 years of age.

While these data are useful, they are insufficient to address the evaluators concerns about the use of BMN 110 in children less than 5 years of age.

Safety

The sponsor should provide the individual liver function data for two patients with abnormalities in their liver function.

The sponsor should reanalyse their current safety database to develop recommended prophylactic antihistamine and steroid regimens for infusion and hypersensitivity reactions. This should be provided for review in the second round.

Subject 1

Data up to the Week 120 study visit of MOR-004/005 combined show that Subject 1 who had elevated liver enzymes at Week 6 did not have abnormally high aminotransferase levels at any subsequent time point tested and the associated adverse event (AE) was considered recovered/resolved two weeks after onset.

Subject 2

Subject 2 completed the Week 96 study visit (MOR-004/MOR-005 combined) and continues to receive study treatment. Liver enzymes were continuously elevated from Week 18 though Week 96. The associated AE of elevated liver transaminases reported at Week 20 is therefore listed as 'Not Recovered/Not Resolved'. In addition, the patient was diagnosed with hepato-lenticular degeneration (Wilson's disease) on the same day as the

AE of elevated liver transaminases, which is a rare autosomal recessive disorder of copper metabolism that may lead to liver failure and explains the persistent elevated liver enzymes.

The evaluator agrees that the sponsor has adequately addressed this question on liver function.

The sponsor provided no new information to support their recommended pre-treatment regimen:

- Recommendations applicable to all patients regarding pre-treatment (antihistamines with or without antipyretics 30 to 60 minutes prior to start of infusion)
- Additional pre-treatment (that is, additional prophylactic antihistamines and prophylactic corticosteroids for severe reactions) for patients who previously experienced infusion reactions.

The sponsor has not addressed the evaluators request for analysis of their database in support of a recommended prophylactic antihistamine and steroid regimens for infusion and hypersensitivity reactions.

An update of safety data was available related to the use of BMN 110 in children less than 5 years. The sponsor anticipates that initiation of Enzyme Replacement Therapy (ERT) early in the course of the disease (< 5 years of age) will maximise the potential skeletal benefits and prevent other irreversible morbidities which increase in frequency with age.

On the basis of these data, the sponsor proposed changes to the proposed product information but the details of these are beyond the scope of this AusPAR.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of BMN 110 in the proposed usage, additional to those identified above (First round) are:

The sponsor has included pharmacodynamic data from Study MOR-007 as evidence of potential benefit in the treatment of children less than 5 years of age.

The evaluator acknowledges these new data but finds that these data are insufficient to recommend that the indication be extended to children less than 5 years of age.

The sponsor has provided more long term efficacy data from Study MOR-005. These new data supports ongoing improvement of 6MWT up to 48 weeks in open label follow-up. Other secondary outcomes showed similar trends to improvements were maintained in the newly provided data. In this extension study, no control group was available for comparative statistical analysis.

The evaluator finds that these new data support that BMN 110 has evidence of ongoing benefit in patients.

There are several ongoing studies for which the sponsor did not provide any new data. A summary of the anticipated completion dates was provided (see above).

The evaluator recommends that these new data are submitted as they become available.

The sponsor identified that the exact mechanism causing time-dependent kinetics of BMN 110 is unknown but postulated that anti-BMN 110 antibodies were a major factor. The sponsor also failed to identify the mechanism of the non-linear dose dependent increase in

plasma concentrations. Furthermore, the sponsor did not address whether there are further changes in exposure with even longer periods of exposure.

The evaluator recommends that the sponsor address these deficiencies in the pharmacokinetic analysis of BMN 110.

The sponsor has not reanalysed the available data to better define the dose-concentration-pharmacodynamic relationship of BMN 110.

The evaluator recommends that the sponsor reanalysed the available data in an attempt to better define the dose-concentration-pharmacodynamic relationship of BMN 110.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of BMN 110 in the proposed usage, additional to those identified above (First round) are:

The safety data from Study MOR-007 in the treatment of children less than 5 years of age are included in the risk assessment.

The sponsor provided no new information to support their recommended pre-treatment regimen:

- Recommendations applicable to all patients regarding pre-treatment (antihistamines with or without antipyretics 30-60 minutes prior to start of infusion)
- Additional pre-treatment (that is, additional prophylactic antihistamines and prophylactic corticosteroids for severe reactions) for patients who previously experienced infusion reactions.

The sponsor should monitor their safety database to develop a specific recommended prophylactic antihistamine and steroid regimens for the management of infusion and hypersensitivity reactions.

Second round assessment of benefit-risk balance

Despite the deficiencies identified in the dossier and the sponsor's responses to the first round evaluation report, the benefit-risk balance of BMN 110 given the proposed usage is favourable in adults and children 5 years of age or older.

Second round recommendation regarding authorisation

The evaluator recommends that Vimizim (elosulfase alfa) be approved for the following indication:

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in adults and children greater than or equal to the age of 5 years.

The evaluator recommends that the pharmacodynamic and safety data from Study MOR-007 be included as evidence of potential benefit in the treatment of children less than 5 years of age. However, the evaluator does not recommend that the indication be extended to children less than 5 years until further evidence of efficacy is available.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1.0 (dated 26 April 2013) with an Australian Specific Annex (ASA) Version: 1.0 (dated 2 September 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 12.

Table 12. Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Infusion reactions (including anaphylaxis and severe allergic reactions)
Important potential risks	Immunogenicity Spinal/Cervical Cord Compression (including laxity and unmasking myelopathic symptoms)
Important missing information	Size of safety database Subgroup experience (pregnant or lactating women, patients with hepatic or renal insufficiency)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns, including targeted questionnaires for the important potential risk: 'Spinal/Cervical Cord Compression (including laxity and unmasking myelopathic symptoms)' and the important missing information: 'Subgroup Experience (specifically pregnant/lactating women)'. Additional pharmacovigilance activities are proposed to further monitor and characterise all the specified ongoing safety concerns.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important missing information: 'Size of safety database' for which no routine risk minimisation activities are proposed; and for the important identified risk: 'Infusion reactions (including anaphylaxis and severe allergic reactions)' for which additional risk minimisation activities in the form of healthcare provider educational materials are also proposed.

Issues surrounding the proposed risk minimisation activities are discussed in Table 13 below.

Reconciliation of issues outlined in the RMP report

Table 13 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 13. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p>The sponsor states: <i>'Based on the review, no new safety consideration has been raised. BioMarin will continue to review safety information related to Vimizim, and for any new safety considerations raised, BioMarin will address the issue in the RMP as appropriate.'</i></p>	<p>This is acceptable.</p>
<p>Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the specified summary of the Ongoing Safety Concerns is considered acceptable.</p>	<p>The sponsor has noted this comment.</p>	<p>n/a</p>
<p>The sponsor should provide an assurance that once it outsources local adverse event reporting to a local organisation, the details of this organisation will be provided to the TGA and the ASA will be updated accordingly. It is expected this should occur before the product is launched.</p>	<p>The sponsor states: <i>'BioMarin assures the TGA that a local organization responsible for local safety reporting will be in place and that the details of this local organization will be provided to the TGA and included in the ASA prior to the product being launched.'</i></p>	<p>This is acceptable.</p>
<p>The sponsor appears to consider targeted follow-up forms to be an additional pharmacovigilance activity (Parts III.1: 'Safety concerns and overview of planned pharmacovigilance actions' and III.2: 'Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures' of the EU-RMP), as well as an additional risk minimisation activity (Part V.3: 'Summary table of Risk Minimisation Measures' of the EU-RMP). In accordance with the relevant EU guideline, the use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine</p>	<p>The updated EU-RMP and the updated ASA have been amended accordingly.</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>pharmacovigilance. Consequently the EU-RMP and the ASA should be amended accordingly when these documents are next updated.</p>		
<p>In addition Part III.1: 'Safety concerns and overview of planned pharmacovigilance actions' of the EU-RMP inadvertently makes no reference to the use of targeted questionnaires for the important missing information: 'Subgroup Experience (specifically pregnant/lactating women)'. This oversight should be corrected when the EU-RMP is next updated.</p>	<p>The updated EU-RMP has been amended accordingly.</p>	<p>This is acceptable.</p>
<p>Part V.1: 'Risk Minimisation Measures by safety concern' of the EU-RMP states that a targeted follow-up form will be used to gather additional information on reported cases of infusion reactions. However, no such reference can be found in Part V.3: 'Summary table of Risk Minimisation Measures' of the EU-RMP or in Part III.1: 'Safety concerns and overview of planned pharmacovigilance actions' of the EU-RMP and no copy of this targeted follow-up form was provided in ANNEX 7: 'Specific Adverse Event Follow-up Forms' of the EU-RMP. The sponsor should correct these internal inconsistencies and provide a copy of the targeted questionnaire for the important identified risk: 'Infusion Reactions (including anaphylaxis and severe allergic reactions)' if it indeed exists.</p>	<p>The observed internal inconsistencies have been corrected in the updated EU-RMP and a copy of the targeted follow-up form for Infusion Reactions (including anaphylaxis and severe allergic reactions) has been provided as Attachment 1 to the ASA. The sponsor has provided an assurance that this form will be included in the EU-RMP at the next update.</p>	<p>This is acceptable.</p>
<p>The multicentre open-label, Phase IIIB study of approximately 10 subjects in Australia to evaluate the efficacy and safety of Vimizim in Australian patients with MPS IVA must be included in the pharmacovigilance plan in a revised ASA. At least a draft protocol for this planned study should be provided to the TGA for review as an attachment to the revised ASA.</p>	<p>The ASA has been revised to include this study in the pharmacovigilance plan and the current version of the study protocol (Protocol Amendment 1, dated March 17, 2014) has been provided as Attachment 2 to the ASA. The sponsor has provided an assurance that this study will be added in the EU-RMP at the next revision.</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>The studies to be referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.</p>	<p>A table with all the forthcoming studies referenced in the pharmacovigilance plan, and the anticipated dates of data submission in Australia, has been provided as Attachment 3 to the ASA.</p>	<p>This is acceptable.</p>
<p>At this time the sponsor's conclusion that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important missing information: 'Size of safety database' for which no routine risk minimisation activities are proposed; and for the important identified risk: 'Infusion reactions (including anaphylaxis and severe allergic reactions)' for which additional risk minimisation activities are also proposed, is acceptable. Nevertheless Section 5: 'Summary of Risk Minimisation Measures by Safety Concern' in Part Vi: Summary Of Activities In The Risk Management Plan By Product of the EU-RMP states: 'This medicine has no additional risk minimisation measures', which appears to be contrary to Part V.3: 'Summary table of Risk Minimisation Measures' of the EU-RMP. This observed internal inconsistency should be corrected when the EU-RMP is next updated.</p>	<p>The observed internal inconsistencies have been corrected in the updated EU-RMP. The text in Part VI Section 5, has been revised as follows: <i>'These additional risk minimisation measures are for the following risks:</i></p> <ul style="list-style-type: none"> • <i>Dosing errors and infusion associated reactions.</i> <p><i>BioMarin will provide Healthcare Professionals with educational materials, informing them of the proper storage, preparation and administration of Vimizim.'</i></p>	<p>This is acceptable.</p>
<p>The sponsor's handling of the potential for medication errors using routine pharmacovigilance and routine risk minimisation activities is considered satisfactory.</p>	<p>The sponsor has noted this comment.</p>	<p>n/a</p>
<p>Apparently in reference to Part V.3: 'Summary table of Risk Minimisation Measures' of the EU-RMP, Section 3: 'Risk minimisation plan' of the ASA states <i>inter alia</i>: 'Proposed additional</p>	<p>The observed internal inconsistencies have been corrected in the updated EU-RMP. The text in Annex 10 has been revised as follows:</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p><i>risk minimisation activities include: Healthcare provider education to ensure that patients and healthcare providers are adequately trained and informed about Infusion Reactions (including anaphylaxis and severe allergic reactions);</i> However, ANNEX 10: 'Details of Proposed Additional Risk Minimisation Activities' of the EU-RMP states: <i>'Not applicable'</i> and ANNEX 11: 'Mock up of Proposed Additional Risk Minimisation Measures' of the EU-RMP states: <i>'No additional risk minimisation activities have been proposed.'</i> These observed internal inconsistencies should be corrected when the EU-RMP is next updated.</p>	<p><i>'Although the overall rate of medication errors was quite low, BioMarin commits to long-term efforts to minimize this potential risk. These efforts include educational materials, which will be provided to Healthcare Professionals informing them of the proper storage, preparation and administration of BMN 110. The objective of providing educational materials is to mitigate the potential for medication errors, as was observed in clinical trials.'</i> Annex 11 of the EU-RMP also includes copies of educational materials that will be provided.</p>	
<p>The sponsor should provide draft copies of the printed healthcare provider educational materials to be used in Australia to the TGA for review, as an attachment to the ASA.</p>	<p>The updated ASA states: <i>'The draft healthcare provider educational materials included in Annex 11 of the RMP are proposed to be adopted in Australia, with amendments as needed to reflect the Australian approved PI text once finalised.'</i></p>	<p>This is acceptable.</p>
<p>The sponsor should provide a table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia in the ASA. Wording pertaining to all the specified ongoing safety concerns in the proposed Australian PI and CMI should be included in the table.</p>	<p>A table summarising the pharmacovigilance plan and risk minimisation plan proposed for Australia has been included in the ASA as requested.</p>	<p>This is acceptable.</p>
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows:</p> <ul style="list-style-type: none"> •For the important identified risk: 'Infusion reactions (including anaphylaxis and severe allergic reactions)', the proposed CONTRAINDICATIONS statement: <i>'None'</i> may be replaced by the sentence: <i>'Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable.'</i> 	<p>The sponsor has agreed to include the following Contraindication statement: <i>'Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable.'</i> The sponsor has provided justification for not including the statement: <i>'Known allergic reaction to hamster protein.'</i> and is of the opinion that the agreed statement is sufficient to address any potential risk of</p>	<p>It is recommended to the Delegate that this is only acceptable if the consumer medicine information document is amended to reflect the draft PI, which states the active ingredient: elosulfase alfa is produced in a</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p><i>Known allergic reaction to hamster protein.</i>, or words to that effect. Such information would then be aligned with the proposed [European Summary of Product Characteristics] SmPC and would enhance safe use of the medicine.</p> <ul style="list-style-type: none"> •In the 'DOSAGE AND ADMINISTRATION' section, the proposed sentence should be amended for clarity in the following manner: <i>'Home administration under the supervision of a healthcare professional <u>trained in recognising and medically managing serious infusion related reactions under the direction of a practicing physician</u> may be considered only for those patients who have been tolerating their infusion well.'</i> 	this nature.	genetically engineered Chinese Hamster Ovary (CHO) cell line. This will alert both informed [Health Care Professionals] HCPs and consumers to this aspect of this important identified risk. Consequently this remains an outstanding issue.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.	The sponsor has provided an assurance that the CMI will be revised to be consistent with the proposed changes to the Product Information.	This is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

It was recommended to the Delegate that for the important identified risk: 'Infusion reactions (including anaphylaxis and severe allergic reactions)', the proposed Contraindications statement in the draft product information document: *'None'* may be replaced by the sentence: *'Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable. Known allergic reaction to hamster protein.'*, or words to that effect. The sponsor has agreed to include the following Contraindication statement: *'Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable.'* The sponsor has provided justification for not including the statement: *'Known allergic reaction to hamster protein.'* and is of the opinion that the agreed statement is sufficient to address any potential risk of this nature. It is recommended to the Delegate that this is only acceptable if the consumer medicine information document is amended to reflect the draft PI, which states the active ingredient: elosulfase alfa is produced in a genetically engineered Chinese

Hamster Ovary (CHO) cell line. This will alert both informed HCPs and consumers to this aspect of this important identified risk.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

The European Risk Management Plan (Version: 4.0, dated 12 February 2014) with an Australian Specific Annex (Version: 2.0, dated 23 May 2014) must be implemented.

Key changes to the updated RMP

In their response to the TGA's requests for further information the sponsor provided an updated EU-RMP (Version 4.0, dated 12 February 2014) with an updated ASA (Version 2.0, dated 23 May 2014). Key changes from the versions evaluated in the first round evaluation are summarised below (Table 14).

Table 14. Key changes to the RMP

Document	Key change
EU-RMP	<ul style="list-style-type: none"> 'Medication errors' is added as an important potential risk to reflect the occurrence of approximately 2.8% observed in clinical trials. Routine pharmacovigilance and additional risk minimisation activities (in the form of healthcare provider educational materials) have been proposed for this new ongoing safety concern. The important missing information: 'Size of safety database' has been renamed: 'Limitations of the safety database'. The important missing information: 'Subgroup Experience (pregnant or lactating women, patients with hepatic or renal insufficiency)' has been renamed as 'Safety in pregnancy and lactation', 'Safety in patients with hepatic impairments' & 'Safety in patients with renal impairments'. No routine risk minimisation is applied to the latter two ongoing safety concerns. 'Safety in patients with cardiac impairments' is added as important missing information to reflect the standard exclusion criteria in clinical studies. Routine & additional pharmacovigilance activities have been proposed for this new ongoing safety concern, while no routine risk minimisation is applied. Internal inconsistencies have been corrected.
ASA	<ul style="list-style-type: none"> Status in Europe updated – approval by EMA as of 28 April 2014: 'Vimizim is indicated for the treatment of mucopolysaccharidosis, type IVA (Morquio A Syndrome, MPS IVA) in patients of all ages'. Inclusion of Study 110-502 (a multicentre, open-label, phase 3B study, being conducted to evaluate the efficacy and safety of VIMIZIM in Australian patients with MPS IVA) to the pharmacovigilance plan. 'Summary Table of Pharmacovigilance and Risk Minimisation Plan for Australia' added and revised in accordance with changes to the EU-RMP. Attachment 1: 'Specific adverse event follow-up form, Infusion Reactions' added.

Document	Key change
	<ul style="list-style-type: none"> Attachment 2: 'Protocol 110-502 Amendment 1, dated March 17, 2014' added. Attachment 3: 'Timelines for studies referenced in the pharmacovigilance plan' added.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The Quality evaluator has no objections to the registration of Vimizim (elosulfase alpha).

Elosulfase alfa is recombinant human N-acetylgalactosamine-6-sulfatase, and is identical to the endogenous human enzyme. Elosulfase alpha is produced by CHO cells that over-express the elosulfase transgene. The cell culture is harvested, concentrated, and conditioned. Elosulfase alfa is purified in a three step sequence, diafiltered in formulation buffer and the concentration is then adjusted.

It is a clear to slightly opalescent, colourless to pale yellow, sterile solution for infusion, packaged in a glass tubing vial. Each vial is filled to a target volume of 5.3 mL of solution, which allows the withdrawal of 5.0 mL deliverable volume. It has a target pH of 5.0 to 5.8. The proposed shelf-life is 3 years when stored at 2°C to 8°C. Compatibility studies have confirmed the Vimizim solutions are compatible with 0.9% saline. The infusion solutions were stable when stored at 5±3°C for at least 24 hours followed by an additional 24 hours of storage at 25±2°C. No bioavailability studies were conducted as this is a simple aqueous solution intended for intravenous infusion.

Nonclinical

The nonclinical evaluator has no objections to the registration of elosulfase alfa. The non-clinical studies support the proposed mechanism of action and indication proposed by the sponsor. *In vitro* and *in vivo* studies showed the uptake and localisation of elosulfase alfa in the lysosomal compartment of the tested mouse heart cells and chondrocytes. In the mouse liver elosulfase alfa was taken up into the sinusoidal endothelial cells and Kupffer cells but not hepatocytes, consistent with the known mechanism of liver dysfunction in humans with MPS IVA. No organ targets for toxic effects were identified in either rats or monkeys. Both species developed neutralising antibodies that blocked binding to cation-independent M6P receptors that block the uptake of elosulfase alfa into cells. Long term genotoxicity and carcinogenic action by elosulfase alfa was not examined but the evaluator considered that this was acceptable because the substance was not expected to interact directly with DNA or other chromosomal material. Reproductive toxicity studies showed an increase in perinatal pup mortality in rats given elosulfase alfa 20 mg/kg/day. Abnormalities of liver morphology were found in rabbit dams given 3 or 10 mg/kg/day. Interpretation of some of the results of the study of elosulfase alfa on male and female fertility and embryofetal development were complicated by the necessity to give animals intravenous diphenhydramine to mitigate anaphylactoid-type reactions. When high doses of elosulfase alfa were administered, it was detected in milk and the fetal circulation. The pregnancy category recommended by the evaluator was B3.

Clinical

The clinical evaluator has recommended approval for elosulfase alfa with a revised indication of

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in adults and children greater than or equal to the age of 5 years.

The evaluator has recommended acceptance of the sponsor's dosage of 2 mg/kg by infusion weekly.

The clinical dossier included the following data:

- Pharmacokinetic and pharmacodynamic data from one pivotal efficacy/safety study and one other efficacy/safety study, additional pharmacodynamic data from one extension study and one other efficacy/safety study.
- One dose finding study
- One pivotal efficacy/safety study
- Three other efficacy/safety studies
- Integrated summaries of efficacy and safety.

Pharmacology

The pharmacology studies noted the following findings regarding pharmacokinetics:

- After the first dose, time to C_{max} (T_{max}) was 172 minutes, volume of distribution at steady-state ($V_{d,ss}$) about 0.4 L/kg, $t_{1/2}$ 7.5 minutes, C_{max} 1.49 $\mu\text{g/mL}$, AUC_{0-t} 237 $\text{min}\cdot\text{mg/mL}$ and clearance (CL) about 10 mL/min/kg .
 - After 22 weeks of dosing T_{max} was 202 minutes, the $V_{d,ss}$ about 0.65 L/kg, $t_{1/2}$ about 35 minutes, C_{max} 4.04 $\mu\text{g/mL}$, AUC_{0-t} 577 $\text{min}\cdot\text{mg/mL}$, CL about 7 mL/min/kg
 - The profile was non-linear over the dosage range tested of 0.1 mg/kg/week to 1.0 mg/kg/week then 2.0 mg/kg/week, suggesting the clearance mechanism may be saturated at relatively low doses. This is supported by an increase exposure and a reduction in clearance in the same individuals with repeated dosing. It is hypothesised by the sponsor that the formation of antibodies that interfere with cellular uptake may also contribute to the increased plasma concentrations
 - Elimination is assumed to be by peptide proteolysis
 - No studies of drug-drug or drug-disease interaction were performed.

The pharmacology studies noted the following findings regarding pharmacodynamics as measured by the urinary excretion of keratan sulphate (uKS):

A dose dependent relationship with uKS clearance was demonstrated in Study MOR-002 (see below) for doses 0.1 mg/kg/week (wk) versus 1.0 mg/kg/wk versus 2.0 mg/kg/wk the mean percent changes from baseline were -23.2% (19.04) versus -27.9% (17.92) versus -40.6% (20.16).

Normalised urinary keratan sulphate (uKS) excretion was measured in Study MOR-004 (described in more detail below). After 24 weeks of therapy the mean percent changes (\pm standard deviation (SD)) from baseline at Week 24 for placebo versus 2 mg/kg/every other week (qow) versus 2 mg/kg/wk were -4.4% (± 27.0) versus -35.2% (± 20.7) versus -45.1% (± 19.9), respectively.

In the extension study (MOR-005) in patients treated continuously with 2.0 mg/kg/wk the mean percentage changes in uKS from MOR-004 baseline were -51.5% (-55.7, -47.3),

and -54.3 (-58.3, -50.3) at Weeks 48 and 72 respectively. In those receiving 2.0 mg/kg/qow until Week 48 and 2.0 mg/kg/wk from Week 48 to Week 72 the least squares (LS) mean changes in uKS from MOR-004 baseline were -45.0% (95% CI; -49.0, -41.1) and -53.8% (95% CI; -57.4, -50.1), respectively. When elosulfase alfa was given to those who had received placebo in initial MOR-004 study uKS fell rapidly after 12 weeks therapy (Week 36) (-33.6% qow group and -48.2% weekly group) and the reduction was maintained after 24 weeks therapy (Week 48) (-30.2% qow group and -45.5% weekly group).

In 15 children <5 years of age (Study MOR-007 – interim report) the mean percent change uKS from baseline at 2 weeks was -30.2% (± 12.68), -39.9% (± 24.03) at 26 weeks and -43.5% (± 22.15 , n=10) at 52 weeks.

Efficacy

Study MOR-004: This was a pivotal, Phase III, double-blind, randomised, placebo-controlled study to evaluate the efficacy of elosulfase alfa 2 mg/kg/week versus 2 mg/kg/qow versus placebo for 24 weeks in patients with a confirmed diagnosis of MPS IVA based on clinical features and reduced fibroblast or leukocyte N-acetylgalactosamine-6-sulfatase enzyme activity or genetic testing, aged ≥ 5 years and with a 6 minute walk test (6MWT) distance of ≥ 30 m but ≤ 325 m at screening. Patients were excluded if they had had a haematopoietic stem cell transplant, previous treatment or hypersensitivity to elosulfase alfa, major surgery within 3 months (including elective orthopaedic procedures) or pregnant or breast feeding. One patient from the 2.0 mg/kg/wk group withdrew consent and was the only discontinuation. A total of 177 patients were randomised, and 176 were treated: 58 in the 2 mg/kg/week and 59 each in the 2 mg/kg/qow and placebo groups respectively. Baseline demographics were similar for age (median age 11.1 to 12.0) and the median age at diagnosis (4.2 to 5.2 years). The median (minimum, maximum) baseline 6MWT distances for the placebo/qow dosing/ weekly dosing groups were 228.9m (36, 312)/218.0m (47, 320)/216.5m (42, 322). Approximately 60% of patients in each group had a 6MWT distance of > 200 m. There were some differences between the placebo/qow dosing/ weekly dosing groups for sex (% female 54.2/42.4/55.2), use of walking aids (% used 18.6/27.1/15.5), 3 minute stair climb test (3MSCT) (median stairs/min 30.8/25.5/30.5) and normalised uKS [median (min, max) 26.7 (2, 53)/27.4 (2, 117)/ 24.1 (2, 59)] indicating slightly more disabling disease in the 2.0 mg/kg/qow group. The study had approximately 90% power to detect a difference of 40 metres between the elosulfase alfa and placebo groups. It was not powered for comparisons between the elosulfase alfa groups.

The primary endpoint of an increase in metres walked in the 6MWT from Baseline to Week 24 in the ITT analysis ([LS] mean change from baseline (Standard Error (SE)) [95 %CI]) was:

- 13.6m (6.57)[0.6, 26.5] on placebo
- 36.0m (6.63) [22.9, 49.1] on elosulfase alfa 2.0 mg/kg/wk (p=0.017 versus placebo)
- 14.1m (6.57) [1.1, 27.1] on elosulfase alfa 2.0 mg/kg/qow (p=0.954 versus placebo)

A responder analysis showed a positive response compared with placebo across various levels of response.

The secondary outcomes were changes in the in 3MSCT and uKS normalised to serum creatinine (see Pharmacodynamics), from Baseline to Week 24. The 3MSCT LS mean treatment difference was 1.1 stairs/min (95% CI -2.1, 4.4; p=0.4935) for the 2.0 mg/kg/week group versus placebo. A step-down statistical testing procedure was used for the secondary outcomes to adjust for multiplicity starting with 3MSCT. Since the 3MSCT result was not statistically significant then any subsequent endpoints cannot be

considered to be statistically significant. Therefore the uKS results as reported in the pharmacodynamic section cannot be declared statistically significant.

Although there were numerical improvements in the other outcomes of change in respiratory function tests, inflammatory biomarkers, markers of bone and cartilage metabolism, anthropometric measurements, x-rays of the lumbar spine and lower limb, audiometry, echocardiography, corneal clouding and response to the MPS Health Assessment Questionnaire, there was no statistically significant difference between the elosulfase groups and placebo. There was variability in the patient response in that an improvement in one efficacy outcome was not necessarily accompanied by an improvement in others for the same patient.

The minimum clinically important difference (MCID) criteria were pre-determined to be 15% improvement in 6MWT, and a 20% improvement in each of the 3MSCT and maximum voluntary ventilation. Improvement in 1 of these 3 parameters was seen in 50%/62.7%/62.5% of the placebo, 2.0 mg/kg/qow, and 2.0 mg/kg/week groups respectively. Improvement in 2 of the 3 parameters was seen in 16%/29.4%/41.7% of the placebo, 2.0 mg/kg/qow, and 2.0 mg/kg/week groups respectively. And all 3 parameters improved in 0%/2%/10.4% of the placebo, 2.0 mg/kg/qow, and 2.0 mg/kg/week groups respectively.

Study MOR-005: This was an extension study of MOR-004, conducted in two parts. In the double-blind Part 1 the participants randomised to an active treatment group in Study MOR-004 remained in that group. The MOR-004 placebo group was re-randomised to the weekly or fortnightly elosulfase alfa treatment regimens from Study MOR-004. In the open-label Part 2 of the study all participants were given elosulfase alfa 2.0 mg/kg/wk. Part 1 ran from July 2011 to 30 November 2012 (Week 48 from the commencement of Study MOR-004) and the study will conclude in 2017. An interim analysis was provided for Part 1 of the study. Elective orthopaedic surgery was permitted in the extension study, in contrast to MOR-004. Of the 173 patients that commenced, 172 completed Part 1 (1 patient withdrew consent), and 169 patients continued to Part 2.

The LS mean increase in 6MWT in the ITT population after 36 weeks total 2.0 mg/kg/wk treatment (24 weeks from MOR-004 + 12 weeks in MOR-005) was 40.9 m (95% CI; 27.8, 54.0) (n=54), after 48 weeks was 29.1 m (95% CI; 8.5, 49.7) (n=26) and after 72 weeks was 30.1m (95% CI; 12.6, 47.6). After 36 weeks in the ITT population receiving 2.0 mg/kg/qow treatment the least mean squares increase in 6MWT distance was 22.7 m (95% CI 9.8, 35.5) (n=58), after 48 weeks treatment 11.0 m (95% CI; -9.6, 31.7) (n=26) and at 72 weeks (that is, after 24 weeks of the 2.0 mg/kg/week treatment regimen) 26.3 m (95% CI; 9.1, 43.5). In the per protocol population of both treatment groups, the initial improvement on therapy was maintained from Week 36 to 72.

The patients from the original placebo groups each improved with their 6MWT. It is difficult to compare the groups as there was no stratification on randomisation leading to a difference in ages between the patients from the initial placebo group that received elosulfase 2.0 mg/kg/qow and those that received elosulfase 2.0 mg/kg/wk in Part 1 of Study MOR-005 that may have explained some of the difference in the results. Also the number of patients in each of these groups is small and the error on the point estimate of comparisons with baseline is large.

The 3MSCT LS mean increase in stairs climbed from MOR-004 baseline was 5.8 (95%CI; 3.0, 8.5) at Week 36 (n=58), 6.9 (95% CI; 3.0, 10.8) at Week 48 (n=26), and 5.3 (95% CI; 2.3, 8.2) for the 2.0 mg/kg/wk group. For the 2mg/kg/qow the LS mean increase was 4.1(95% CI; 1.4, 6.8) at Week 36, and 2.9 (95% CI; -0.9, 6.8) at Week 48. After 24 weeks of dosing with elosulfase the PBO-QW group had a LS mean difference from baseline increased to 5.0 stairs (95% CI; 2.1, 7.9). The PP population again performed better than the ITT in both treatment groups.

The normalised standing height z-score⁹ at Week 48 for the 2.0 mg/kg/wk continuous treatment group increased by 0.5 (95% CI; 0.2, 0.9) compared to the MOR-004 baseline.

Dose-finding Study MOR-002: This was a multicentre, open-label study in 12 boys and 8 girls with MPS IVA children 5 to 18 years, with a median age of 7.5 years. This study had an initial Dose Escalation phase which commenced with 0.1 mg/kg/wk and increased at 12 week intervals through 1.0 mg/kg/wk to 2.0 mg/kg/wk. At the end of this phase there was a continuation phase of 36 weeks of 1.0 mg/kg/wk. The mean 6MWT declined below baseline during the initial 12 week period (-20.7 m), increased by 16.3 m after 12 weeks of 1 mg/kg/wk treatment, 24.5 m after 6 weeks of 2.0 mg/kg/wk therapy but this subsequently declined over the next 6 weeks to 13.8 m by the end of that treatment period. During the Continuation phase (1.0 mg/kg/day) the mean 6MWT distance reduced to 4 m greater than baseline. Three children underwent elective knee surgery during the study which may have impacted the results. The dose related improvements in 3MSCT and respiratory function tests did not decline after the dose reduction in the continuation phase. Based on the decline in response during the Continuation phase a dose of 2.0 mg/kg was chosen.

MOR-100: An interim report of this extension study of Study MOR-002 provided data from 17 subjects having completed an additional 74 to 87 weeks of treatment with elosulfase alfa 2.0 mg/kg/wk. Four of the 17 participants underwent orthopaedic surgery within 4 weeks of the Week 72 assessment and only 8 had completed 84 weeks at the time of the report. Overall the improvement in the 6MWT, 3 MSCT and respiratory function tests at the end of Study MOR-002 were sustained through the extension study until week 84, although there were some fluctuations over time. The study is ongoing and is designed to run for 240 weeks. Small patient numbers and wide confidence intervals around the point estimates limit the interpretation of the efficacy results for this study.

MOR-007: An interim study report of this Phase II, open-label study to evaluate the safety and efficacy of elosulfase alfa 2.0 mg/kg/wk in paediatric patients < 5 years of age was provided. It has a 52 week primary treatment phase and a long-term extension phase of up to 156 additional weeks. The primary outcome was safety and the key secondary outcomes were reduction in uKS (see Pharmacodynamics above) and the effect on growth velocity. A number of tertiary outcomes included change in growth plate morphology and bone density, cervical spine and spinal cord morphology, developmental status and quality of life, hearing, cardiac valve function, skeletal deformities, corneal clouding, plasma KS levels and procollagen type IIA N-propeptide (PIIANP) levels, responsiveness of different phenotypes and to characterise dental abnormalities. Fifteen children completed the first 52 weeks. Premedication with antihistamines ± antipyretics was given for the first 26 weeks of therapy. The patients were 46.7% male with a mean age 3.1 (± 1.34) years at enrolment. Seven were < 3 years of age and the majority were White (66.7%). The mean baseline uKS was 35.9 (range 18.8 to 56.5 µg/mg). The mean duration of treatment was 51.9 (±0.18) weeks. The mean normalised standing height z-score decreased from -1.6 to -1.9 at Week 52 for all subjects and -2.0 to -2.2 for children ≥ 2 year of age (compared with a mean z-score of -5.00 for ages 5 to 11 and -7.27 for ages 12 to 18¹⁰). The mean normalised growth rate z-scores for all subjects increased from a baseline of -0.6 (±0.64) to -0.4 (±0.53) at Week 52, and from -0.8 (±0.78) to -0.3(±0.53) for those ≥ 2 years of age.

⁹ Z-scores for growth: These are standard deviation scores. In these studies they are used for height and weight analysis. The score expresses the anthropometric value as a number of standard deviations (z-scores) below or above the reference mean or median value. As an example, z-score of -3 is 3 standard deviations below the reference value for the age of the child.

¹⁰ Harmatz P. et. al. Safety and pharmacodynamic activity of elosulfase alfa in pediatric patients less than 5 years of age with Morquio A Syndrome (Mucopolysaccharidosis IVA). SSIEM Annual Symposium 2014.

Safety

MOR-008: This is a randomised, double-blind, pilot study of the safety and physiological effects of weekly doses elosulfase alfa 2.0 mg/kg and 4.0 mg/kg in patients with MPS IVA. Safety data from this ongoing study contributed to the overall safety summary (below).

Safety Summary: The sponsor provided an updated safety summary with responses to the First Round Clinical Questions. As of 11 March 2013, 244 clinical trial patients had been treated with at least one dose of elosulfase alfa (all exposed population) and 231 had been treated with the 2.0 mg/kg/wk regimen (proposed dose population). Of these, 155 were exposed for more than 48 weeks, and 88 of those were given elosulfase alfa weekly. The ages ranged from 0.8 to 57.4 years and those treated weekly were aged 1.4 to 57.4 years. Most were < 12 years of age.

The percentage (annualised frequency) patient experiencing at least one AE was 98% (23.42 per subject-year) in the all exposed population and 91.3% (22.64 per subject-year) in the proposed dose population. The annualised frequencies of AEs were 31.83 AEs per subject-year in the first 12 weeks and 14.19 AEs per subject-year with > 48 weeks exposure. In the proposed-dose population approximately 91% (22.64 per subject-year) experienced AEs, with 28.96 AE per subject-year in the first 12 weeks and 13.27 with > 48 weeks exposure. The most common AEs in the all-exposed population were headache, fever and vomiting, occurring in 30.3%, 28.3% and 28.3% of patients respectively in the first 12 weeks of exposure and this decreased to 23.2%, 22.6% and 25.8% of patients after 48 weeks of exposure. In the proposed dose population headache, fever, and vomiting occurred in 26.8%, 23.8% and 27.7% of patients in the first 12 weeks of exposure and 25%, 25% and 22.7% with > 48 weeks exposure. Other events occurring in more than 10% of patients included cough, arthralgia, gastrointestinal upset, upper respiratory tract symptoms, abdominal and back pain, fatigue, rash and pruritis.

Serious AES (SAEs) occurred in 34% (0.46 per subject-year) and 23% (0.38 per subject-year) in the all exposure and proposed-dose populations respectively. Of those, 16 to 17% of the events were considered related to the study drug. The most common SAEs were knee deformity/operation, central line insertion, otitis media and pneumonia. There was 1 case each of status asthmaticus, and asthma with a cardio-pulmonary arrest, and one case of pneumonia were reported during the extension Study MOR-005. Cervical cord compression, quadriplegia and spinal decompression were reported in four different patients in the extension Study MOR-005. Study-drug related SAE occurred in 5.3% and 3.9% of the all-exposed and proposed-dose populations respectively, with no clear pattern of incidence diminution over time.

Study drug-related AEs in the all exposure population occurred in 77% of patients, and 59% of patients the proposed dose population. The highest incidence was in the first 12 weeks of therapy in both populations. Infusion-associated reactions (IARs) are discussed below.

There were no deaths in the clinical trial program. The only AE related discontinuation was because of anaphylaxis after a dose of 0.1 mg/kg/week.

There was no apparent safety signal for haematological, renal disorders or hepatotoxicity. The only ECG changes from baseline were the development of sinus tachycardia by two patients which was not considered to be related to the study drug. Fever was the most commonly abnormal vital sign. Three events of moderate hypotension and the three reported events of blood pressure increases were IARs.

To date in the study of children < 5 years of age there have been no negative signals for growth and development and no amplification of the safety signals detected in older patients, although this conclusion is limited by the small number of patients studied and the duration of exposure.

Infusion Associated Reactions: IARs in the all-exposure population were reported in 95.9% (11.43 per subject-year) and in 81% of the proposed-dose population (11.78 per subject-year). The majority occurred during the infusion but IAR SAEs occurred in 8.2% (0.11 per subject-year) and 5.6% (0.08 per subject-year) of the all-exposure and proposed-dose populations. Interruption of the infusion occurred during IARs of 42.6% (1.93 per subject-year) and 29.4% (1.22 per subject-year) of the all-exposure and proposed dose populations, respectively, but all infusions were completed. Approximately 20% of the all-exposure population and 15% of the proposed-dose population had IARs that led in discontinuation of the infusion. Medical intervention was required for IARs in 25% and 17% of the all-exposure and proposed-dose populations. Interruption or discontinuation of an infusion with an IAR requiring medical intervention occurred in approximately 0.8% of infusions. IARs disrupting infusions and/or requiring medical intervention occurred more frequently in the first 12 weeks of therapy. The majority of the reactions reported were fever, headache, vomiting and nausea.

Hypersensitivity: In the all-exposure population 31.6% (0.85 per subject-year) and 20.3% (0.71 events per subject-year) of the proposed dose population experienced hypersensitivity events. No single reaction term was reported in more than 10% of either the all-exposure or proposed dose populations. Those reported in >1% in either population were urticaria, peripheral oedema, wheeze, hypersensitivity, cough, dyspnoea, flushing and rash. Hypotension occurred in 0.9% of the proposed-dose population (0.01 events per person-year). One patient in Study MOR-002 and one in the 2.0 mg/kg/qow group in Study MOR-005 experienced a life-threatening type I hypersensitivity reaction. The event in Study MOR-002 occurred with a dose of 0.1 mg/kg/week. No patient in the proposed dose population reported an anaphylactic reaction.

Immunogenicity: Total antibodies, which included Neutralising antibodies (NAb) and anti-elosulfase alfa antibodies, were measured. All patients exposed developed anti-elosulfase alfa Ab after 24 weeks of therapy and all patients dosed weekly developed antibodies within 4 weeks. Titres were sustained during MOR-004 and the extension study. NAb can inhibit the binding to the cation-independent mannose-6-phosphate receptor and partially inhibit cell uptake. At least 80% of those exposed developed NAb after 12 weeks of exposure and approximately 70% were NAb+ after 72 weeks. There was no clear correlation between antibody development and lack of efficacy or pharmacodynamic effect or with an increase in infusion-related events. The association between antibody development and long-term safety and efficacy is unclear.

Drug-specific IgE was detected in approximately 8% of patients in the pivotal study and 10% in the extension study among those exposed to elosulfase in both studies. IgE Ab developed in 2/29 patients (7%) of the patients that switched to weekly elosulfase in the extension study and 1/29 (3.45%) of those that switched to fortnightly.

Clinical evaluator's recommendation

The evaluator recommends that Vimizim (elosulfase alfa) be approved for the following indication:

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome) in adults and children greater than or equal to the age of 5 years.

The evaluator recommends that the pharmacodynamic and safety data from Study MOR-007 be included as evidence of potential benefit in the treatment of children less than 5 years of age. However, the evaluator does not recommend that the indication be extended to children less than 5 years until further evidence of efficacy is available.

Risk management plan

The Office of Product Review (OPR) has accepted the EU Risk Management Plan for Vimizim (elosulfase alfa) version 4.0 dated 12 February 2014 with an updated ASA (version 2.0 date 23 May 2014).

The following was an outstanding matter and should be followed up in the sponsor's Pre-ACPM response:

- The request from the evaluator that the information to the effect that elosulfase alfa is produced in a genetically engineered Chinese Hamster Ovary cell line should be included in the CMI.

Risk-benefit analysis

Delegate's considerations

Efficacy: The efficacy of elosulfase in treating MPS IVA aged 5 years and above was demonstrated in one pivotal Phase III study for 24 weeks, a Phase II dose-response study, and two extension studies for 72 to 87 weeks. A Phase II study in children < 5 years (interim report at 52 weeks) provided some additional supportive data for use in this age group. Surrogate endpoints of efficacy have been chosen in the pivotal studies that support this submission. These endpoints are consistent with those used in studies of ERT for other MPS types. The primary endpoint of improvement in 6MWT was met using 2.0 mg/kg/week. The improvements in the pivotal study were modest but were sustained in the extension study. Patients transitioned to the 2.0 mg/kg/week regimen from the every other week regimen showed additional improvement over 24 weeks of therapy with the weekly regimen. There was some improvement in the 3MSCT but this was not statistically significant. Although not statistically significant, the initial reduction in uKS was maintained over time and was sensitive to changes in the dosage regimen but the clinical evaluator has noted that this did not appear to translate into clinical improvement over time. Other efficacy parameters were not significantly better compared with placebo. The long term efficacy including improved life expectancy and reduced morbidity is yet to be determined. The development of NAb has the potential to reduce efficacy. Because of the high proportion of patients developing NAb and the small number of patients in the studies it is difficult to determine the impact at this time.

Safety and RMP: The primary source of concern is hypersensitivity reactions. Infusion-associated reactions and hypersensitivity type reactions occurred frequently in the clinical trials. Although these events occurred more frequently early in treatment with elosulfase, approximately 50% of patients in the proposed dose population experienced an IAR AE during the infusion and 9% of patients experienced a hypersensitivity AE after more than 48 weeks of therapy. This is of particular concern as the sponsor has proposed that elosulfase alfa could be administered outside the hospital setting. Most of the study drug related AEs were headache, vomiting and fever, and these are potentially manageable with premedication and adjustment of the infusion rate. However, anaphylaxis occurred in just under 1% of the patients exposed and a severe reaction was reported with a very low dose of elosulfase alfa. The sponsor's proposed wording of the contraindication states that severe or life-threatening hypersensitivity events are contraindicating if the events are not controllable. Other similar enzyme replacement therapies list anaphylactic reactions as a contraindication and no re-challenge is suggested. There is insufficient evidence presented in the submission to suggest that re-challenging patients after an episode of life-threatening anaphylaxis is a safe practice and the sponsor has been requested to provide additional information in support of this statement and amend the contraindication to remove this option. Spinal cord compression was noted during clinical trials, however these events are consistent with the natural history of MPS IVA. There is limited safety

information in young children; however the information that is available does not suggest there are specific safety concerns for this age group.

Home Based Therapy: The sponsor has proposed the use of home based therapy. No evidence of the safety of elosulfase alfa used outside the hospital setting was included in the submission. The proposed model of care for home based infusions including the criteria for selection of patients suitable for home therapy, the protocols for the administration of the infusions and other medical interventions, the experience and training of staff administering the infusions and quality management have not been provided. World-wide there is limited experience with elosulfase alfa in the postmarket setting. There is insufficient information to make a judgement about the safety of its use outside the hospital setting at this time. Consideration of the merits or otherwise of home based therapy would be best deferred until more information is available. The sponsor has been asked to provide comment.

Dose: The proposed dosage regimen of 2.0 mg/kg/week is supported by the statistically significant improvement in 6MWT compared with placebo and the dose dependent reduction in uKS, although this was not statistically significant.

Indication: The clinical evaluator recommended the indication be modified to limit the population to patients aged ≥ 5 years because of a lack of efficacy data. In all the studies the endpoints are surrogates for disease modification. In general there are practical issues with administering endurance based tests of efficacy in children aged < 5 years. In these circumstances passive measure such as uKS and anthropomorphic measurements are more appropriate endpoints. Study MOR-007 in young children is limited by the small number of patients enrolled and the interim nature of the study report. Prescribers may wish to commence enzyme replacement therapy soon after the diagnosis of MPS IVA is confirmed, particularly in those patients with the most severe disease who are likely to be diagnosed at a young age. However, the efficacy and safety data is limited in this < 5 years age group. The clinical evaluator has commented that dosing data are only supported by the pharmacokinetic and clinical studies in children aged ≥ 5 years. The sponsor's proposed indication may be acceptable given the rarity and nature of the disease, the lack of specific treatments and with the limitations of the paediatric data clearly articulated in the precautions section of the PI. ACPM's advice is requested on this matter.

Overall conclusion: Overall, the sponsor has submitted reasonable evidence and justification to support elosulfase alfa for the treatment of mucopolysaccharidosis type IVA (Morquio A syndrome). However the approvability in children < 5 years of age is unclear and home based therapy is not recommended.

Data deficiencies: The low prevalence of the disease limits the sampling frame for these studies, therefore the patient numbers are small and the error on the point estimates is large. The long term safety data is limited and the patient numbers included in the studies are insufficient to detect rare events. There are limited data on growth and development. There is a lack of long term efficacy data including clinical outcomes and morbidity data. There is limited data in children < 5 years of age.

Conditions of Registration: The following are proposed as conditions of registration:

1. The implementation in Australia of the EU Risk Management Plan for Vimizim (elosulfase alpha) Version 4.0 dated 12 February 2014 with Australian Specific Annexe (version 2.0 dated 23 May 2014) and any subsequent revisions, as agreed with the TGA.
2. A condition relating to batch release testing as outlined in the *Quality findings* above.
3. A condition relating to the provision of Certified Product Details as outlined in the *Quality findings* above.

4. The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission or submissions:
 - a. MOR-007 Phase 2 Open-label study in subjects < 5 years of age
 - b. MOR-100 Open-Label Extension Study
 - c. MOR-005 Phase 3 Extension, Double-Blind Study followed by an Open-Label study
 - d. Study 110-502 Phase 3B, open label study of Australian patients
5. Provide regular reports of the findings of the proposed 10 year registry of patients treated with elosulfase alfa, as outlined in Attachment 3 to the ASA of the RMP in accordance with the reporting plan outlined in RMP version 4.0 dated 12 February 2014.

Questions for the sponsor: The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Whilst it is recognised that there are small numbers of patients enrolled in the PK study, please discuss any PK differences between the children aged 5 to 11 and older patients.
2. The PK characteristics of elosulfase alfa both with initial dosage and at steady state show features of non-linear kinetics. Please indicate whether the sponsor has proposed further studies or reanalysis of the studies to further investigate this. Please indicate the rationale for not including this information in the PI.
3. Please provide the time 0 results for the Week 22 PK samples from the PK population of Study MOR-004 to support the proposed PI statement that there was no accumulation with weekly dosing.
4. The European Union (EU) Summary of product Characteristics (SmPC) for Vimizim states that each vial contains 8 mg of sodium. Please indicate the reason this information has not been included in the Australian PI and CMI.
5. The sponsor, in its responses to the First Round Clinical questions, has indicated that Study MOR-007 that enrolled children \leq 5 years of age has enrolled the target number of children. The data presented in the submission is dated March 2013. Please provide an update on safety information you hold for this age group. Please indicate when the CSR for the 52 week primary treatment phase of Study MOR-007 will be available.
6. The per protocol (PP) population performed better than the ITT population in the endurance tests in Study MOR-005. The comment in the Clinical Study Report and Additional Study Report for this study by the sponsor is that no single factor was responsible. Please describe the factors that may have influenced the outcome, and how these impacted the outcomes for each of the treatment groups.
7. There are small differences between the primary analysis ANCOVA derived LS means for the efficacy and pharmacodynamic outcomes as reported in the company study report (CSR) for MOR-005 as compared with the addendum provided with the First Round Clinical question responses. Please provide an explanation for these differences.
8. Please indicate whether neutralising antibody titres were measured in any of the clinical trials. If so, please discuss a possible association between antibody titre and safety or efficacy.

9. The US product monograph notes 18/235 (7.7%) of patients experienced anaphylaxis. The clinical evaluation report and the safety update describe two patients with anaphylaxis. Please explain the difference.
10. Please provide the evidence you hold that Vimizim can be safely given following a severe or life-threatening episode of anaphylaxis? Which medications can be used to prevent these reactions? The CMI states other measures may be used. What other measures might the patient expect to manage life-threatening anaphylaxis?
11. Please justify how elosulfase alfa can be safely used outside the hospital setting to support the proposed statement about home-based therapy. Please indicate how home based therapy is to be delivered and the sponsor's role in its delivery. Please indicate how patients will be selected, how staff will be selected and trained and how adverse events will be reported.
12. Please provide an update on Study MOR-007 and Study MOR-008 if available.
13. Please discuss the evidence or provide further information or justification to support the use of elosulfase alfa in children aged <5 years.

Summary of issues

The primary issues with this submission are:

- The relative absence of efficacy and safety data in children aged <5 years
- Issues surrounding home based therapy.

Proposed action

The Delegate had no reason to say, at this time, that the application for Vimizim (elosulfase alfa) should not be approved for registration with the exception of patients <5 years of age where further information and advice is requested.

Request for Advisory Committee on Prescription Medicines (ACPM) advice

The committee is requested to provide advice on the following specific issues:

1. Whether there is sufficient data/justification to support the use of elosulfase alfa in patients <5 years of age and whether the indication should be modified to restrict the population to patients ≥ 5 years of age?
2. Whether home based therapy should be included as an optional treatment setting and whether the risks are sufficiently mitigated?
3. Whether life-threatening anaphylaxis should be a contraindication to further treatment?
4. Whether it is acceptable for no long term genotoxicity and carcinogenicity data to have been presented, based on the assumption that there is unlikely to be any direct interaction between elosulfase alfa and DNA or other chromosomal material?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

Vimizim (elosulfase alfa) is proposed for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome), a rare, debilitating disorder, for which there is currently

no approved treatment in Australia. BioMarin acknowledges the positive outcome following evaluation of the application by the TGA and believes the availability of this medicine will benefit Australian MPS IVA patients with marked improvements across multi-systemic symptoms leading to an overall better quality of life. The Delegate has requested additional discussion from the sponsor and advice from the ACPM on specific topics; they are addressed by subject matter in the response below.

Use of Vimizim in patients < 5 years of age

Question 1 for ACPM: Whether there is sufficient data / justification to support the use of elosulfase alfa in patients < 5 years of age and whether the indication should be modified to restrict the population to patients ≥ 5 years of age?

Question 13 for sponsor: Please discuss the evidence or provide further information or justification to support the use of elosulfase alfa in children aged <5 years.

The sponsor proposes that Vimizim should be approved in Australia for patients of all ages, including children less than 5 years of age based on the available data supporting safety and efficacy, and early intervention benefits. Use of Vimizim in children less than 5 years of age is supported by the results in the double-blind placebo-controlled study in 176 patients aged 5 to 57 years (MOR-004 study) combined with additional pharmacodynamic (PD) and safety data in 15 paediatric patients aged < 5 years (MOR-007 study) exposed to Vimizim for 52 weeks. Efficacy of Vimizim in adults and older children can be extrapolated to the less than 5 age group because the underlying pathology of MPS IVA and the mechanism for uptake of the enzyme are not expected to differ with age. Furthermore, preliminary data from the MOR-007 study endpoints based on measures of growth suggest improvement after 52 weeks of treatment relative to untreated patients of the same age.¹⁰ Therefore, current knowledge of the MPS IVA disease progression and available Vimizim data are supportive of treatment in paediatric patients less than 5 years of age.

MPS IVA is an inherited disorder where clinical presentation occurs in early childhood, with most patients presenting signs and symptoms by the age of 3 years.¹¹ The most common features of patients with MPS IVA are skeletal dysplasia, frequent surgical procedures mostly related to musculoskeletal or respiratory dysfunction, and a significant limitation in mobility, endurance and respiratory function.^{12, 13} The natural history study shows that patients experience a worsening of clinical symptoms with age.¹³ Due to the progressive nature of these symptoms, it is important to initiate treatment as early as possible. Therefore, initiation of enzyme replacement therapy (ERT) early in the course of the disease is important to maximise the potential benefits and prevent irreversible morbidities which increase in frequency with age, as observed with other ERTs such as Naglazyme (galsulfase) for MPS VI.¹⁴ MPS IVA prevalence in Australia has been estimated at 25 to 49 patients; all 11 identified paediatric patients in Australia are currently enrolled in the Phase IIIB Study 110-502, 2 of whom are less than 5 years of age.

The efficacy of Vimizim was assessed in a 24 week, randomised, double-blind, placebo-controlled clinical trial of 176 patients aged 5 years and older with MPS IVA as established by measures of endurance (6 Minute Walk Test [6MWT]) and pharmacodynamic data (reductions in urine keratan sulfate [KS]). Measures of endurance used as the basis for

¹¹ Tomatsu, S, Montano, AM, Nishioka, T, Gutierrez, MA et. al. Mutation and polymorphism spectrum of the GALNS gene in mucopolysaccharidosis IVA (Morquio A). *Hum Mutat* 26[6], 500-512. 2005.

¹² Montano, AM, Tomatsu, S, Gottesman, GS, Smith, M et. al. International Morquio A Registry: clinical manifestation and natural course of Morquio A disease. *J Inherit Metab Dis* 30[2], 165-174. 2007

¹³ Harmatz P, Mengel, E, Giugliani R, Valayannopoulos V. et. al. The Morquio Clinical Assessment Program: Base line results illustrating progressive, multisystemic clinical impairments in Morquio A subjects (In Press). *Mol Genet Metab* . 2013.

¹⁴ McGill, JJ, Inwood, AC, Coman, DJ, Lipke, ML et. al. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age - a sibling control study. *Clin Genet*. 2009.

assessing efficacy in patients 5 years and older (Phase III population) were not appropriate to study patients less than 5 years of age as these endpoints require a level of developmental maturity to reliably perform, including the 6MWT. Therefore, endpoints assessed in the MOR-007 study included reduction in urine KS levels from baseline and measures of growth such as growth velocity.

Treatment with Vimizim led to a substantial decrease in mean normalised urine KS levels within 2 weeks and the decreased levels were maintained over 52 weeks in children less than 5 years of age. These results are comparable to the urine KS reductions observed in older children and adult subjects in other studies. Furthermore, preliminary findings in the MOR-007 study on growth endpoints as determined by height z-scores compared to data collected on untreated MPS IVA children from the natural history study show that early intervention with Vimizim may help to ameliorate the impact of this disorder on growth.¹⁰

Safety results from the MOR-007 study were consistent with the results observed in patients 5 to 57 years old and comparable to those described for approved ERT products (such as Naglazyme, Elaprase). After 52 weeks of treatment, no new or unexpected safety signals were observed and no expedited safety reports were required. No subject permanently discontinued treatment due to an adverse event (AE). Only one subject experienced a serious adverse event (SAE), a Grade 2 hypersensitivity event that was assessed as related. The subject continued to receive subsequent infusions and completed the 52 weeks of treatment without experiencing additional hypersensitivity events. There were no deaths in the study. All treated subjects developed total anti-drug antibodies (TAb) by Week 4; titres increased in all subjects and were generally sustained by end of study. However, there was no definitive trend observed between TAb titres and efficacy/pharmacodynamics or safety.

Moreover, the mechanism of action of Vimizim at the cellular level is expected to be the same across all age groups. PK was not assessed in the MOR-007 study due to ethical considerations regarding multiple blood sampling required for PK testing in children of this age. However, Vimizim is a protein, and it is expected to be cleared in a similar way through cellular uptake and peptide hydrolysis in vivo in young children as in older children and adults. Furthermore, an analysis of the impact of age on PK in the MOR-004 study suggests that after 22 weeks of treatment, no clinically significant differences can be observed with age (see 'Question 1 for Sponsor' below).

Despite the difficulties faced in investigating this orphan disease and identifying age-appropriate efficacy endpoints, the data available for Vimizim are reassuring and no specific risk has been identified that would warrant withholding treatment in patients with a disease of this nature with no other treatment options. BioMarin is committed to continuing investigations in young children with the ongoing Studies MOR-007, 110-502 and the 10 year registry. In conclusion, the data available to date support the use of Vimizim in MPS IVA patients of all ages, and approval of Vimizim should not be limited by age.

Question 5 for sponsor: The sponsor, in its responses to the First Round Clinical questions has indicated that Study MOR-007 that enrolled children \leq 5 years of age has enrolled the target number of children. The data presented in the submission is dated March 2013. Please provide an update on safety information you hold for this age group. Please indicate when the CSR for the 52 week primary treatment phase of Study MOR-007 will be available.

All data available to date have been provided in the response to TGA's request. The MOR-007 clinical study report (CSR) was submitted with the response (report dated 13 May 2014) and includes the final analysis for the primary treatment phase (52 weeks) and the data cut-off date was the completion of Week 52 visit for each patient. A report with

results from the extension phase will be prepared after study completion and is planned to be available in first quarter of 2016.

Home-based therapy of Vimizim

Question 2 for ACPM: Whether home based therapy should be included as an optional treatment setting and whether the risks are sufficiently mitigated?

Question 11 for sponsor: Please justify how elosulfase alfa can be safely used outside the hospital setting to support the proposed statement about home-based therapy. Please indicate how home based therapy is to be delivered and the sponsor's role in its delivery. Please indicate how patients will be selected, how staff will be selected and trained, and how adverse events will be reported.

Home care administration for Australia will be consistent with the approach taken for administration in other regions where Vimizim is approved (US, Canada and EU). The standard of care for home administration is described below.

Identifying patients for home-based therapy is the decision of the treating physician

As with other ERTs, Vimizim is first administered in a clinical setting for a period of time to allow the physician to assess patient's tolerability to the infusion. This time period will be determined by the treating physician on an individual patient basis. Clinical judgment of the treating physician is required to guide whether home administration is appropriate for each patient based on individual benefit: risk assessments.

Administering Vimizim in a home based setting

Administration in the home setting is performed by a trained, experienced healthcare professional (HCP) using a home infusion company with established protocols for managing medical emergencies. In the home, the HCP provides the same care as in hospital, with a pre-treatment antihistamine and/or antipyretic medications as needed.

Prior to infusion, the HCP performs a patient assessment, including vital signs and review of recent health history.

- The HCP is a qualified nurse, who is experienced in administration of intravenous infusion products with the ability to manage medical emergencies
- The HCP remains with the patient during and after the administration of Vimizim. Typically, the HCP observes the patient 30 minutes to 1 hour after the infusion period. This standard practice is also applicable in the clinical setting before the patient is sent home.

Management of severe allergic reactions or recurrent infusion reactions

The HCP must be prepared to manage anaphylaxis and hypersensitivity reactions. The HCP is experienced in recognition of the signs and symptoms of anaphylaxis. If there is an acute reaction requiring an intervention, this will be managed by either temporarily interrupting or discontinuing infusion and administering additional antihistamines, antipyretics or corticosteroids. For any patient suspected to have a severe anaphylactic reaction, the HCP is instructed to stop the infusion immediately, provide needed medication (such as adrenaline or steroids) and have the patient transported via emergency services to a local hospital. For recurrent infusion reactions, which are difficult to manage, patients will be referred back to the hospital setting and the HCP will contact the prescribing physician.

BioMarin's role

BioMarin will provide training materials. These materials will include disease overview training, 'Dosing and Administration' guidelines of Vimizim and a 'Patient Guide'. BioMarin and the Metabolic Clinical Nurse Consultants in the hospitals will provide training on

administration of Vimizim including premedications and how to gradually increase the infusion rate and make adjustments as needed.

Adverse event reporting

All adverse events will be reported to BioMarin's appointed Australian agent handling local adverse events according to TGA guidelines and the company's global pharmacovigilance system.

Anaphylaxis, hypersensitivity and rechallenge

Question 3 for ACPM: Whether life-threatening anaphylaxis should be a contraindication to further treatment?

BioMarin does not propose to modify the contraindication wording. In view of the nature of MPS IVA, physicians may decide that the benefit: risk balance is supportive of rechallenge after a severe hypersensitivity reaction, provided that precautionary measures are taken to control the hypersensitivity. Clinical trial experience has shown that severe hypersensitivity reactions can be controlled with infusion rate adjustment, additional antihistamines, antipyretics and/or corticosteroids. These measures are described in the *Precautions* section of the Product Information (PI). Therefore, BioMarin considers that Vimizim should only be contraindicated in situations of '*Severe or life-threatening hypersensitivity to the active substance or to any of the excipients, if hypersensitivity is not controllable*'.

Question 9 for sponsor: The US product monograph notes 18/235 (7.7%) of patients experienced anaphylaxis. The clinical evaluation report and the safety update describe two patients with anaphylaxis. Please explain the difference.

The two patients originally described in the clinical evaluation report and safety update were identified as experiencing anaphylaxis reported by the investigator based on the event term 'anaphylactic reaction'.

In collaboration with and at the request of the US Food and Drug Administration (FDA) during review of the Biologics License Application, BioMarin retrospectively evaluated all reported AEs against published clinical criteria for the diagnosis of 'anaphylaxis' established by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN).¹⁵ Based on BioMarin/FDA assessment of reported AEs, 18 of 235 (7.7%) subjects exposed to Vimizim experienced signs and/or symptoms consistent with a clinical diagnosis of anaphylaxis per NIAID/FAAN criteria, which is the anaphylaxis rate cited in the US PI. These 18 patients experienced a total of 26 anaphylactic events out of >11,000 infusions (0.24%). Events were close to time of injection, of short duration, self-limited and resolved without sequelae. Out of the 26 events, 20 were assessed as mild to moderate in severity, four as severe and two as life threatening. Five of the 26 retrospectively derived anaphylactic events were reported as serious and 21 non-serious. There were no fatal anaphylaxis events. This NIAID/FANN-derived rate of anaphylaxis is comparable to other enzyme replacement therapies (for example Elaprase®, 10%¹⁶).

Question 10 for Sponsor: Please provide the evidence you hold that Vimizim can be safely given following a severe or life-threatening episode of anaphylaxis? Which medications can be used to prevent these reactions? The CMI states other measures may be used. What other measures might the patient expect to manage life-threatening anaphylaxis?

¹⁵ Sampson HA, Munoz-Furlong, A, Campbell, RL, Adkinson, NF, Jr. et. al. Second symposium on the definition and management of anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 117[2], 391-397. 2006.

¹⁶ Elaprase US Prescribing Information. Shire Human Genetic Therapies, Inc., USA. Most recent amendment: June 2013; available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125151s0184bl.pdf

Of the 26 anaphylaxis events per NIAID/FAAN criteria, most were graded as mild to moderate in severity. Four of the 26 anaphylaxis events were assessed as severe or Grade 3, and two were assessed as Grade 4. All 26 anaphylaxis events were successfully managed with infusion rate adjustments and/or medical intervention with no sequelae.

Of the 18 patients who experienced anaphylaxis, 17 patients (94.4%) resumed treatment with Vimizim after the first event. Five out of the 17 patients who resumed treatment experienced recurrences following rechallenge. A total of 3 out of 18 patients permanently discontinued treatment.

In the 18 patients who experienced an anaphylactic event, all but one received premedication. Premedications were not required prior to the first reported 'type 1 hypersensitivity' event. Subsequently, all protocols required premedication with an antihistamine with or without an antipyretic 30 minutes to 1 hour prior to each infusion.

Adrenaline was administered as treatment in 4 of 18 patients who experienced anaphylactic events. Fifteen patients continued to receive Vimizim. None of these patients required intubation or cardiopulmonary resuscitation, two required hospitalisation, and all were successfully treated with supportive care (such as antihistamines and corticosteroids).

Therefore, in the majority of cases, prevention and/or management of anaphylaxis events have been successful and most subjects have been able to resume treatment. Measures described above are in line with the recommendations included in the PI. BioMarin has revised the CMI language to clarify what 'other measures' can be used to manage anaphylaxis reactions.

Genotoxicity and carcinogenicity

Question 4 for ACPM: Whether it is acceptable for no long term genotoxicity and carcinogenicity data to have been presented, based on the assumption that there is unlikely to be any direct interaction between elosulfase alfa and DNA or other chromosomal material

As noted by the nonclinical evaluator, the absence of genotoxicity or carcinogenicity studies for Vimizim is consistent with currently accepted international guidelines for the nonclinical testing of biotechnology-derived products. Based on ICH Guideline S6, genotoxicity and carcinogenicity studies are not considered appropriate.¹⁷

Pharmacokinetics

Question 1 for Sponsor: Whilst it is recognised that there are small numbers of patients enrolled in the PK study, please discuss any PK differences between the children aged 5-11 and older patients.

Analysis was performed to compare the PK differences between patients aged 5 to 11 and older patients in Study MOR-004. The results were consistent with the analysis presented in the CSR in which clearance appeared to be higher in the 5 to 11 year old group than older patients at Week 0 but comparable in the two groups at steady-state (Week 22). As discussed in the MOR-004 study report, there was no apparent association between elosulfase alfa exposure and 6MWT or 3MSCT results, urine KS reduction or increased occurrence of AEs at 2.0 mg/kg/w or 2.0 mg/kg/qow. These results, along with the lack of difference at Week 22, suggest that the apparent difference observed in elosulfase alfa clearance with age at Week 0 is not clinically significant.

Question 2 for sponsor: The PK characteristics of elosulfase alfa both with initial dosage and at steady state show features of non-linear kinetics. Please indicate whether the sponsor has

¹⁷ Preclinical safety evaluation of Biotechnology-derived pharmaceuticals S6(R1), ICH Harmonised Tripartite Guideline, June 2011.

proposed further studies or reanalysis of the studies to further investigate this. Please indicate the rationale for not including this information in the PI.

Dose-dependent non-linearity (confounded with time-dependency) of PK in MOR-002 and time-dependent non-linearity of PK in MOR-004 have been analysed based on PK parameters generated using non-compartmental analysis (NCA). Dose dependency of PK is being further investigated between 2.0 and 4.0 mg/kg/week in the ongoing MOR-008 study. The current PI contains the time-dependent non-linear PK information from MOR-004 study. The dose-dependent non-linear PK information in MOR-002 is not included in the PI as it is confounded with time-dependent non-linearity due to the within-patient dose escalation design.

Question 3 for Sponsor: Please provide the time 0 results for the Week 22 PK samples from the PK population of Study MOR-004 to support the proposed PI statement that there was no accumulation with weekly dosing.

BioMarin has provided the time 0 results for the Week 22 PK samples as requested by the Delegate. Among 22 predose PK samples from the 2.0 mg/kg/week treatment group at Week 22, elosulfase alfa was not detected in 21 samples. One sample showed detectable, but low, elosulfase alfa concentration of 32.8 ng/mL (Below Level of Quantification=10.0 ng/mL). This result in combination with short plasma half-life (36 min) indicated that there was no accumulation of elosulfase alfa following weekly dosing.

Other matters

Question 4 for sponsor: The EU SPC for Vimizim states that each vial contains 8 mg of sodium. Please indicate the reason this information has not been included in the Australian PI and CMI.

This information was added to the SmPC based on specific European requirements. The sodium content per vial has been added to the Australian PI and CMI to address the Delegate's request.

Question 6 for sponsor: The PP population performed better than the ITT population in the endurance tests in Study MOR-005. The comment in the Clinical Study Report and Additional Study Report for this study by the sponsor is that no single factor was responsible. Please describe the factors that may have influenced the outcome, and how these impacted the outcomes for each of the treatment groups.

It is expected that the per-protocol (PP) population performs better than the intent-to-treat (ITT) population as PP population is defined as a subset of ITT population who are compliant with the protocol. Factors determining subjects excluded from the PP population include major protocol deviations affecting data interpretability and repeated skipped doses of study drug, such as missed doses, inconsistent use of walking aids during assessment as well as patients undergoing orthopaedic surgery which likely compromised endurance test results. All these factors may have influenced the outcomes due to exclusion of subject data from the PP population at different study weeks.

Question 7 for sponsor: There are small differences between the primary analysis ANCOVA derived LS means for the efficacy and pharmacodynamic outcomes as reported in the CSR for MOR-005 as compared with the addendum provided with the First Round Clinical question responses. Please provide an explanation for these differences.

The differences observed were a result of the different numbers of data points included in the analyses. The efficacy endpoints were analysed using a repeated measures model. The least square (LS) mean estimates at each visit are a function of the data across all visits. For the original CSR submitted, the visits for 6MWT and 3MSCT were at Weeks 0, 12, 24, 36, 48 and the LS mean estimates at each visit are a function of the data across these visits. The addendum CSR included an additional visit at Week 72 and the LS means depend on the data of Week 72 in addition to Weeks 0, 12, 24, 36 and 48. This means that the

estimates for the addendum CSR are different from the estimates for the original CSR. The estimates for the 2 CSR versions are very close at Weeks 12, 24 and 36 since most of the data were available at these visits.

Question 8 for sponsor: Please indicate whether neutralising antibody titres were measured in any of the clinical trials. If so, please discuss a possible association between antibody titre and safety or efficacy.

Neutralising antibodies (NAb) capable of preventing elosulfase alfa from binding to the cation-independent mannose-6-phosphate (CIM6P) receptor were assessed in all Phase II and Phase III clinical studies with the exception of MOR-007. NAb results were reported as Positive or Negative following confirmation of specificity with elosulfase alfa; however, titrating of NAb was not performed. The rate of positivity, the number of NAb positive results over the total number of NAb results for each subject, was used as a surrogate for assessing the cumulative effect of NAb on safety and efficacy. There was no association of NAb with either the incidence of hypersensitivity adverse events or the degree of improvement in 6MWT, 3MSCT, or maximum voluntary ventilation (MVV).

Question 12 for sponsor: Please provide an update on Study MOR-007 and Study MOR-008 if available.

Please refer to the response 1a below.

Additional questions received via email on 03 September 2014

1. *The sponsor is requested to address the clinical evaluator's following recommendations from the Second Round clinical evaluation report:*
 - a. *There are several ongoing studies for which the sponsor did not provide any new data. The evaluator recommends that these new data are submitted as they become available. Please confirm that these studies will be submitted as soon as they become available.*

The anticipated CSR completion dates have changed since the dates were last provided to the TGA, due to changes in anticipated last patient out date (LPO). A revised timetable was provided with this response. BioMarin agrees to provide new data from the ongoing studies to the TGA. As new data may lead to revisions of the PI, BioMarin would like to propose bundling the submissions as follows for the ease of review:

- MOR-100 and MOR-008 primary treatment phase
 - MOR-006 and MOR-008 extension phase and MOR-007 extension phase
 - MOR-005 and 110-502.
- b. *The sponsor identified that the exact mechanism causing time-dependent kinetics of BMN 110 is unknown but postulated that anti-BMN 110 antibodies were a major factor. The sponsor also failed to identify the mechanism of the non-linear dose dependent increase in plasma concentrations. Furthermore, the sponsor did not address whether there are further changes in exposure with even longer periods of exposure. The evaluator recommends that the sponsor address these deficiencies in the pharmacokinetic analysis of BMN 110.*

As discussed in the response to a TGA request for further information, the time-dependent changes in PK of elosulfase alfa are likely due to binding of neutralising antibodies interfering with cellular uptake and/or protecting elosulfase alfa from protein hydrolysis. The postulation of neutralising antibodies having an impact on increased exposure is supported by data from the Phase I/II dose-escalation study (MOR-002) and the Phase III study (MOR-004). Dose dependent PK was observed in MOR-002 indicating saturation of clearance in the dose range of 0.1 to 2.0 mg/kg/week. Due to the within-subject dose escalation design in MOR-002, the dose dependent nonlinearity could be confounded with

time dependent nonlinearity. In MOR-008, dose dependency of PK is further investigated between 2.0 and 4.0 mg/kg/week and the results will be submitted when available. Based on the association between exposure and PD (see response to Question c), exposure is expected to be stabilised over time, as decline in urine KS is stabilised with long term treatment (as measured thus far). Despite the absence of longer-term PK data, safety and efficacy data support long-term treatment with Vimizim.

- c. *The sponsor has not reanalysed the available data to better define the dose-concentration-pharmacodynamic relationship of BMN 110. The evaluator recommends that the sponsor reanalyse the available data in an attempt to better define the dose-concentration-pharmacodynamic relationship of BMN 110.*

The current PK analysis includes non-compartmental analysis based on individual intensive PK samples. The dose-concentration relationship has been defined. Dose and time dependent linearity, impact of immunogenicity and patient demographics on PK have been evaluated. In addition, for each PK visit, PD (urine KS) was measured at one time point after the PK visit as it is not expected to be dynamically linked to PK profile. Therefore, a population PD analysis with available individual exposure results from the NCA analysis was conducted to define the exposure response relationship for combined data from MOR-002 and MOR-004 and the results are summarised below.

The data were best described by a log-linear model. The estimated slope of the log (AUC) effect on PCHG is -3.02. At steady state, the urine KS level is approximately reduced by 40% from baseline at the mean AUC value of the 2.0 mg/kg/week at Week 22 in MOR-004 (577371 ng/mL*min). Majority of subjects in the dataset (for example, all subjects from MOR-004) only have AUC and PD measurements from one visit. Therefore, the inter-subject variability of the slope was not estimated due to high eta-shrinkage. Subsequently, covariate effect of patient demographics or immunogenicity on the PD parameter was not investigated. The exposure-response model suggests that the greatest exposure in the 2.0 mg/kg/week group resulted in the greatest urine KS reduction and supports the dose selection.

- d. *The sponsor should monitor their safety database to develop a specific recommended prophylactic antihistamine and steroid regimens for the management of infusion and hypersensitivity reactions.*

In clinical trials, premedication with antihistamines was required but antipyretics and steroids were given at the discretion of the investigator. These instructions allowed investigators to determine the appropriate premedication needs for each patient.

BioMarin has assessed the use of premedications across the 5 studies where premedication data were available (MOR-004, MOR-005, MOR-008, MOR-007, and MOR-100) in patients that were exposed to Vimizim in the clinical trial program. Given the variability of specific medications taken during clinical trials, no pattern can be derived to form more specific recommendations on prophylactic antihistamine and steroid regimens that would be applicable to all patients.

In practice, each physician will follow their own institution/department management guidelines or may have his/her own preferred regimen developed in consultation with the institution immunologist or based on prior experience with the patient. BioMarin does not want to recommend a premedication regimen that may prevent the clinics from following locally defined procedures or physicians from making treatment decisions based on individual patients' condition.

2. *Study MOR-005 in the Development Safety Update submitted with the section 31 Response, indicated there was a death in a patient taking elosulfase. Please provide further details on this case and further information on any other deaths reported from the clinical trial database or post-marketing with elosulfase.*

The death reported in MOR-005 was a young female who developed respiratory complications following corrective spinal surgery for compressive myelopathy and spinal cord compression. The investigator assessed the death as not related to treatment with Vimizim. This patient was in the 2.0 mg/kg every other week dose group in MOR-004 and switched to 2.0 mg/kg/week in Part 2 of MOR-005. There have been no other deaths reported from the clinical trial database or postmarketing use with Vimizim.

Conclusion

MPS IVA is a rare, debilitating disease that can progressively lead to a wide spectrum of functional deficits. There is currently no approved treatment for MPS IVA other than supportive care in Australia. As observed with other ERTs, initiation of treatment early in the disease course will maximise the potential benefits and prevent irreversible morbidities. Safety and efficacy data derived from the clinical development program demonstrate that Vimizim, at the recommended dose of 2.0 mg/kg/week has a favourable benefit: risk profile and is an ERT that addresses the significant unmet medical need for patients with MPS IVA of all ages.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Vimizim concentrate for solution for infusion, containing 1 mg/mL of elosulfase alfa to have an overall positive benefit–risk profile for the indication;

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration, particularly on;

- The submission to the TGA of all reports on studies currently being undertaken or planned as soon as available
- The provision of regular reports on the findings of the proposed 10 year registry.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Whether there is sufficient data/justification to support the use of elosulfase alfa in patients <5 years of age and whether the indication should be modified to restrict the population to patients ≥ 5 years of age?*

The ACPM advised that there are limited data in children aged < 5 years but these are supportive. There is no plausible reason to consider that it would be less effective, more poorly tolerated or unsafe in younger patients. It would seem desirable that this

treatment, which is probably only modestly effective, be available at the earliest possible age in order to maximise benefits. Additionally, the ACPM noted that the three jurisdictions that have granted approval to date have not stipulated an entry age for treatment. Therefore the ACPM recommends that the indication not be restricted by age.

2. *Whether home based therapy should be included as an optional treatment setting, and whether the risks are sufficiently mitigated?*

Clearly, for patients with significant mobility issues there are distinct advantages for a home based program. The experience of home based therapy with elosulfase alfa in Europe is consistent with the experience of other recombinant therapies for the lysosomal storage disorders. The ACPM was of the view that home based therapy would be an acceptable treatment option and that the statement in the proposed PI seems appropriate to mitigate risk: *'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.'*

3. *Whether life-threatening anaphylaxis should be a contraindication to further treatment?*

The ACPM noted only one patient in the trial program discontinued following anaphylaxis. It is not at all clear that patients who have experienced significant hypersensitivity reactions should be precluded from attempts to continue this therapy, especially in the absence of alternatives. The contraindication wording proposed by the sponsor in the PI is acceptable.

4. *Whether it is acceptable for no long term genotoxicity and carcinogenicity data to have been presented, based on the assumption that there is unlikely to be any direct interaction between elosulfase alfa and DNA or other chromosomal material?*

The ACPM was unaware of any evidence of a direct interaction between any recombinant enzyme replacement therapy and DNA or other chromosomal material, therefore the lack of long term genotoxicity and carcinogenicity data is acceptable.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Vimizim solution for injection vial, containing the new biological entity elosulfase alfa (rch) 1 mg/mL indicated for:

Vimizim is indicated for the treatment of mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).'

Specific conditions of registration applying to these goods

1. The Vimizim (elosulfase alfa) Risk Management Plan (RMP), version 4.0, dated 12 February 2014, revised as specified by the Australian Specific Annex version 2.0, dated 23 May 2014, included with submission PM-2013-02807-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Batch Release Testing: It is a condition of registration that, as a minimum, the first five independent batches of Vimizim elosulfase alfa (rch) 1 mg/mL solution for injection vial AUST R 215523 imported into Australia are not released for sale until samples

and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.

3. Certified Product Details: An electronic draft of the Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
4. The final study reports for the following studies must be submitted to the TGA, as soon as possible after completion or as per the submission plan outlined in the sponsor's email of 3 November 2014, for evaluation as a Category 1 submission or submissions:
 - MOR-100 Open-Label Extension Study
 - MOR-005 Phase 3 Extension, Double-Blind Study followed by an Open-Label Study
 - MOR-006 Non-ambulatory Study
 - MOR-007 Phase 2 Open-label study in subjects < 5 years of age
 - MOR-008 Cardiopulmonary Study
 - Study 110-502 Phase 3B, Open Label Study of Australian patients (Executive Summary acceptable)
5. Provide regular reports of the findings of the proposed 10 year registry of patients treated with elosulfase alfa, as outlined in Attachment 3 to the ASA of the RMP in accordance with the reporting plan outlined in RMP version 4.0 dated 12 February 2014 or any subsequent revisions, as agreed with the TGA.

Attachment 1. Product Information

The Product Information approved for Vimizim at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>