EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/636347/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimizim

International non-proprietary name: ELOSULFASE ALFA

Procedure No. EMEA/H/C/002779/II/0004

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Rapporteur and type of application	
CHMP Rapporteur:	Pieter de Graeff
This application is in the area of:	Clinical

Assessment Timetable / Steps taken for the assessment

Timetable	Date
Start of procedure:	24 August 2014
CXMP Rapporteur Assessment Report	26 September 2014
CXMP comments	13 October 2014
Rapporteur Revised Assessment Report	N/A
Opinion	23 October 2014

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioMarin Europe Ltd submitted to the European Medicines Agency on 6 August 2014 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIB

Update of sections 5.1 and 4.8 of the Summary of Product Characteristics following 52 weeks results of clinical study MOR-007 conducted in paediatric patients with MPS IVA (under the age of 5 years). Deletion of the revision date for the Package Leaflet has also been proposed.

The requested variation proposed amendments to the Summary of Product Characteristics and the Package Leaflet.

1.2. Rationale for the proposed change

The MAH has provided additional supportive efficacy and safety data and more specifically 52 weeks results of clinical study MOR-007 conducted in paediatric patients with MPS IVA (under the age of 5 years). On this basis, the MAH proposed limited updates to sections 4.8 and 5.1 of the SmPC.

2. Overall conclusion and impact on the benefit/risk balance

With a new study completed (study MOR-007), the total number of studies supporting the Vimizim MA has increased from six to seven, and the total number of patients exposed to any dose of elosulfase alfa (safety population) increased from 235 to 244. The total duration of treatment ranges to 203 weeks (previously 167 weeks) and 185 patients were exposed for a duration longer than 48 weeks (previously 86 patients).

No new safety signals emerged from the new study MOR-007.

The proposed Product Information changes are sufficiently supported by the data provided and are accepted. The benefit-risk balance of Vimizim in its approved indication remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIB

Update of sections 5.1 and 4.8 of the Summary of Product Characteristics following 52 weeks results of clinical study MOR-007 conducted in paediatric patients with MPS IVA (under the age of 5 years). The date of latest revision is deleted in the Package Leaflet.

☒ is recommended for approval.

The requested variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

4. Scientific Discussion

4.1. Introduction

Vimizim contains the active substance elosulfase alfa (recombinant). It is an approved enzyme replacement therapy (ERT) for the treatment of mucopolysaccharidosis IV Type A (Morquio A syndrome, MPS IVA).

MPS IVA is a rare and severely debilitating and progressive disease, 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. With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues.

MPS IVA is a rare disorder, with an estimated incidence of 0.06 in 10,000 live births, which leads to an approximate 1300 MPS IVA patients in the EU. Therfore, Vimizim received an orphan designation in the EU.

Vimizim was approved in the EU on 28 April 2014.

The MAH of Vimizim, BioMarin Europe Ltd., has recently completed an additional clinical trial. The MA dossier now includes data from seven clinical studies, including two completed studies and five ongoing studies. The MA is supported primarily by final results from the completed randomized, double-blind, placebo-controlled pivotal Phase 3 study MOR-004, with supportive data from the completed Phase 1/2 study MOR-002, two ongoing long-term extension studies (MOR-005 and MOR-100), and three ongoing ancillary Phase 2 studies (MOR-006, MOR-007, and MOR-008).

Efficacy and safety data collected from each study (except MOR-006 and MOR-008) include data up to the data cut-off date for each study; for MOR-006 and MOR-008, only safety data are reported.

4.2. Clinical aspects

Study MOR-007

4.2.1. Methods –analysis of data submitted

Study MOR-007 is an ongoing Phase 2, open-label, multicentre study to evaluate safety and tolerability of infusions of elosulfase alfa (BMN 110) at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA patients.

Patients with a documented clinical diagnosis of MPS IVA and less than 5 years of age at the time of the first study-drug infusion, who had not previously had hematopoietic stem cell transplants or been previously treated with BMN 110, were eligible to participate in this study.

Patients received intravenous infusions of BMN 110 at a dose of 2.0 mg/kg/week for up to 208 consecutive weeks. Each infusion is administered over a period of approximately 4 hours.

The primary objective of the completed primary treatment phase (52 weeks) and the ongoing extension treatment phase (up to an additional 156 weeks for a total treatment period of 208 weeks) of the study is to

evaluate safety and tolerability of infusions of elosulfase alfa (BMN 110) at a dose of 2.0 mg/kg/week over a 52-week period in MPS IVA patients less than 5 years of age at time of first study drug infusion.

Secondary objectives of the completed primary treatment phase and the ongoing extension treatment phase of the study were:

- To evaluate the ability of 2.0 mg/kg/week BMN 110 to reduce urine KS levels in MPS IVA patients less than 5 years of age at time of first study drug infusion.
- To evaluate the ability of 2.0 mg/kg/week BMN 110 to affect growth velocity in MPS IVA patients less than 5 years of age at time of first study drug infusion.

Criteria for evaluation included the following:

Primary Safety Variables

- AEs
- vital signs
- echocardiograms
- ECGs
- immunogenicity tests
- physical examinations (including neurologic examination)
- standard clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- concomitant medications
- cervical spine radiography

Secondary Variables

- normalized urine KS concentration (normalized to urinary creatinine)
- anthropometric measurements (length, sitting height, standing height, knee height, weight, and head circumference (all measurements possible based on age and condition of patient)
- radiographs of the lower extremities (bone length only)

The ongoing extension treatment phase of the study is designed to evaluate the long term safety and efficacy of BMN 110 treatment in patients with MPS IVA who completed the initial 52-week primary treatment phase of the MOR-007 study. During the extension treatment phase, patients will continue to complete safety and efficacy assessments for up to an additional 156 weeks. Assessments will be the same as those for the primary treatment phase, but with a reduced frequency.

As patients may experience hypersensitivity reactions associated with the administration of BMN 110, there is a requirement for premedication with an antihistamine for all age-appropriate patients within 1 hour prior to the start of each BMN 110 infusion. In addition, antipyretics may also be utilized as a premedication 30 to 60 minutes prior to the start of the infusion at the discretion of the investigator. However, if a patient has tolerated infusions of BMN 110 for 26 weeks, premedication with antihistamine may be discontinued at the investigator's discretion. Vital signs are measured just before, during, and following the infusion, and patients are monitored by continuous pulse oximetry during and following the infusion. Changes in concomitant medications and adverse events (AEs) are recorded throughout the study.

If a severe or serious infusion associated reaction (IAR) or an IAR requiring cessation of the infusion occurs, blood samples are collected for immunogenicity testing, including total IgE, drug-specific immunoglobulin E

(IgE), complement component 4 (C4), serum tryptase, and pharmacokinetics (PK) (in order of decreasing priority, based on the quantity of blood available from the patient).

An independent Allergic Reaction Review Board (ARRB), appointed by BioMarin and composed of physicians not directly involved with the study (including at least one allergist/immunologist), serves as consultants to BioMarin, the clinical team, and the Medical Monitor. The ARRB reviews severe or serious IARs, and may make recommendations regarding the appropriate prevention and management of IARs. A Data Monitoring Committee serves in an advisory capacity to BioMarin to monitor the safety of BMN 110 in patients who participate in clinical trials in the Morquio A program, including MOR-007.

4.2.2. Results

A total of 15 patients were enrolled in Study MOR-007. As of the data cut-off date of the study (completion of Week 52 Visit for each patient), all patients have completed the primary treatment phase (52 weeks of treatment with BMN 110). All 15 patients entered the extension treatment phase of the study as of the data cut-off date. As this is a report of an ongoing study, final results from the extension treatment phase will be provided in a subsequent report.

The study included 7 males (46.7%) and 8 females (53.3%) with mean (±SD) age of 3.1 (±1.34) years at enrollment. Seven of the patients were 0 to <3 years of age and 8 of the patients were ≥ 3 to<5 years of age. Ten (66.7%) patients were White, 4 (26.7%) patients were Asian, and 1 (6.7%) patient was East Asian/African American. The distribution of patients of White and Asian descent was evenly divided in both age groups. The mean (±SD) Baseline normalized urine KS was 35.9 (±12.32) µg/mg and ranged from 18.8 to 56.5 µg/mg.

The mean (± SD) duration of BMN 110 dosing was 51.9 (±0.18) weeks. The mean (±SD) weekly dose received was 1.9 (±0.08) mg/kg/patient, and the mean (±SD) total dose received was 98.7 (± 4.21) mg/kg/patient.

Safety Results

The safety and tolerability of BMN 110 at 2.0 mg/kg/week over 52 weeks in MPS IVA patients less than 5 years of age at the first study drug infusion was the primary endpoint. No patients withdrew from the study or permanently discontinued treatment due to an AE as of the completion of the primary treatment phase (through Week 52 for each patient). Few infusions were missed (<5%). Overall, this suggests good compliance with drug administration and thus supports the tolerability of the infusions.

All patients experienced at least one AE during the 52 weeks. The most common AEs were pyrexia (100% of patients), vomiting (80.0% of patients), and cough (73.3% of patients). Although pyrexia and vomiting were more common in this study, 46.3% of pyrexia events and 36.1% of vomiting events occurred outside the IAR window (>1 day following the end of the infusion) and were likely related to intercurrent illnesses common in early childhood. The majority of AEs were mild (grade 1) or moderate (grade 2) in severity (NCI CTCAE v. 4.0). One patient experienced severe (grade 3) AEs of tonsillar hypertrophy, tonsillectomy, and cervical cord compression that were all assessed as not related to study drug. There were no life-threatening AEs (grade 4 or above) and no deaths in the study.

Eleven (73.3%) patients experienced at least one drug-related AE; the most common were pyrexia (40.0% of patients) and vomiting (33.3% of patients). All drug-related AEs were mild (grade 1) to moderate (grade 2) and resolved with symptomatic treatment and/or infusion interruption or temporary discontinuation. The frequency of drug-related pyrexia and vomiting events was similar to other BMN 110 studies.

Treatment-emergent SAEs were reported for 4 (26.7%) patients. Three patients experienced SAEs (spinal cord oedema, joint instability, tonsillar hypertrophy, cervical cord compression, device-related infection,

skin infection, and sepsis) that were assessed as not related to study drug and were either device-related infections or consistent with underlying disease comorbidities. Only one patient experienced a SAE (grade 2 Hypersensitivity) that was assessed as related to BMN 110.

The Hypersensitivity occurred during the Week 14 infusion of BMN 110 and resolved the next day with symptomatic medical treatment and infusion discontinuation. The patient completed the 52 weeks of treatment without experiencing additional Hypersensitivity events

Potential Hypersensitivity AEs were identified by utilizing the broad Anaphylactic Reaction algorithmic Standardized MedDRA (v. 15.0) Query (SMQ) and the broad Angioedema SMQ. A Hypersensitivity AE was reported for 4 (26.7%) patients from the Angioedema SMQ: grade 1 and 2 urticaria in 2 (13.3%) patients, grade 2 hypersensitivity in 2 (13.3%) patients, and grade 1 wheezing in 1 (6.7%) patient. No patients experienced a Hypersensitivity AE based on the Anaphylactic Reaction SMQ.

All patients experienced at least one IAR. IARs were mild to moderate in severity and generally manageable with symptomatic treatment and infusion rate adjustment. Infusions requiring interruption or discontinuation due to an AE and requiring medical intervention represented a very small percentage of all 743 infusions (0.8%). All patients who experienced an IAR requiring infusion interruption or discontinuation and medical intervention were successfully retreated at subsequent visits.

Efficacy Results

Normalized Urine KS: Treatment with BMN 110 led to a substantial decrease in mean normalized urine KS levels within 2 weeks and the decreased levels were maintained over 52 weeks. The mean (±SD) percent change from Baseline in urine KS was -30.2% (±12.68; n=15) at 2 weeks, and -39.9% (±24.03; n=15) at 26 weeks, and -43.5% (±22.15; n=10) at 52 weeks. These results, as of the data cutoff date for this report, show a comparable decline in urine KS to the reduction observed in older children and adult patients in the BMN 110 Phase 1/2 and Phase 3 studies.

Normalized standing height z-score: There was minimal change in mean normalized standing height z-score after 52 weeks of treatment with the mean normalized standing height z-score decreasing slightly from Baseline to Week 52 (-1.6 to -1.9 for all patients; -2.0 to -2.2 for patients ≥ 2 years of age). Given the typical progression of disease in older children which shows an increasing deviation from normal standing height with age [mean z-score -5.00 for ages 5 to11 and -7.27 for ages12 to18 (Harmatz, 2013, Mol Genet Metab)], the suggestive trend towards stabilization of normalized standing height z-scores in this young patient group (< 5 years of age) after 52 weeks of treatment may indicate that BMN 110 slows the progressive negative deviation.

Normalized growth rate z-scores: The mean normalized growth rate z-scores numerically improved for all patients (n=15) and for the subgroup of patients ≥ 2 years of age (n=12) indicating a trend towards normal growth rates with long term BMN 110 treatment. The Baseline and Week 52 mean (± SD) normalized growth rate z-scores were -0.6 (± 0.64) and -0.4 (± 0.53), respectively, for all patients and -0.8 (± 0.78) and -0.3 (± 0.53), respectively, for patients ≥ 2 years of age.

Positive changes in the absolute values of anthropometric measurements (length, sitting height, knee height, weight, and head circumference) and measurements of lower extremities by radiographs were observed. However, given the paucity of longitudinal natural history data in this age range and the variability in these parameters in the normal populations, further data from the extension phase of the study will be needed in order to determine the significance of these early changes.

The mean (± SD) skeletal bone age (as determined by hand/wrist radiographs) at Baseline was 3.6 (± 1.23) years and at Week 52 was 4.6 (± 0.63) years. The mean change was 0.8 (± 0.85) years and is within anticipated changes in normal children.

Immunogenicity Results

BMN 110-specific antibody development (TAb) was universal among all treated patients and was sustained by Week 51 with a mean (±SD) titer of 135600.0 (± 139016.8). No patients tested positive for BMN 110-specific IgE as of completion of their Week 52 Visits.

Reductions in urine KS occurred and were maintained, despite the development of anti-BMN 110 antibodies. Patients with TAb titers greater than the mean had similar decreases in urine KS compared to patients with TAb titers below the mean by the end of their Week 52 Visits: mean (± SE) urine KS 18.5 (± 1.90) versus 15.0 (± 2.92), respectively. No apparent relationship was observed between TAb titers and height z-score measurements.

The overall number of patients that experienced Hypersensitivity AEs was low making it difficult to identify a persistent trend between incidence rate of Hypersensitivity AEs and TAb titers.

4.2.3. Discussion

The results of the submitted study MOR-007 support the existing indication in patients of all ages. Based on the review of the newly available data, no Adverse Drug Reactions (ADRs) that are not covered by the current SmPC have been identified and the frequency of occurrence of the ADRs is equal to what was already known. Therefore no changes to the table of ADRs in section 4.8 are necessary.

4.3. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are being updated.

As study MOR-007 was designed to study the effects in younger patients (<5 years of age), the MAH proposes to add the following wording to section 4.8 of the SmPC (newly added text in blue, and removed text in red):

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

In relation to the same results the MAH also updates the paragraph *Paediatric population* in section 5.1 with the following wording:

> 'It is important to initiate treatment as early as possible. ~~Treatment of young children < age 5 years might be started although this population was not included in the pivotal study.~~
>
> The majority of patients who received Vimizim during clinical studies were in the paediatric and adolescent age range (5 to 17 years). In an open-label trial, 15 paediatric patients with MPS IVA under the age of 5 years (9 months to <5 years) received 2 mg/kg of Vimizim once a week for 52 weeks. Safety and pharmacodynamic results in these patients are consistent with results observed in patients 5 to 57 years old (see sections 4.8).'
>
> ~~Safety results to date in 15 patients less than 5 years of age are consistent with results observed in patients 5 to 57 years old.~~