Cost-effectiveness of elosulfase alfa (Vimizim®) for the treatment of Morquio A Syndrome in patients of all ages.

The NCPE has issued a recommendation regarding the cost-effectiveness of elosulfase alfa (Vimizim®). Following NCPE assessment of the applicant's submission elosulfase alfa (Vimizim®) is not considered cost-effective for the treatment of of Morquio A Syndrome in patients of all ages and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (BioMarin) economic dossier on the cost effectiveness of elosulfase alfa (Vimizim®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **December 2016**

Summary

In April 2016, BioMarin Europe Ltd submitted a pharmacoeconomic dossier to the NCPE on the cost effectiveness of elosulfase alfa (Vimizim®) for the treatment of Morquio A Syndrome (MPS IVA) in patients of all ages. Elosulfase alfa is the first medicine licensed for the treatment of MPS IVA, for which only supportive care is currently available; this includes medications (e.g. antibiotics and analgesics) and surgical interventions. The aim of treatment with elosulfase alfa is to stabilise the disease or to reduce progression and improve patients' quality of life.

1. Comparative effectiveness of elosulfase alfa (Vimizim®)

The applicant presented data from the MOR-004 trial, an RCT which compared two different dosing schedules of elosulfase alfa with placebo. Results of this trial (24 week duration) showed that weekly doses of 2.0mg/kg elosulfase alfa led to statistically significant improvements in the primary outcome (six minute walk test (6MWT), a surrogate outcome) when compared with placebo. Confidence intervals for secondary and tertiary outcomes in the trial were in most cases crossing the line of no effect. The applicant also presented data from an extension study to the 24-week RCT, the MOR-005 study. This study reported data for a longer-period of time (72 weeks), however, the study design did not include a comparator group and therefore observed treatment effects should be interpreted cautiously. Results of this study found a relatively sustained effect of elosulfase alfa 2mg/kg every week; at weeks 48, 72 and 120; the 6MWT distance (primary outcome) for these time-points was comparable to that of week 24 in MOR-004. Patients treated with elosulfase alfa continued to show improvement in 6MWT distance until 72 weeks of treatment; after this time point, the 6MWT seemed to decline back to values approaching those at baseline of MOR-005.

During the evaluation of elosulfase alfa by the EMA, the CHMP questioned the discriminatory ability of the 6MWT as an outcome in the MPS IV A population and also whether clinically relevant differences in the parameter could be expected in a 24-week timeframe. However, it was concluded that a more sensitive endpoint could not be identified at the time of application for licensing. The CHMP also determined that the clinical relevance of the observed 6MWT difference (22.5m) was supported by the secondary parameters and additional information on clinically important events; trends towards improvement, though not statistically significant, were observed in the three minute stair climb test (3MSCT), maximum voluntary ventilation (MVV), wheelchair dependence, orthopaedic surgery and

activities of daily living (ADL) function. However, it was concluded that the long-term efficacy and safety of elosulfase alfa could not be established at the time of licensing. Due to the limited numbers of patients in the trials, and the heterogeneity of disease severity and progression, the CHMP imposed a disease-specific registry to be maintained in the post-authorisation phase to collect long-term data (up to 10 years).

2. Safety of elosulfase alfa (Vimizim®).

In the pivotal study, MOR-004 there were no deaths and none of the 176 patients who received a dose withdrew or discontinued treatment due to an adverse event. Also, few infusions were missed by the participants (<2%). However, nearly all participants reported at least one treatment-emergent adverse event during the trial.

Most subjects in MOR-004 experienced at least one infusion-associated reaction (91.5% placebo, 89.7% elosulfase weekly, 94.9% elosulfase every second week) but these were predominantly mild to moderate in severity. Hypersensitivity adverse events occurred in 11.9%, 20.7%, 27.1% of patients treated with placebo, elosulfase alfa weekly and elosulfase alfa every second week, respectively, and were mostly mild or moderate in severity. Serious adverse events occurred in 15.5% of patients receiving elosulfase alfa once weekly versus 3.4% of patients receiving placebo. Serious adverse events related to the study drug included one anaphylactic reaction, one hypersensitivity reaction and one severe case of vomiting, all of which resolved either with treatment or without. The most common drug-related adverse events in the placebo, elosulfase alfa weekly, and elosulfase alfa every second week regimens were pyrexia, vomiting, and headache and nausea, respectively, and were mild to moderate in severity.

No new safety signals were observed in the extension study between week 24 (end of the MOR-004 trial) and week 120. At week 120, less than 3% of the patients permanently discontinued the study drug, though all of the participants had experienced at least one adverse event.

3. Cost effectiveness of elosulfase alfa (Vimizim®).

A cost-utility analysis was presented in the submitted dossier. This aimed to estimate the lifetime impact of elosulfase alfa in terms of costs and QALYs. The model population consisted of people diagnosed with MPS IV A and was based on the MOR-001 natural

history study population (n=325). The comparator defined in the economic model was the current standard of care, i.e. symptomatic treatment involving, for example, orthopaedic surgery, pain management and the treatment of infections.

The economic model submitted by the Applicant involves a number of assumptions, most importantly that treatment with elosulfase alfa modifies the disease course and delays the development of disease manifestation in asymptomatic patients. The Applicant used data from the elosulfase alfa arm of MOR-005, an open-label extension study, as the source of effectiveness data for elosulfase alfa. The source of information on the effectiveness of standard-of-care was the MOR-001 natural history study.

Results

After discounting the health effects by 5% annually, MPS IVA patients receiving standard medical care generated 7.07 QALYs during their lifetime, while patients on elosulfase alfa generated 14.97 QALYs. After discounting costs by 5% annually, MPS IVA patients on standard-of-care generated €33,080 while elosulfase alfa treated patients generated €8,187,681 during their lifetime. The discounted incremental cost-effectiveness ratio (ICER) of elosulfase alfa treatment against standard medical care was €1,032,228 per QALY.

Sensitivity analysis

The one way sensitivity analysis presented by the applicant showed that the most important parameters in the model affecting the modelled outcomes were the discount rate used for costs and the QALYs. The change in the annual decline in the 6MWT values, surgery costs, utility values and average body weight per health state all had very minimal impact on the outcomes. The cost effectiveness acceptability curve of elosulfase alfa against standard medical care showed that the probability of elosulfase alfa treatment being cost-effective at WTP values of about €500,000, €750,000, €1,000,000 and €2,000,000 per QALY were 0%, 6%, 86% and 100% respectively.

4. Budget impact of elosulfase alfa (Vimizim®).

The price to the wholesaler of elosulfase alfa is €750 per 5mg vial. As the cost of treatment with elosulfase alfa depends on patient weight (2mg/kg dose), the Applicant has costed the treatment based on the average weight of a patient according to the same health states as the

economic model. The annual acquisition cost of elosulfase alfa per person excluding VAT is estimated at €395,480 and €486,440 when VAT is included.

The applicant estimates that there are 10 known patients (adult and paediatric) with MPS IVA in Ireland. Four of these patients will be eligible for elosulfase alfa treatment in year 1. The applicant estimates that the total eligible population by year 5 would be approximately 6 patients (based on an incidence of 1 in 220,000 live births).

The gross drug budget impact as outlined in the applicants submission ranges from; €1,945,762 (year 1), €1,945,762 (year 2), €2,324,143(year 3), €2,208,824 (year 4), € 2,540,442 (year 5). The cumulative 5 year gross drug budget impact (including VAT) is estimated at €10.97 million.

There are no displaced treatment cost offsets associated with the uptake of elosulfase alfa. Therefore, the net drug budget impact is equivalent to the gross drug budget impact.

5. Patient submissions

A patient submission was received from the Irish Society for Mucopolysaccharide Diseases.

6. Conclusion

Elosulfase alfa is the first medicine licensed for the treatment of MPS IVA, for which only supportive care is currently available**.** Overall the results from the most methodologically reliable study, the MOR-004 RCT, were statistically significant on the primary outcome (6MWT) only. The 6MWT provides an indirect assessment of endurance and functionality, but does not provide a direct measure of the effect of treatment on survival.

Results from the longer-term, uncontrolled studies, appear to show an effect of treatment, but without a comparator can only be compared with the natural history of MPS IVA. It was also difficult to establish which patients would respond to treatment and which would not. Treatment with elosulfase alfa will be lifelong, and although the applicant presented data for 72 weeks, there was no clear evidence of the effects or harms of the treatment over the lifetime of an individual with MPS IVA. Also the outcomes employed in the included studies were surrogate outcomes, and therefore there is uncertainty around how results from these outcomes should be interpreted.

Due to assumptions in the analysis regarding the long-term clinical benefit of elosulfase alfa

compared with supportive care, considerable uncertainty remains regarding the true cost-effectiveness of treatment with elosulfase alfa.

Following NCPE assessment of the applicant's submission, the cost effectiveness of elosulfase alfa (Vimizim®) for the treatment of Morquio A Syndrome has not been demonstrated, and therefore is not recommended for reimbursement