Zorginstituut Nederland

Elosulfase alfa (Vimizim®) for the treatment of Morquio A syndrome

Summary of recommendations by *Zorginstituut Nederland* dated 24 April 2017

Zorginstituut Nederland carried out a re-assessment of the medicinal product elosulfase alfa (Vimizim®), whereby they reached the following conclusion.

Zorginstituut Nederland sent a letter on 29 May 2017 to the Minister of Health Welfare and Sport (WVS) about the results of the re-assessment of the medicine elosulfase alfa (Vimizim®) for the treatment of the Morquio A syndrome. With the advice of the Scientific Advisory Board (WAR), the Zorginstituut has now completed its assessment.

Previous Assessment

In a previous letter dated 1 March 2016, the Zorginstituut informed the Minister about their earlier assessment of this product. At that time, the Zorginstituut was of the opinion that elosulfase alfa does not comply with 'established medical science and medical practice'. As a consequence of that assessment, treatment of Morquio A patients with elosulfase does not fall under the basic health insurance. As a consequence of that assessment, patients who were still being treated with this product in 2016 no longer receive treatment.

Basis for the re-assessment

The marketing authorisation holder of elosulfase alfa has submitted a dossier and a request for a reassessment that is predominantly based on *follow-up* data from clinical research. The initial assessment involved data relating to 72 weeks; now the data relate to 120 weeks.

Outcome of the assessment

Due to the lack of a direct comparative placebo-arm, the use of elosulfase alfa during 120 weeks (in addition to best supportive care) was compared with a historic cohort of patients (MorCAP) in which patients with Morquio A syndrome who received only best supportive care were followed during 2 years. The crucial outcome parameters for the assessment are: mobility (based on the six-minute walking test [6MWT]), mobility and stamina (tested by climbing stairs), a number of respiratory functions and lastly the frequency of (severe) adverse effects related to the treatment in the long term.
In making its re-assessment, the Zorginstituut was advised by the Scientific Advisory Committee (WAR).

Despite the fact that long-term treatment with elosulfase alfa seems to counteract deterioration in mobility, stamina and respiratory functions, the results of the MOR-005 study (an uncontrolled, open label study) do not give any points of departure for revising the assessment of the adverse effects of elosulfase alfa. Due to the lack of a placebo-arm, in combination with the limited effects on crucial outcome parameters, this leads to the opinion that – for the *overall* population – the medicine does not comply with established medical science and medical practice. Furthermore, the new data from the

uncontrolled, open-label MOR-005 extension study provide no new insights that make it possible to determine for which patients, with which characteristics, this medicine does have a therapeutic added value. This is despite the fact that the Zorginstituut had emphatically asked the manufacturer for such stratification.

In summarising, the Zorginstituut feels that the additional data do not provide any substantially different picture of the product's performance than the data submitted previously.

Conditional reimbursement

In our previous assessment we advised the Minister that elosulfase alfa is not considered a potential candidate for conditional inclusion in the basic package of reimbursable products. Based on this reassessment, our recommendation on this matter is unaltered. Because the effects of elosulfase alfa are not expected to increase substantially in the long term and there is little chance that treatment will be cost-effective, the Zorginstituut feels that elosulfase alfa is not a promising product for inclusion in the conditional reimbursement system.

Situation in other countries

A number of our neighbouring countries have included elosulfase alfa in their packages (whether or not subject to limiting conditions regarding access and reimbursement). Interested parties will undoubtedly emphatically point this out to the Minister. Nevertheless, the way the health care systems in those countries are designed differs significantly, while the assessment of the product's performance barely differs from that of the Netherlands, though this had a different ending in some countries as far as access is concerned.

Obtaining experience with the product outside the insured package

Although the Zorginstituut is firm in its conclusion that elosulfase alfa is a product that does not justify payment via the insured package, we do suggest that the Minister considers investigating alternative options for funding its use in an experimental environment. The following arguments exist for doing this. When registering this product, the EMA explicitly referred to its expectation that further development of the file's evidence would benefit from the product's use in practice. This will require the proper integration of data that have been collected internationally. A key role is played here by the manufacturer, as the party who manages the register that the EMA wants.
Nevertheless, the company has not disclosed matters adequately. There is no certainty that the company will do this in response to a second request. This is potentially disadvantageous to the patients. To an extent, this is a form of system failure. On the other hand, the professional group has submitted a proposal within this framework that deserves contemplation.

Moreover, the professional group is convinced of the need to share data on a European level and on previous occasions has indicated a willingness to play a leading role in this matter. It is important that primarily the collaborating professionals rather than the company have a complete overview of the *real world evidence* on elosulfase alfa.
Furthermore, due to its commercial interests, a role for the manufacturer in determining a proper positioning and/or patient segmentation for this product is less credible. In the end, it is in the patients'

interest that this takes place. The government has a good argument for playing a facilitating role in resolving this impasse. After all, if specialized treating physicians are allowed to spend a given budget on treating patients, they will be better able to play a connecting role on a European level. This will simultaneously exert pressure on the manufacturer to supply the product at a greatly reduced price that does justice to the product's performance, which is, for the moment, quite limited. The proposed newly designed conditional reimbursement instrument may present an opportunity in this respect. If not, then perhaps a different instrument would be more appropriate.

For further information, please contact: MGraaf@zinl.nl; warcg@zinl.nl

The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.