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Our reference
2023004477

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Date 13 December 2023
RE: GVS advice orphan drug migalastat (Galafold®) for the treatment of Fabry disease

Dear Mr Kuipers,

In your letter of 1 May 2023 (CIBG-23-05421), you asked the National Health Care Institute to carry out a reassessment, on the basis of newly published research results, of the orphan drug migalastat (Galafold®) for the treatment of patients with Fabry disease aged 12 and older who have an amenable mutation and an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2. Here is our package advice on this matter.

Registered indication
Migalastat is indicated for the treatment of patients aged 12 years and older with Fabry disease who have an amenable treatable mutation and an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m^2.

Claim by the marketing authorisation holder
Migalastat has an equal value to enzyme replacement therapy (ERT) with agalsidase-α and -β for the registered indication.

GVS advice

The National Health Care Institute advises you not to include migalastat in the basic health care package for the treatment of patients aged 12 years and older with Fabry disease who have an amenable mutation and an eGFR >30 ml/min/1.73 m^2. According to the National Health Care Institute, migalastat does not meet the legal criterion for 'established medical science and medical practice' for this indication. The development of this package advice is explained below.

Effectiveness
Established medical science and medical practice after initial assessment (2017)
In 2017, the National Health Care Institute recommended that migalastat should not be included in the basic health care package for the treatment of adult patients with an amenable mutation of Fabry disease and an eGFR > 30 ml/min/1.73 m^2. This initial assessment and advice were based on the results of the FACETS and ATTRACT studies. In the randomised, double-blind, placebo-controlled FACETS study, the effect of migalastat was compared with a placebo after 6 months on the crucial outcome parameters such as cardiac measurements, cerebrovascular events and pain, as well as the important outcome of quality of life. The randomised, open-label switching study (ATTRACT) assessed the same outcomes at 18 months in patients taking migalastat or ERT. The evidence of a similar effect of migalastat and ERT on the key outcome parameters above was of

very low quality. The quality of evidence for a similar effect on the important outcome parameter 'quality of life' was low. The evidence that migalastat has a similar safety profile to ERT was also of low quality. Based on these findings, the National Health Care Institute concluded that there was insufficient evidence to establish that migalastat has an equivalent value to ERT. Unlike the intravenous administration of ERT, migalastat can be administered orally. This is an important benefit for these patients in terms of ease of use. It was therefore considered appropriate to further investigate the value of migalastat.

Established medical science and medical practice after reassessment (2023)
Since the first assessment in 2017, the indication of migalastat has been extended to patients aged 12 years and older. The present reassessment was performed with new data from the 12-month open label extension (OLE) studies from the above randomised studies, OLE-FACETS and OLE-ATTRACT, respectively. In both extension studies, patients were treated with migalastat; however, without a control group. The endpoints included left ventricular mass change (LVMi) and change in renal function (eGFR). The cerebrovascular event endpoint was no longer rated as critical in this assessment. OLE-ATTRACT also includes a composite parameter for cardiac, cerebral, and renal events. At 24 months, the mean difference in LVMi in the FACETS population was -7.7 g/m2 (95% confidence interval [CI]: -15.4; -0.01 (n=27). In the ATTRACT population, this mean difference at 30 months was -3.8 g/m2 (95% CI: -8.9; 1.3). In OLE-ATTRACT there were a total of 32 events for the composite outcome parameter, 29 of which were renal and 3 cardiac. Both extension studies show that the use of migalastat reduces the LVMi. However, it is very uncertain whether this effect is clinically relevant. No new data have been published for quality of life. There is as yet insufficient evidence that the use of migalastat results in a clinically relevant effect on quality of life.

The extension studies also do not provide additional evidence on the comparability of migalastat and ERT with regard to adverse effects. The evidence that migalastat has a similar safety profile compared to ERT was and remains of low quality.

All in all, the quality of the available evidence is so low that no equal value can be established for migalastat compared to ERT. Based on the present new data, the National Health Care Institute concludes that migalastat does not meet the established medical science and medical practice for patients aged 12 years and older who have an amenable mutation of Fabry disease and an eGFR >30 ml/min/1.73 m^2.

Appropriate care
For the present indication, migalastat is not proven effective care and is therefore not appropriate care. For orphan drugs, *conditionals* and *exceptionals* that do not (yet) meet the legal criterion 'established medical science and medical practice' due to insufficient evidence, there is a conditional inclusion (CI) arrangement.[1] In principle, migalastat meets the criteria for this arrangement for a small subgroup of patients who cannot be treated with ERT (antibody formation, anaphylaxis) and therefore have no other treatment options. However, since according to the professional group in the Netherlands this only affects about 2 patients, the

[1] Procedure for initiating conditional inclusion of orphan medicinal products conditionals exceptionals (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

National Health Care Institute has doubts about the effectiveness. The National Health Care Institute has asked the marketing authorisation holder to discuss this with the professional group and is awaiting the outcome.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report is attached.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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