National Health Care Institute

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2024029353

Our reference
2024029353

Date 30 July 2024
Subject Package advice on Pombiliti® in combination with Opfolda®

Dear Ms Agema,

This is a corrected version of the package advice previously sent on 22 July 2024 (reference 2024025464) in which the term 'evergreening' was used inappropriately. The Insured Package Advisory Committee (ACP) did not make any statements about evergreening with respect to this medicinal product and the term has therefore been removed from this letter.

The National Health Care Institute is advising you about the assessment of cipaglucosidase alfa (Pombiliti®, hereinafter CIPA for short) as long-term enzyme replacement therapy, used in combination with the enzyme stabiliser miglustat (Opfolda®) for treating adults with late-onset Pompe disease (LOPD). The reason for this advice was the placement of CIPA in what is known as the 'package lock procedure' for expensive medicinal products. In addition, your predecessor asked the National Health Care Institute in her letter dated 25 March 2024 [CIBG-24-06770] to examine whether miglustat (Opfolda®) is interchangeable with a product that is included in the health insurance package, and to assess the therapeutic value if that is not the case.

Licensed indications
CIPA (Pombiliti®) is a long-term enzyme replacement therapy that is used in combination with the enzyme stabiliser miglustat for treating adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

Miglustat (Opfolda®) is indicated as an enzyme stabiliser for cipaglucosidase alfa in long-term enzyme replacement therapy for adults with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency).

Claim by the marketing authorisation holder
For the licensed indication, CIPA in combination with miglustat has an equivalent therapeutic value to alglucosidase alfa (Myozyme®, hereinafter ALG for short).

Background
Pompe disease is a rare, inherited muscular disease in which patients have a deficiency of the enzyme α-glucosidase. This deficiency leads to accumulation of glycogen, especially in the cardiac muscle and skeletal muscles (including the

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respiratory muscles), resulting in muscle damage and muscle weakness. Pompe disease is a life-threatening and chronically debilitating condition. A distinction is made between two forms, namely infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). CIPA+miglustat is currently not yet licensed for IOPD or children with LOPD. One difference between CIPA and ALG is that the molecular structure of CIPA contains more mannose-6-phosphate (M6P) groups. Additionally, CIPA needs to be used in combination with miglustat, which is not the case for ALG. Miglustat makes CIPA more stable and therefore effective for longer.

Package advice

The National Health Care Institute has determined that CIPA+miglustat meets the legal criterion of 'established medical science and medical practice' for the indication stated. The National Health Care Institute advises you to include CIPA+miglustat in the basic health insurance package, provided that price negotiations result in a lower price and therefore more favourable cost-effectiveness based on the maximum reference value of €80,000 per QALY, as we also recently recommended for avalglucosidase alfa (Nexviadyme®, hereinafter AVA for short) (30 May 2024). The National Health Care Institute also recommends negotiating prices at the same time for the various medicinal products for Pompe disease (CIPA+miglustat, AVA and ALG). This means that the price negotiations will also have to be reconsidered for ALG.

The National Health Care Institute also recommends that you include Opfolda® in List 1A of the GVS (Medicine Reimbursement System) in cluster 0A16AXDO V along with miglustat (generic) and Zavesca®. In addition, the National Health Care Institute recommends that you amend the List 2 conditions for miglustat as given below, on the condition that a socially acceptable price is achieved for CIPA+miglustat.

<u>Conditions for miglustat</u>
Only for insured persons

1. with Niemann-Pick disease type C
2. *with Pompe disease, where it is used in combination with cipaglucosidase alfa*

We explain the preparation of this package advice below.

General

At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. The National Health Care Institute assesses on the basis of the four package criteria[1]: effectiveness,[2]cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR)

[1] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[2] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[4] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[5] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of

advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment (scientific weighting). If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in a wider social context of the four package criteria. The Insured Package Advisory Committee (ACP) advises the Executive Board of the National Health Care Institute in this regard. This appraisal (social weighting) results in the package advice. Stakeholders are consulted during the process.

Interchangeability
Miglustat is currently included in List 1A and List 2 of the Medicine Reimbursement System (GVS) at a different dosage (100 mg). This cluster contains both generic variants with the active ingredient miglustat and a brand-name variant (Zavesca®). The current List 2 conditions are as follows: *only for an insured person with Niemann-Pick disease type C.*

Based on the criteria for interchangeability, miglustat (Opfolda®) is not interchangeable with the other medicinal products included in cluster 0A16AXDO V of the GVS that have miglustat as the active ingredient. The standard dose of miglustat has already been set to 300 mg.

Comprehensive weighting of package criteria
Scientific weighting
Established medical science and medical practice
A phase-3, randomised trial (PROPEL) was conducted in adult patients with LOPD in which CIPA+miglustat was directly compared against ALG. This study looked not only at patients who had not previously been treated with enzyme replacement therapy but also at patients who had received such treatment. That study showed that CIPA+miglustat and ALG had comparable positive effects after 52 weeks on the motor functioning and quality of life of LOPD patients. The exploratory analyses do not allow any statements to be made about possible differences in effect on pulmonary function between CIPA+miglustat and ALG.

The results show that CIPA+miglustat is at least equivalent to ALG in its effect on several crucial measures of outcome. This conclusion is in line with the view of the European Medicines Agency (EMA), which concluded that there is insufficient evidence of significant differences between CIPA+miglustat and ALG in terms of safety and/or efficacy.

Given the conclusion that the value is equivalent, CIPA+miglustat meets the criterion of established medical science and medical practice.

Cost-effectiveness
Because of the equivalent therapeutic value, the National Health Care Institute has not asked the marketing authorisation holder for a cost-effectiveness analysis. The cost-effectiveness of ALG is known to be highly unfavourable. Dutch studies into the cost-effectiveness of ALG have reported an ICER of around €1–

care in the basic health care package. It is therefore mainly a test of various implementation aspects, such as the health care organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

3 million per QALY compared to best supportive care[6,7]. This is expected to apply to CIPA+miglustat as well.

Budget impact analysis
The overall average costs per annum for CIPA+miglustat are €357,633 per adult patient with LOPD, of which €351,932 is for CIPA within medical specialist care and €5,701.28 for miglustat within the GVS. The costs per patient per year for CIPA+miglustat are virtually the same as those for ALG and AVA, which are €357,519. Based on estimates from the professional field, it is expected that 34 patients will be under treatment with CIPA+miglustat after three years. This takes into account the fact that CIPA+miglustat is becoming available at the same time as AVA. It is expected that 34 patients will be under treatment with AVA after three years as well. The comparable prices of CIPA+miglustat and ALG mean that there is a very limited budget impact of €3,210 in the third year. Introducing CIPA+miglustat into the treatment landscape involves a cost impact of approximately €10 million in the third year.

The National Health Care Institute further notes that introducing CIPA+miglustat could disrupt the entry of ALG biosimilars. Despite the fact that no biosimilars are expected for ALG, whereas ALG has been off-patent for some time, the National Health Care Institute has calculated a scenario for exploratory purposes to quantify the impact of this disruption. This shows that the additional costs for CIPA+miglustat in year 3 would range from €4 million to €16 million respectively if the prices of a biosimilar were 20% and 80% lower than the branded drug.

Social weighting
Data from the GIP database shows that €59.7 million was spent on ALG in the Netherlands in 2022 (based on the list price, i.e. excluding any price discounts). This amount was higher in the past (€68.6 million in 2020). In total, about €633 million was spent on ALG in the Netherlands between 2012 and 2023. Actual expenditure is lower in practice because of price negotiations at earlier dates; how much lower is unknown because the negotiated price is confidential. The 'Orphan Drugs in Practice Monitor for 2021' shows that ALG was the most expensive orphan drug in the Netherlands in 2020 based on the total amount declared in that year. The lower expenditure in 2022 compared to previous years may be due to more efficient use of the medication as well as a reduction in the pharmacy purchasing price. The financial arrangement for ALG was recently abandoned and the list price is currently being paid for ALG.

In the package advice for AVA, based in part on the recommendations of the Insured Package Advisory Committee, the National Health Care Institute advised your predecessor not to start the price negotiations for AVA yet but instead to combine them with those for ALG and CIPA+miglustat, if the National Health Care Institute's assessment was that CIPA+miglustat complies with established medical science and medical practice. Given that it has now been concluded that CIPA+miglustat does also comply with established medical science and medical practice, the National Health Care Institute – in line with the earlier advice –

[6] Kanters TA, Hoogenboom-Plug I, Rutten-Van Mölken MP *et al.* Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease. Orphanet J Rare Dis 2014; 9:75.

[7] Kanters TA, van der Ploeg AT, Kruijshaar ME *et al.* Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in adult patients with Pompe disease. Orphanet J Rare Dis 2017; 12:179

recommends starting price negotiations for CIPA+miglustat and AVA, combining them with the negotiations for ALG.

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Non-cost-effective standard treatment
If the National Health Care Institute considers that a new treatment has an equal value compared to the standard treatment, the price of the new treatment may not exceed the price of the standard treatment. In that case, a cost-effectiveness analysis is not relevant. After all, when a new medicinal product does not have any added value, we are not prepared to pay more for it. However, when the standard treatment is a non-cost-effective treatment that is already included in the basic health care package, the new treatment will also not be cost-effective at an equal price. This undesirable situation has been identified by the National Health Care Institute, and we are considering how best to deal with it in the future. This undesirable situation is also being discussed with the members of the WAR and the ACP.

Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as annexes (pharmacotherapeutic report and budget impact analysis).

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board