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Our reference
2024015406

Date 30 May 2024
Subject Package advice for avalglucosidase alfa (Nexviadyme®)

Dear Ms Dijkstra,

The National Health Care Institute is advising you about the assessment of avalglucosidase alfa (AVA, Nexviadyme®) as a long-term enzyme replacement therapy for treating patients with Pompe disease. The reason for this advice was AVA being placed in the lock procedure for expensive medicinal products.

Licensed indication
AVA is indicated for long-term enzyme replacement therapy in the treatment of patients with Pompe disease (deficiency of the enzyme alpha glucosidase).

Claim by the marketing authorisation holder
For the licensed indication, AVA has an equivalent therapeutic value to alglucosidase alfa (ALG, Myzome®).

Package advice
The National Health Care Institute has determined that AVA meets the legal criterion of 'established medical science and medical practice' for the indication stated. The National Health Care Institute, after advice from the Package Advisory Committee (ACP), advises you to include AVA 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. The National Health Care Institute also recommends negotiating prices simultaneously for the various medicinal products for Pompe disease (AVA, cipaglucosidase alfa and ALG). This means that the price negotiations will also have to be reconsidered for ALG.

We have explained below how we reached this package advice.

General
At your request, the National Health Care Institute assesses whether care should be part of the standard health care package from the perspective of the basic health care package paid from joint premiums.
The National Health Care Institute assesses on the basis of the four package criteria of effectiveness, cost-effectiveness, necessity and feasibility. The Scientific

Advisory Board (WAR) 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 societal context of the four package criteria. The 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.

Comprehensive weighting of package criteria

Scientific weighting

Established medical science and medical practice

Pompe disease is a rare, inherited (autosomal recessive) muscular disease in which patients have a deficiency of the enzyme alpha glucosidase. This deficiency leads to accumulation of glycogen, especially in the cardiac muscle and skeletal muscles (including the 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). The difference between AVA and ALG is that the molecular structure of AVA contains more mannose-6-phosphate (M6P) groups.

A phase-3, randomised trial (COMET) was conducted in patients with LOPD in which AVA was directly compared with ALG. This showed that AVA and ALG had similar positive effects after 52 weeks on the pulmonary function of LOPD patients. Both medicines also had similar positive effects on motor function.

An open-label, dose-escalation, phase-2 study (MINI-COMET) was also conducted in which IOPD patients who were no longer responding to ALG (or responding inadequately) were treated with AVA. Because of the study design and the very low number of patients in the MINI-COMET study, the data on AVA in IOPD patients is limited. However, this seems acceptable given the very low incidence and the young age of the patients. Also ongoing is an open-label, single-arm, phase-3 BABY-COMET study that will provide additional information about the effect of AVA in IOPD patients aged <1 year who have not previously been treated with enzyme replacement therapy. Given that the pathophysiology of IOPD is similar to that of LOPD and that the mechanism of action and pharmacokinetic profile of enzyme replacement therapy is consistent across the disease spectrum, the National Health Care Institute is sufficiently confident that the efficacy of AVA is comparable to that of ALG in IOPD patients.

The results show that AVA is at least equivalent to ALG in its effect on several crucial outcomes. AVA is therefore in line with established medical science and medical practice. 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 AVA and ALG in terms of safety and/or efficacy.

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 €1-3 million per QALY compared to best supportive care. This is expected to apply to AVA as well.

Budget impact analysis
The total average cost per year for AVA is €804,417 per IOPD patient and €335,174 per LOPD patient. The difference in costs per patient per year between IOPD and LOPD patients is driven by differences in dosage and treatment frequencies. In IOPD patients, the professional group indicates a dosage of 40 mg/kg per week. For LOPD patients, the label is followed and AVA is administered every two weeks at a dose of 20 mg/kg. The average annual cost per patient is €397,521. The costs per patient per year for ALG are the same as those for AVA.

The professional group expects 76 patients (about half of the total number of patients with Pompe disease) to be receiving AVA after three years. The equal prices of AVA and ALG mean there is a cost-neutral budget impact. Using AVA in the treatment landscape is accompanied by high macro costs (€27.3 million).

The National Health Care Institute further notes that introducing AVA could be seen as an 'evergreening'[1] strategy that 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 AVA in year 3 would range from €5.5 million to €21.9 million respectively if the prices of a biosimilar were 20% and 80% lower than the branded drug. The budget impact analysis does not take into account the substitution by future competitive medicinal products.

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 (PPP). The financial arrangement for ALG was recently abandoned and the list price is currently being paid for ALG.

The Package Advisory Committee advises you not to include AVA in the basic health insurance package, unless price negotiations result in a lower price and therefore more favourable cost-effectiveness based on the maximum reference value of €80,000 per QALY.

It is also important to note that a new medicinal product was licensed in May 2023 for adults with LOPD: cipaglucosidase alfa (Pombiliti®) in combination with the enzyme stabiliser miglustat (Opfolda®). It is expected that this medicine will also be licensed in the future for treating children with LOPD and children with IOPD. The National Health Care Institute has already started assessing this medicine. If it transpires that cipaglucosidase alfa in combination with miglustat

[1] Evergreening is a strategy used by manufacturers to impede competition to their medicinal products from biosimilars and generics by means of additional patents. From: SiRM. (N)evergreening: Analysis of evergreening and policy options for the National Health Care Institute, by SiRM 2024.

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can acquire the same place as ALG and AVA, in whole or in part, it will provide opportunities for competition in the market. The ACP therefore recommends keeping AVA in the 'lock' until the third medicinal product for treating Pompe disease (cipaglucosidase alfa) has also been assessed by the National Health Care Institute. Depending on the outcome of that assessment, this will promote competition and improve the options during negotiations. The ACP recommends combining the price negotiations for AVA with those for cipaglucosidase alfa and ALG.

The National Health Care Institute has adopted that advice and recommends not starting the price negotiations for AVA yet, instead combining them with those for ALG and cipaglucosidase alfa, provided the National Health Care Institute assesses that cipaglucosidase complies with established medical science and medical practice.

Non-cost-effective standard treatment
If the National Health Care Institute concludes that a new treatment has equivalent value to the standard treatment, the price of the new treatment must not exceed the price of the standard treatment. A cost-effectiveness analysis is not relevant in such cases. After all, if a new medicinal product has no added value, we are not willing to pay a higher price for it. However, if the standard treatment is not cost-effective and it is already included in the basic package, the new treatment will also not be cost-effective at the same price. The National Health Care Institute has flagged this situation as undesirable and we are considering the best way of dealing with it in future. This undesirable situation is also under discussion with the members of the Scientific Advisory Council and Package Advisory Committee.

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

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board