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National Health Care Institute
Care
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Contact
Ms M.J.S. de Vries
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Our reference
2024027390

Date 21 August 2024
Re: Package advice for olipudase alfa (Xenpozyme®)

Dear Ms Agema,

The National Health Care Institute advises you on the assessment of olipudase alfa (Xenpozyme®) as long-term enzyme replacement therapy for the treatment of patients with *Acid Sphingomyelinase Deficiency* (hereafter abbreviated as ASMD). ASMD is also called Niemann-Pick disease. The reason for this advice was the placement of olipudase alfa in the lock procedure for expensive medicinal products.

ASMD is a very rare, hereditary metabolic disorder where a genetic error in a specific enzyme results in harmful accumulation of certain fats in the cells of the spleen, liver and lungs. In the worst case, there is also accumulation in the brain and nerves. The accumulation of these fats in tissues and organs reduces the function of these organs and ultimately leads to complications such as liver failure, interstitial lung disease and bleeding. Accumulation in the brain leads to neurological deterioration and this can affect the motor skills and cognitive development of children. In the Netherlands, 28 patients have been diagnosed with ASMD. There are three different forms of ASMD. Type A is the most serious form of the disease and these patients have very little to no enzyme activity. The symptoms start after birth and patients die before their third year of life. Type B is the most heterogeneous form of the disease. These patients still have sufficient enzyme activity in the brain that prevents them from developing neurological symptoms. Disease progression is slower than in type A. There is a wide variation between patients in the severity of symptoms, disease course and life expectancy. The age of diagnosis varies from young children aged several months to middle-aged adults. Type A/B is a hybrid of the other two forms. Unlike patients with type B, these patients have neurological symptoms and lower enzyme activity than patients with type B. The neurological symptoms can be progressive but can also remain stable for years or worsen very slowly. The diagnosis of type A/B is made at a younger age, and patients also die at a younger age than patients with type B ASMD.
This assessment only applies to type A/B or type B.

Registered indication
Olipudase alfa is indicated as an enzyme replacement therapy for the treatment of non-central nervous system manifestations of Acid Sphingomyelinase Deficiency (ASMD) in paediatric and adult patients with type A/B or type B.

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Claim by the marketing authorisation holder

Olipudase alfa has an added therapeutic value compared to the current available treatment (best supportive care) for the therapeutic indication.

Package advice

The National Health Care Institute has determined that olipudase alfa meets the legal criterion of 'established medical science and medical practice' for the therapeutic indication. The National Health Care Institute advises to include olipudase alfa in the basic health care package, provided that price negotiation results in a lower price and therefore more favourable cost-effectiveness based on the maximum reference value of 80,000 euro per QALY. Based on the marketing authorisation holder's file, we would not be paying €80,000 (the maximum reference value) for a QALY, but at least 12 times (in children) to at least 20 times (in adults) as much. It is the opinion of the National Health Care Institute, based on arguments from both the scientific and social weighting, that a price reduction is required that amounts to a price at least 12 times lower than the asking price.

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) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. 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 the wider societal 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 societal 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

The effectiveness and safety of olipudase alfa for the treatment of ASMD type A/B or type B was investigated in one randomised placebo-controlled study (ASCEND)

[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 care in the basic health care package. It is therefore mainly a test of a number of 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).

in adults and in one open-label single-arm study (ASCEND-PEDS) in children. For the treatment of children, the effectiveness on some outcome parameters was compared with a historical control cohort reflecting the natural course of a longitudinal prospective study (SPHINGO-100). As there were different studies for adults and children, the results are displayed separately for both patient groups. Both studies had a follow-up duration of 52 weeks.

The results from the studies show that olipudase alfa provides clinically relevant reductions in spleen and liver volumes in adults and children with ASMD type A/B and type B. In addition, olipudase alfa also provides clinically relevant improvements in lung diffusion capacity in adults. The effects seen on spleen and liver volumes in children are approximately the same as those observed in adults. There is therefore sufficient confidence that the effectiveness of olipudase alfa in children with ASMD type A/B and type B is similar to that of adults with the same disease, despite the very low quality of evidence in children.

Olipudase alfa is generally well tolerated and causes few intervention-related serious adverse effects. None of the patients in the clinical trials discontinued treatment due to adverse effects.

No data are currently available as to whether treatment with olipudase alfa also leads to a reduction in the number of ASMD-related complications (such as pneumonia, liver failure and bleeding), an improvement in life expectancy, and a reduction of the mortality risk. In the open-label follow-up studies of the ASCEND and ASCEND-PEDS studies, none of the patients had died after 2 years of treatment with olipudase alfa. Also, the effects found on spleen volume, lung diffusion capacity and liver volume were at least maintained during this period and even seemed to improve.

Despite the clinically relevant effects on the different surrogate outcome parameters, it remains unclear which patients benefit the most from treatment with olipudase alfa. ASMD has a very multifaceted disease in which the level of enzyme activity determines the extent to which the patient experiences disease symptoms. Olipudase alfa does not cross the blood brain barrier and thus has no effect on the neurological symptoms of the disease. For all these reasons, agreements should be made to ensure that only those patients who benefit from this treatment are treated. The centre of expertise has already developed concept appropriate use agreements in which the above considerations are already included.

Budget impact
On the basis of estimates from the expertise centre, the National Health Care Institute estimates that 20 patients will be treated with olipudase alfa in the third year after market introduction: Treatment costs vary based on the patient's body weight, ranging between €526,991 and €819,764 per patient per year. In total, the budget impact will reach €13.1 million in the third year after market introduction.

Cost-effectiveness
In this case, the National Health Care Institute has chosen to write a brief note, instead of a complete cost-effectiveness report. A full pharmaco-economic report does not seem appropriate in this case because 1) it is clear that the new

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treatment is not cost-effective, and 2) a comprehensive assessment of the cost-effectiveness of olipudase alfa by the National Health Care Institute will not provide reliable advice on a socially acceptable price. The National Health Care Institute is therefore of the opinion that a complete pharmaco-economic report will add little compared to the analysis described in the note.

This means that the National Health Care Institute did not make a substantive assessment of the cost-effectiveness analysis submitted by the marketing authorisation holder. The results presented below are as reported by the marketing authorisation holder.
The calculated ICER, as reported by the marketing authorisation holder, amounts to approximately €1.60 million per additional Quality-Adjusted Life Year (QALY) for adults and €1.07 million/QALY for children, compared to best supportive care. The relevant reference value (calculated by the marketing authorisation holder) appears to be €80,000/QALY. Thus, the ICER calculated by the marketing authorisation holder is at least a factor of 12 (in children) to 20 (in adults) above the reference value of €80,000/QALY related to the highest disease burden category.

The National Health Care Institute will not comment on the methodological quality of the analysis submitted by the marketing authorisation holder. However, the National Health Care Institute has nevertheless decided that the submitted analysis contains sufficient leads for decision-making. On this basis, the National Health Care Institute has determined that treatment with olipudase alfa is not cost-effective.

Societal weighting
Olipudase alfa is a first, promising treatment for ASMD, a serious ultra-rare hereditary disorder, that may have an effect on disease progression. In addition to a high burden of disease, in absolute terms, these patients also lose many QALYs. The asking price of olipudase alfa is extremely high for life-long treatment (€526,991 to €819,764 per patient per year). The National Health Care Institute understands that the cost of development is less recoverable because it is a medicinal product for an ultra-rare condition, but the effects should outweigh the cost.

Appropriateness
Because olipudase alfa has no effect on the neurological symptoms of the disease, there is a risk that although patients may live longer, they may do so with severe neurological symptoms. The National Health Care Institute considers it necessary to define the agreements on the use of the indication committee, start and stop criteria, data collection and monitoring through appropriateness arrangements. The physicians' association has already submitted a valid concept to the National Health Care Institute. In the context of cyclical package management, the results of olipudase alfa could be monitored over time and it could be checked whether new data would lead to a change in conclusions.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board