National Health Care Institute

> Return address PO Box 320, 1110 AH Diemen

Minister of Medical Care
PO Box 20350
2500 EJ THE HAGUE

2024021900

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
K. Watson
warcg@zinl.nl

Our reference
2024021900

Date 12 June 2024
Re: Package advice pegunigalsidase alfa (Elfabrio®) for the treatment of adult patients with Fabry disease

Dear Ms Dijkstra,

This message contains the package advice on pegunigalsidase alfa (Elfabrio®) for the long-term treatment of adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase-A). The reason for this advice was the placement of pegunigalsidase alfa in the lock procedure for expensive medicinal products.

Registered indication
Pegunigalsidase alfa has been registered for long-term enzyme replacement therapy (ERT) in adult patients with a confirmed diagnosis of Fabry disease (deficiency alpha-galactosidase-A).[2].

Claim by the marketing authorisation holder
Pegunigalsidase alfa has an equivalent value to agalsidase beta (Fabrazyme®).

Package advice
The National Health Care Institute advises you to include pegunigalsidase alfa in the health insurance package for long-term enzyme replacement therapy in adult patients with a confirmed diagnosis of Fabry disease (deficiency of alpha-galactosidase), provided that price negotiation results in a lower price and therefore a more favourable cost-effectiveness. The development of this package advice is explained 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-

[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.

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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. Interested parties were also consulted in this context.

Comprehensive weighting of package criteria

Established medical science and medical practice

Fabry disease is a rare, hereditary metabolic disease in which the enzyme alpha-galactosidase-*A*, which is essential to break down waste from cells, is inactive or less active. As a result, fatty substances accumulate in cells of different organs, such as the brain, heart and kidneys. As a result, these organs often do not work properly at a later age. The life expectancy of patients with Fabry disease is 10-20 years less than that of the general population.

In the treatment of Fabry disease, in addition to symptom control (e.g. for nerve pain), enzyme replacement therapy (ERT) is key. ERT aims to reduce symptoms and slow disease progression. In this treatment, agalsidase alfa (Replagal®) or agalsidase beta (Fabrazyme®) is administered intravenously every two weeks. According to the Expertise centre on Fabry disease (Amsterdam-UMC; SPHINX Lysosome centre), agalsidase beta is preferred. This would better inhibit the deterioration in renal function and prevent clinical events[6],

The effectiveness and safety of pegunigalsidase alfa were investigated in a phase 3 direct comparative study (BALANCE) with agalsidase beta in 77 adult patients with Fabry disease. In this international, multicentre, double-blind, randomised clinical trial, results for pegunigalsidase alfa and agalsidase beta were similar at 24 months with regards to the outcome parameters for cardiac and renal function, pain and quality of life. Intervention-related adverse events and the number of discontinuations also matched. However, the study population was not fully representative of Dutch patients with Fabry disease in terms of patient characteristics. The study results are therefore only partly directly applicable to the treatment of Fabry disease in the Netherlands.

The effects of pegunigalsidase alfa have also been researched in two switch-over phase 3 studies. The BRIDGE study enrolled 22 adult patients with Fabry disease who had previously been treated with agalsidase alfa. The BRIGHT study enrolled 30 adult patients with Fabry disease who had been treated with agalsidase alfa or agalsidase beta for at least 3 years. Due to the small patient populations, the lack of direct comparative treatment and the inclusion of patients taking agalsidase alfa (instead of the clinical standard agalsidase beta), the effects observed in these studies are also of limited significance for the clinical practice in the Netherlands. Although infusion-related reactions occurred in all ERTs, the incidence was lowest with pegunigalsidase alfa (6.3%) and highest with agalsidase beta (67%).

Based on the available data, the National Health Care Institute concludes that

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

[4] Necessity deals with both the medical necessity and the result of 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).

[6] e.g. hospital admissions due to heart failure or arrhythmias.

pegunigalsidase alfa is equivalent to agalsidase beta in the treatment of adult patients with Fabry disease. During the consultation, the professional association also considered it likely that the effects of pegunigalsidase alfa in the clinical practice in the Netherlands will be similar to the existing ERTs. Therefore, in patients with Fabry disease, pegunigalsidase alfa meets the established medical science and medical practice.

Budget impact analysis
Approximately 230 Fabry patients are currently being monitored by the Expertise centre (Amsterdam UMC). Approximately 110 of them are being treated with agalsidase beta. Based on equal therapeutic effectiveness, the majority of them do not appear to prefer either pegunigalsidase alfa or agalsidase beta. According to the Committee for Orphan Drugs (Commissie Wees), a switch to pegunigalsidase alfa could be considered directly for a small number of patients (estimated 0 – 3 per year) with uncontrollable infusion reactions and/or with many antibodies to agalsidase beta. There is no immediate clinical need for this for the other patients. The Commissie Wees also first carefully wants to collect additional data on the effectiveness of pegunigalsidase alfa in, among others, untreated patients in Dutch practice. In this context, the National Health Care Institute currently assumes that *no more than* 8, 12 and 15 Fabry patients will be treated with pegunigalsidase alfa in years 1, 2 and 3 after reimbursement, respectively.
The costs of pegunigalsidase alfa and agalsidase beta are €153,485 and €159,719 per patient per year, respectively. This results in possible macro costs for pegunigalsidase alfa of *no more than* €2.3 million in the 3rd year after reimbursement. The budget impact including substitution then results in estimated cost savings of €93,506.
The greatest uncertainty in this budget impact analysis is related to the speed of market penetration.

Cost-effectiveness
Due to its equal therapeutic value, the National Health Care Institute has not asked the marketing authorisation holder for a cost-effectiveness analysis. In 2012, the Health Care Insurance Board (CVZ; the legal predecessor of the National Health Care Institute), advised you, after testing agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) against the aforementioned four package criteria, on their reimbursement via the basic health care package for Fabry patients. At that point, an incremental cost-effectiveness ratio (ICER) of €3.3 million per QALY was established. This was mainly determined by their high costs and their relatively limited (clinical) impact. The CVZ saw *'insufficient reason to find the unfavourable cost-effectiveness acceptable'*.[7] Since collective funding was the only way to keep these orphan drugs available to these patients, CVZ recommended their reimbursement on conditions.

This dilemma recurs in the present advice on pegunigalsidase alfa. The price and effectiveness of pegunigalsidase alfa and agalsidase beta are similar. This means neither of them is cost-effective. The National Health Care Institute therefore advises you to negotiate prices for pegunigalsidase alfa and agalsidase beta to establish a price that results in a more favourable cost-effectiveness. The National Health Care Institute suggests that these negotiations could take place

[7] Advice regarding agalsidase alfa (Replagal®) and agalsidase beta (Fabrazyme®) in patients with deficiency of α-galactosidase A (Fabry disease) dated 29 November 2012.

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decentrally. In this context, the National Health Care Institute notes that the patent for agalsidase beta has already expired. Although a biosimilar has been on the market in Japan since 2018, this has not yet been the case in the Netherlands (and the rest of Europe).

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.

Conclusion
The National Health Care Institute advises you to include pegunigalsidase alfa in the health insurance package for the treatment of adult patients with Fabry disease, provided that (decentralised) price negotiation results in a lower price and therefore a more favourable cost-effectiveness.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board