Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

Date 15 July 2024
Re: Package advice lock procedure medicinal product etranacogene dezaparvovec (Hemgenix®)

Dear Ms Agema,

The National Health Care Institute advises you on the assessment of etranacogene dezaparvovec (Hemgenix®) for the treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors. Haemophilia B is a rare genetic disease. Patients produce no or fewer coagulation factors that are essential for the proper coagulation of the blood. Some 180 people in the Netherlands suffer from haemophilia B, of which about 85 have a serious form of the disease. The reason for this advice was the placement of etranacogene dezaparvovec in the lock procedure for expensive medicinal products.

This assessment is part of a joint evaluation under the *Beneluxa Initiative*[1]. In this initiative, the National Health Care Institute collaborates with other EU countries on, among other things, the joint assessment of the reimbursement of medicinal products. The National Health Care Institute is committed to this collaboration in view of the forthcoming *Health Technology Assessment Regulation* (HTAr)[2,3] which will take effect on 11 January 2025. In this case, it was a collaboration between the Netherlands and Belgium. The attached reports were used by the National Health Care Institute and the Belgian Medicine Reimbursement Commission (CRM). All assessment procedures run parallel according to national legislation.

Registered indication
Etranacogene dezaparvovec (ED) is indicated for the treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

Claim by the marketing authorisation holder
Reimbursement is requested for patients from the registered indication who have a severe manifestation of the disease (with spontaneous bleeding). The marketing authorisation holder claims an equivalent value to the current prophylaxis treatment with coagulation factor IX concentrates.

1 https://beneluxa.org/
2 https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment_en
3 https://www.zorginstituutnederland.nl/over-ons/programmas-en-samenwerkingsverbanden/eu-htar

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Package advice

The National Health Care Institute advises you to include etranacogene dezaparvovec (Hemgenix®) in the basic healthcare package for this indication after successful price negotiations.

The National Health Care Institute has established that etranacogene dezaparvovec for the above indication meets the legal criterion of 'established medical science and medical practice' and that there is an equal value compared to the standard treatment with coagulation factor IX concentrates. In view of the equal value, the net expenditure for medicinal products to treat these patients should not increase.

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[4]: effectiveness[5]cost-effectiveness[6], necessity[7] and feasibility[8]. 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 appraisal results in the package advice. Stakeholders are consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

Haemophilia B is a very serious disease; without treatment, it is life-threatening. Since the availability of the current standard treatment (coagulation factor IX concentrate), the life expectancy of patients with haemophilia B is almost comparable to that of the average population. ED is a single gene therapy studied in 54 patients in a single arm study. The effectiveness was assessed through intrapatient comparison. At 24 months post-treatment, ED resulted in a clinically relevant reduction in annual incidences of bleeding, compared to prophylactic treatment with coagulation factor IX concentrate given to these patients prior to

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

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

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

[7] 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).

[8] 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).

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treatment with ED. Of the patients receiving the single treatment, 2 still had to continue prophylactic treatment with coagulation factor IX concentrates. ED demonstrated a statistically significant but not clinically relevant improvement in quality of life based on the disease-specific quality of life score after 12 months of follow-up. On other generic scales, no significant differences in scores were observed. There have been no intervention-related serious adverse effects so far.

Due to the single-arm design of the study and the relatively short follow-up time for a one-time administered treatment that is intended to potentially last for life, the quality of the evidence is considered to be very low. Based on the available data, it can be concluded that ED is at least as effective for the critical outcome parameters as prophylactic treatment with coagulation factor IX concentrates, with no increase in adverse effects. It thus complies with the established medical science and medical practice (SWP). On the other hand, the relatively short follow-up results in a high degree of uncertainty about the duration of the effectiveness. Additionally, there are no long-term safety data. Based on the 2-year follow-up, there is sufficient confidence that the effect will last at least 4 to 5 years. There is too much uncertainty to draw conclusions about the duration of the treatment effect beyond 4 to 5 years after infusion.

Cost-effectiveness
Since ED has an equal value compared to the standard treatment, the cost-effectiveness of ED has not been assessed by the Beneluxa assessment team. The cost-effectiveness of the comparative treatment is also unknown.

Budget impact analysis
The National Health Care Institute estimates that a total of 26 patients will be treated with ED in the Netherlands during the first three years after inclusion in the package. The asking price for ED is €2.8 million per patient. Currently, the costs of prophylactic treatment range from €150.488 to €350.526 per patient per year, which will be substituted. The budget impact then amounts to €36.5 to €39.6 million in year 1 and €-1.2 to €4.3 million in year 3.

In the budget impact analysis, the National Health Care Institute shows the costs of factor IX concentrates at different time horizons, based on the list prices (scenario 1) and based on an estimate of the negotiated prices (scenario 2). In light of the principle that, if the value is equal, the costs of the medicinal product in the new situation are not higher than in the current situation and the outcomes of the SWP assessment (proven effectiveness of 4-5 years), scenario 1 (list prices) results in a maximum price for ED of €1.4 to 1.8 million and in scenario 2 (real estimate based on negotiated prices) in €604,574 to €757,302.

The marketing authorisation holder indicates that the asking price of ED (€2.8 million per patient) is based on the cost of 10 years of prophylactic treatment. calculated on the basis of the list prices of coagulation factor IX concentrates. The marketing authorisation holder proposes to link the payments for the medicinal product to a 10-year pay-for-performance agreement.

When considering the price negotiations, the National Health Care Institute advises to take into account other medicinal products that may become available for this indication.

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. The National Health Care Institute has identified this undesirable situation, 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

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