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

2023042296

National Health Care Institute

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
Ms Dr H. Schelleman
warcg@zinl.nl

Date 16 November 2023
Re: Package advice emicizumab (Hemlibra®)

Our reference
2023042296

Dear Mr Kuipers,

The National Health Care Institute advises you on emicizumab (Hemlibra®) for routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII inhibitors who have moderate disease with severe bleeding phenotype. The reason for this advice was the placement of emicizumab in the lock procedure for expensive medicinal products.

The National Health Care Institute has concluded that emicizumab meets the statutory criterion of 'established medical science and medical practice' for this indication. For routine prophylaxis of bleeding episodes, emicizumab has an equal value to that of factor VIII. It is an effective medicinal product that reduces the number of bleeding episodes in patients with haemophilia A with severe bleeding phenotype. A disadvantage is that the treatment is more expensive than that with the current usual care. The National Health Care Institute therefore recommends that emicizumab should only be included in the basic health care package if the net price of prophylactic treatment with emicizumab does not exceed that of prophylactic treatment with factor VIII. It is important to note that the treatment centres have agreed on large discounts with the various factor VIII manufacturers and with the emicizumab manufacturer, which has resulted in a significant reduction in the net price of factor VIII and emicizumab. However, the National Health Care Institute has been made aware by the parties that the price of factor VIII has decreased even further since the initial price negotiation. I therefore recommend that we renegotiate the price for this indication in a decentralized manner.

I would like to explain the findings and final conclusion below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the health insurance package from joint premiums. The National Health Care Institute considers this both in the scientific sense and in terms of public support, and also reviews the aspects of efficiency and transparency. The National Health

Care Institute assessed emicizumab on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute is advised by its Scientific Advisory Board (WAR) for the review of data according to the established medical science and medical practice. Relevant parties were also consulted in this context.

Comprehensive weighting of package criteria

Established medical science and medical practice

Haemophilia A is a rare, recessive hereditary, X-linked blood clotting disorder due to the absence or deficiency of coagulation factor VIII. Based on the remaining factor VIII plasma concentration, haemophilia A can be divided into severe (remaining factor VIII plasma concentration <1%), moderate (1-5%) and mild (5-40%). This classification was applied when deciding whether prophylactic treatment is indicated. However, the current policy in the Netherlands is to base this decision on the occurrence of joint or muscle bleeding and the associated cause.

In patients with moderate haemophilia A, the standard treatment is routine prophylaxis with coagulation factor VIII. In the exploratory HAVEN 6 study, the effect of emicizumab was assessed in 37 subjects with moderate haemophilia A who received prophylactic treatment with coagulation factor VIII. The calculated median annual bleeding rate was 1.5 with emicizumab and 2.2 with factor VIII. Quality of life appeared similar before and after the start of the emicizumab treatment, despite the fact that emicizumab has an easier administration route and lower administration frequency than factor VIII. No further serious adverse events related to treatment occurred during the study.

In 2020, the National Health Care Institute concluded that in patients with severe haemophilia A without inhibitors, emicizumab prophylaxis is at least as effective as factor VIII prophylaxis without increased side effects. Since this population also has a severe bleeding phenotype and the same starting criteria apply, the National Health Care Institute has taken into account the study data for this indication in its decision.

Based on all available data, the National Health Care Institute concludes that emicizumab is equivalent to factor VIII for routine prophylaxis of bleeding episodes in patients with haemophilia A without factor VIII inhibitors who have moderate disease with severe bleeding phenotype. As such, emicizumab meets the established medical science and medical practice for this indication.

Budget impact

Approximately 63 haemophilia A patients without coagulation factor VIII inhibitors with moderate disease and with severe bleeding phenotype are expected to be prophylactically treated with emicizumab in the third year after inclusion in the basic health care package. This results in additional costs of approximately €3.3 million in the third year after reimbursement.

Cost-effectiveness

Due to the conclusion that emicizumab has an equal value to prophylaxis with factor VIII, a cost-effectiveness analysis is not deemed necessary for

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

[2] Established medical science and medical practice assessment: updated version (2023). National Health Care Institute. Via www.zorginstituutnederland.nl

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

reimbursement.

Appropriateness agreements
In 2020, the health care insurers, in collaboration with the centres of expertise, concluded an orphan drug arrangement for emicizumab for severe haemophilia A. According to the agreements, the centres produced an annual aggregated report on the use of emicizumab in the Netherlands. Based on these reports, we have obtained sufficient insights to evaluate the use of this medicinal product three years after its market introduction.

Evaluation of appropriateness of emicizumab three years after market introduction
In the Netherlands, 1,447 participants with haemophilia A were registered in the Dutch Haemophilia Register (HemoNED Register') in the second quarter of 2023. A total of 653 participants received prophylactic treatment, 337 of whom were treated with emicizumab.
Of the 337 registered users, 321 (95%) had the indication severe haemophilia A. In 35 users, the presence of an inhibitor was the main reason for initiating emicizumab. Based on these data, the National Health Care Institute has calculated that approximately 280 patients with severe haemophilia A without inhibitors will be taking emicizumab in the third year after inclusion in the package. In the 2020 budget impact analysis, the National Health Care Institute assumed that there would be 350 users, three years after market introduction. On the basis of these data, the National Health Care Institute concludes that the medicinal product has been introduced gradually, as expected.
In addition, there are no signs that the medicinal product is not effective or safe. In total, only 23 patients have discontinued treatment, of which 1 patient reported this to be due to side effects.
The HemoNED Foundation report does not include data on the budget impact of emicizumab. However, the report did provide more insight into the administration frequency (49% of subjects take emicizumab once every 2 weeks) and dosage (average 1.46 mg/kg/week). The National Health Care Institute used the preliminary figures in the GIP database about the healthcare costs of factor VIII (B02BD02) and emicizumab (B02BX06) for an estimation of the budget impact. Based on these provisional figures, the overall budget impact of these medicinal products appears to have increased from €75.35 million in 2019 to €102.39 million in 2021, despite a sharp decrease in the budget impact of factor VIII following the introduction of emicizumab. Some of this increase may be explained by the fact that the price reductions have not yet been (fully) incorporated into these provisional figures. The parties further indicated that the price of factor VIII has decreased in recent years.
Based on this information, it is important that the moderate haemophilia indication is renegotiated in a decentralized manner. The National Health Care Institute is therefore of the opinion that emicizumab should only be included in the basic health care package if the net price of a prophylactic treatment with emicizumab does not exceed that of the prophylactic treatment with factor VIII.

Updating the appropriateness agreements
For the indication in question, the National Health Care Institute considers it important that the professional group describes the starting criteria for prophylactic treatment with a clear definition of severe bleeding phenotype in patients who have moderate disease with factor VIII. The National Health Care Institute will contact the relevant parties for this purpose.

National Health Care Institute

Date
16 November 2023

Our reference
2023042296

Package advice
The National Health Care Institute advises the Minister to include emicizumab in the basic health care package for the indication mentioned here, provided the price negotiations with the marketing authorisation holder result in a net price that does not exceed the price of the existing factor VIII prophylaxis.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board