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*2023013133*

**National Health Care Institute**
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**Contact**
Ms. A. Link

Date 8 May 2023
Re: Cyclical package management: evaluation of orphan drugs arrangement eculizumab for the aHUS indication

**Our reference**
2023013133

Dear Mr Kuipers,

I would like to offer you the 'Evaluation of the orphan drugs arrangement eculizumab for the aHUS indication'. This evaluation is an example of cyclical packet management. The National Health Care Institute intends to monitor and evaluate already included medicinal products more often and on a risk-focused basis.

Eculizumab is an expensive orphan drug that has been registered, among other things,for the treatment of patients with atypical Haemolytic Uraemic Syndrome (aHUS).In 2016, when eculizumab was reimbursed as part of specialist medical care, the National Health Care Institute placed eculizumab on the agenda for the indication aHUS as part of its risk-focused package management. An assessment was appropriate due to the high cost per patient per year (€478,000) and the consequent very unfavourable cost-effectiveness and the high macro budget (€34 million). At that time, the National Health Care Institute proposed to continue to reimburse eculizumab for this indication on the condition that patients would be treated in accordance with the Dutch treatment guideline (which was also supported by the patient organisation) and that a study would be carried out on the cost-effectiveness of eculizumab when used in accordance with the Dutch treatment guideline. This was relevant because the Dutch treatment guideline, in terms of treatment duration (three months if possible) deviated significantly from the treatment plan recommended by the marketing authorisation holder (life-long every two weeks). In the context of cyclical package management, we have evaluated the results of the research and the experiences with the orphan drugs arrangement. Below are the main conclusions and recommendations. These conclusions and recommendations are supported by the Insured Package Advisory Committee (ACP) (see annex for full ACP advisory report).

*No reason to reconsider package advice 2016*
The National Health Care Institute compliments the centre of expertise and the patient organisation on the way in which appropriate care for aHUS patients has evolved over the years and is still being optimised.

Dutch studies have shown that in almost all cases, life-long treatment every two weeks is not necessary and treatment could be discontinued after approximately 3 months. The risk of the aHUS reoccurring is expected to be between 20 and 28%. In these cases, treatment is restarted (short-term). In addition to patient convenience, the average cost of medicinal products per patient per year during the study (follow-up 25 months) is significantly lower, at around €121,000, than the €478,000 per patient per year in case of life-long treatment every two weeks. It should be noted that the focus of costs is in the first year and the costs per patient will decrease in case of a longer follow-up with a recurrence risk of 20-28%. As a result of the lower average cost per patient, the budget impact is also significantly lower, €8 million, in 2021. Approximately five patients per year are diagnosed with aHUS.
In view of these positive results and the limited risk for the basic health insurance, the National Health Care Institute does not see any reason at this time to revise the 2016 package advice.

*Continuing orphan drugs arrangement*
Given the small number of patients treated in accordance with the Dutch treatment guideline and the limited international experience gained in the temporary treatment of aHUS patients, the National Health Care Institute advises the occupational group/centre of expertise to continue to check individual cases, in consultation with the indication committee, to see whether discontinuation or reduction of the dose/treatment frequency is justified in individual cases. Data collection and international collaboration remain important in this respect. The National Health Care Institute therefore wants to maintain the agreements from the orphan drugs arrangement (start and stop criteria, indication committee and data collection).

*Further optimization of appropriate care possible*
We conclude that the arrangements from the orphan drugs arrangement contribute to appropriate care, but as mentioned earlier in the monitors for orphan drugs, improvements are possible.

- *The right care in the right place: under the guidance of the centre of expertise*

Looking at the appropriate care principle 'the right care in the right place', the National Health Care Institute believes that treatment with eculizumab should remain possible in all UMCs due to the importance of rapid access to eculizumab. However, given the low number of new patients per year (five on average), the National Health Care Institute also believes that treatment during the first treatment period after diagnosis (about three months) should only be carried out under the responsibility of the centre of expertise. This has the added advantage that this will facilitate data collection and thus contribute to further optimisation of the treatment. The National Health Care Institute advises health care insurers to make arrangements with the UMCs when purchasing eculizumab.

- *Less non-commitment and need for structural funding agreements*

The National Health Care Institute shares the concerns of the centre of expertise regarding the possible lack of (complete) compliance with the arrangements in the orphan drugs arrangement by some of the UMCs. As previously concluded in the monitor for orphan medicinal products, the conditions of the orphan drugs

arrangement are non-binding. Legal anchoring of such conditions would limit the non-commitment of these conditions. Until the non-commitment of such conditions is determined, we ask health care insurers to monitor compliance with these agreements. Health care insurers have indicated that they will do this and have made a change to the reimbursement system to verify that a patient has been discussed by the indication committee.

In order to (continue to) optimise care, it is necessary to have an overview of the data from all patients. The non-committing nature of the agreements and the lack of structural funding for data collection and evaluation is a recurring bottleneck. The results of this orphan drugs arrangement show that structural data collection contributes to increasing the efficiency of care for aHUS patients. For example, short-term treatment has reduced eculizumab spending by around €14 million over 4.5 years. The use of an indication committee has also proved to be of added value. Not only for the diagnosis of aHUS, but even more often for establishing alternative diagnoses (in approximately 90 patients), and thus limiting the use of eculizumab. The National Health Care Institute therefore reiterates the recommendation from previous monitors and the advice of the Managing Registries programme that structurally more money is needed for setting up registrations, and for carrying out appropriate use agreements and research into further optimisation.

*Financial arrangement*
If, at the end of the financial arrangement, competition (new products or the advent of biosimilars) has not been sufficiently developed or the public list price of eculizumab has not been significantly reduced, the National Health Care Institute considers a significant price reduction to be appropriate for the following reasons:
- The global revenues for eculizumab were around $4 billion in 2021. The declared amount in the Netherlands (more than €340 million) since 2008 is also high. It can be concluded that it is likely that the development costs have now been recovered.
- The total budget impact in the Netherlands of all indications is high (€33-€38 million per year). Partly because the negotiated price of eculizumab is confidential, it is not possible to make a ruling on the cost-effectiveness for the different indications. In 2017, the National Health Care Institute recommended for the PNH indication that a 90% price reduction was necessary for it to be considered a cost-effective treatment. If this price reduction is not achieved, the high budget impact will lead to a significant displacement of other care. In that case, it is important to keep the overall budget impact as low as possible.
A framework is currently being developed to achieve socially responsible pricing. Based on that, the National Health Care Institute may be able to provide concrete pricing advice in the future.

*Progress on other orphan drugs arrangements*
There are currently nine orphan drugs arrangements (negotiated by the National Health Care Institute or health care insurers) and a number of arrangements are being prepared. The National Health Care Institute is monitoring the progress of these arrangements. If warranted on the basis of the interim/final reports, the National Health Care Institute will schedule the orphan drug for evaluation. Reasons for the scheduling can be, for example, that the orphan drug is not being applied in accordance with the start and stop criteria, that the cost per patient or the macro budget are significantly higher than expected, or a lack of long-term

(cost) effectiveness of the medicinal product. Depending on the results of the evaluation, the National Health Care Institute will consider which instrument should be used to improve appropriate care, which may include adapting the arrangement in consultation with the parties, or carrying out a reassessment.

Yours sincerely,

**National Health Care Institute**
Package

**Date**
8 May 2023

**Our reference**
2023013133

Sjaak Wijma
*Chairperson of the Executive Board*

Annexes:

1. Evaluation of orphan drugs arrangement eculizumab for the aHUS indication
2. ACP advice evaluation of orphan drugs arrangement eculizumab aHUS