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National Health Care Institute
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2023047538

Our reference
2023047538

Date 12 December 2023
Re: Package advice for the lock procedure medicinal product ravulizumab (Ultomiris®)

Dear Mr Kuipers,

The National Health Care Institute advises you about the evaluation of the medicinal product ravulizumab (Ultomiris®) for the treatment of adult patients with refractory generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

This advice was prompted by the inclusion of ravulizumab in the lock procedure for expensive medicinal products, excluding ravulizumab for all future indications.

Registered indication:
Ravulizumab has been registered for several indications; the National Health Care Institute has previously advised you on the indications paroxysmal nocturnal haemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (aHUS). Ravulizumab (Ultomiris®) is now also indicated as an additional standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor (AChR) antibody-positive.

The marketing authorisation holder requests reimbursement for additional standard therapy in the treatment of adult patients with *refractory* gMG who are anti-acetylcholine receptor (AChR) antibody-positive.

Package advice
The National Health Care Institute has established that ravulizumab for the above indication meets the legal criterion of 'established medical science and medical practice' and that there is a therapeutic equal value. The National Health Care Institute advises you to include ravulizumab (Ultomiris®) in the basic health care package for the stated indication, provided that the price negotiations successfully deliver a net price for a treatment with ravulizumab that does not exceed that of the treatment with eculizumab. We would like to point out that the Insured Package Advisory Committee (ACP) has advised the National Health Care Institute in general terms that the price for a treatment should be reduced when several medicinal products are available for the same indication. In addition, this indication extension for ravulizumab leads to an increase in sales and volume.

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Therefore, the negotiated price of ravulizumab in previously negotiated indications should be the starting point, as indications extensions should not generally be accompanied by price increases.

We explain the formation of this package advice 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 paid from joint premiums. We consider this both in the scientific sense and in terms of public support. We also review the aspects of efficiency and transparency.

The National Health Care Institute has assessed ravulizumab on the basis of the four package criteria: [1]effectiveness[2], cost-effectiveness[3], necessity [4]and feasibility[5]. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on determining the budget impact and cost-effectiveness; and the Insured Package Advisory Committee for the social assessment. We also consulted stakeholders during the assessment process.

Comprehensive weighting of package criteria

Established medical science and medical practice
Myasthenia gravis (MG) is a chronic autoimmune disease that affects neuromuscular transmission. This leads to fatigue and musculoskeletal weakness. Muscle weakness in patients with MG manifests in various ways over time. Ocular MG, which occurs mostly early in the disease, affects the eye muscles. This may result in an asymmetrically drooping upper eyelid and/or double vision. In gMG, muscle groups in the head, neck, torso, and/or extremities are affected. The involvement of the respiratory muscles may result in respiratory insufficiency. This is called a myasthenic crisis; it occurs in about 15% of patients with MG, especially in the early years of the disease. Although patients with MG generally have normal life expectancy, a myasthenic crisis is a life-threatening exacerbation of MG that can sometimes be fatal.

The beneficial and adverse effects of ravulizumab for the registered indication were researched in the CHAMPION-MG study. This was a randomized, double-blind, placebo-controlled, multicentre phase III study in 175 patients. The REGAIN study, also a randomized, double-blind, placebo-controlled, multicentre Phase III study, studied the effect of eculizumab in these patients. As no direct comparative study with eculizumab is available, there was a need for an indirect comparison.

[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] Rapport kosteneffectiviteit (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.

[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 health care organisation, support, ethical and legal aspects, budget impact and so on.

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Based on the beneficial and adverse effects, the effectiveness of ravulizumab is considered to be similar to eculizumab.

In Dutch medical practice, eculizumab is prescribed only after approval by an indication committee. The procedure applies start and stop criteria that ensure that treatment will only take place if clinically relevant results are achieved. When included in the package, ravulizumab will be prescribed in the same way.

Ravulizumab is a modified variant of eculizumab, extending the half-life in the body. This allows for a lower administration frequency. As a result, ravulizumab may be more user-friendly than eculizumab, which patients could consider a valuable characteristic.

Cost-effectiveness
Due to the equal therapeutic value of ravulizumab compared to the standard treatment, the National Health Care Institute did not assess the cost-effectiveness analysis. The National Health Care Institute also did not perform a cost-effectiveness analysis of eculizumab for this indication; it is therefore unknown what a cost-effective price would be in the Netherlands.

Budget impact analysis
The National Health Care Institute estimates that 13 patients per year will be treated with ravulizumab for this indication in year 3 after inclusion in the package. The total costs per patient per year are €316,181, based on the list price. This results in possible macro costs of €4.7 million in the third year. Taking into account the substitution of eculizumab, this may result in savings of €1 million in year 3 based on the list price.

There is uncertainty about the actual extent of the potential savings because the price discount on eculizumab is not publicly available. In addition, there is uncertainty about the growth of patient numbers. Also, in practice, the potential savings due to the reduced treatment frequency and dosage of eculizumab based on the orphan drug arrangement for eculizumab for the treatment of gMG have not been taken into account .

Appropriate care
Arrangements for appropriate use
Appropriate use arrangements should be made to ensure the appropriate use of ravulizumab. The current arrangement for eculizumab should be adjusted accordingly.

Final conclusion:
Based on the fact that eculizumab is now reimbursed care and, through an appropriate use arrangement, is being used appropriately for a select group, plus the similar effectiveness of ravulizumab and eculizumab, where ravulizumab can be dosed at a lower frequency, I recommend that you include ravulizumab in the package. However, the National Health Care Institute recommends that ravulizumab be included in the package only when the net price for ravulizumab treatment after successful price negotiations with the marketing authorisation holder does not exceed the net price of eculizumab treatment and the current arrangement is adjusted with the addition of ravulizumab.

Ravulizumab is a modified version of eculizumab with an equal therapeutic value. Because ravulizumab has an equal value to eculizumab, ravulizumab should not cost more than eculizumab. It should be taken into account that the introduction of future eculizumab biosimilars may lead to a decrease in the price of eculizumab. This price decrease should also have an impact on the price of ravulizumab, so that ravulizumab will continue to cost no more than eculizumab. Re-negotiation at the time of introduction of biosimilars should be considered to promote this price reduction.

Indication extensions lead to a larger sales market and more volume. Therefore, the negotiated price of ravulizumab for previously negotiated indications should be the starting point, as indication extensions should not generally be accompanied by price increases. There may also be further indication extensions for ravulizumab, which should also play a role in price negotiation.

Should you need any further information, please do not hesitate to contact us.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annexes:
ACP advice
FT report
BIA

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