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National Health Care Institute
Care
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Our reference
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Date 15 December 2021
Subject Package advice ravulizumab (Ultomiris®)

Dear Mr Blokhuis,

The National Health Care Institute advises you on the medicinal product ravulizumab (Ultomiris®) for the following indications:

- treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
  - in patients with haemolysis with clinical symptom(s) indicative of high disease activity;
  - in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.
- treatment of patients with a body weight of 10 kg or above with atypical haemolytic uraemic syndrome (aHUS), who are complement inhibitor-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

The reason for this advice was the placing of the ravulizumab (for this indication) in the lock procedure for expensive medicinal products.

The National Health Care Institute has concluded that ravulizumab for the aHUS indication does not meet the statutory criterion of 'established medical science and medical practice'. Due to the limitations in the design of the studies, there is a very low quality of evidence. This results in very little confidence in the effect of ravulizumab on the crucial outcome measures. Therefore, ravulizumab is not eligible for reimbursement from the basic insurance scheme for the treatment of patients with aHUS.
For the PNH indication, ravulizumab does comply with the 'established medical science and medical practice'. The National Health Care Institute has determined that the therapeutic value of this medicinal product is comparable to that of eculizumab. Both treatment options have a clinically relevant effect on the relevant outcome measures, such as transfusion dependence/independence. Ravulizumab is a long-acting version of eculizumab; ravulizumab must be administered every eight weeks; eculizumab every two weeks.

However, the use of ravulizumab is associated with additional costs. The National Health Care Institute is unable to determine the amount of these additional costs because the actual price of eculizumab is not known. We advise you to include the new treatment in the package, provided that a substantial price reduction is

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achieved. In 2017, the National Health Care Institute recommended a 90% discount for eculizumab.
The price of ravulizumab cannot be higher than the negotiated price of eculizumab, but there are some arguments for negotiating a lower price:

- Competitive medicinal products are expected in the foreseeable future (biosimilars of eculizumab and a new product).
- There are doubts about the relationship between the asking price for ravulizumab and the investments made by the marketing authorisation holder.

Furthermore, it is expected that ravulizumab, just as eculizumab, will be available for more indications in the future. The National Health Care Institute recommends that this should already be taken into account during the price negotiations. This would justify demanding a significant price reduction due to the limited investments the marketing authorisation holder has to make for indication extensions.

General

At your request, the National Health Care Institute assesses whether new care should be part of the health insurance package, and makes a decision based on the health insurance package paid from joint premiums. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects. The National Health Care Institute has assessed ravulizumab on the basis of the four package criteria[1] of effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute is advised by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness, and the Insured Package Advisory Committee for the social assessment. We also consulted stakeholders during the assessment process.

Integral weighting of package criteria

Established medical science and medical practice
In two phase 3, randomised, open-label, non-inferiority studies with adult patients with PNH who were complement inhibitor-naive (study 301) and with adult patients who were clinically stable on treatment with eculizumab (study 302), the desirable and undesirable effects of ravulizumab have been studied compared to eculizumab. Treatment with ravulizumab is not inferior to eculizumab with regards to the desirable effects of transfusion independence and degree of haemolysis. In the clinical study with adult complement inhibitor-naive PNH patients, 92 patients (73.6%) in the ravulizumab group and 80 patients (66.1%) in the eculizumab group avoided transfusion.
In the clinical study with adult PNH patients who were clinically stable on eculizumab, 85 patients (87.6%) in the ravulizumab group and 81 patients (82.7%) in the eculizumab group avoided transfusion.
Both ravulizumab and eculizumab probably have a clinically relevant effect on quality of life.

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

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

The side effects profile of ravulizumab corresponds to that of eculizumab.

Budget impact
The price of ravulizumab per patient per year is similar to that of eculizumab (in the first year with loading dose €373,421 versus €316,853; in subsequent years €312,224 versus €308,931).
In the third year, taking into account a market penetration of 65%, a total of 48 PNH patients who would otherwise use eculizumab, are expected to be eligible for treatment with ravulizumab. This accounts for a budget impact of €0.3 million in the third year. It is expected that in the long term, the use of eculizumab will be completely substituted by ravulizumab.

Cost-effectiveness
Because of the similarities in effectiveness (equal therapeutic value) of ravulizumab and eculizumab, the National Health Care Institute has not carried out any cost-effectiveness analysis. The cost-effectiveness of eculizumab was investigated at the time. However, the National Health Care Institute considered that the cost-effectiveness analysis provided was of insufficient methodological quality. It was concluded that the estimated ICER of €482,334 per QALY was probably an underestimation.

Final conclusion
The National Health Care Institute advises you to include Ultomiris® only for the indication PNH in the health insurance package, provided the price negotiations with the marketing authorisation holder (MAH) successfully deliver a net price that does not exceed that of the existing treatment with eculizumab. Since there is an equal value compared to eculizumab, which is already being reimbursed, and there are no indications that one product is preferable to another, we advise you to take into account during the price negotiations the existing discount on eculizumab. The price reduction recommended at the time for eculizumab, the arrival of biosimilars and other treatment options in the (near) future, and the doubts about the relationship between the asking price and the investments made by the marketing authorisation holder should also play a role in the negotiations.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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