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To the Minister of Health, Welfare and Sport
PO Box 20350
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2024026246

Date 29 August 2024
Subject GVS advice for zilucoplan (Zilbrysq®)

Dear Ms Agema,

The National Health Care Institute hereby advises you about including zilucoplan (Zilbrysq®) in the Medicine Reimbursement System (hereinafter "GVS") for treating adult patients with generalised myasthenia gravis (gMG) who test positive for antibodies to the acetylcholine receptor (AChR). The reason we are issuing this advice is the request your predecessor made in the letter of 27 May 2024 [CIBG-24-06986].

Myasthenia gravis (MG) is a chronic autoimmune disease that affects neuromuscular transmission. This leads to fatigue and skeletal muscle weakness. Approximately 2,500 people in the Netherlands suffer from MG. When the disease worsens and muscle groups in the head, neck, torso and/or limbs are affected, this is termed 'generalised MG' (gMG). Weakening of the respiratory muscles may result in respiratory insufficiency (problems breathing). 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 expectancies, a myasthenic crisis is a life-threatening flare-up of the disease that can sometimes be fatal.

The standard therapy for MG consists of 3 steps (acetylcholinesterase inhibitors, immunosuppressive treatment and intravenous immunoglobulin – IVIg – or plasmapheresis/plasma exchange in acute exacerbations of MG). There are however patients for whom the standard therapy does not work; they are referred to as 'refractory' patients. There are various definitions of refractory MG in the literature and – depending on the definition used – the prevalence of refractory MG is between 10% and 20%.

Licensed indication

Zilucoplan is indicated as an addition to the standard therapy for treating adult patients with generalised myasthenia gravis (gMG) who test positive for antibodies to the acetylcholine receptor (AChR).

Claim by the marketing authorisation holder

The marketing authorisation holder is asking for the medicine to be included on List 1B of the Healthcare Insurance Regulations for treating adult patients with *refractory* gMG who test positive for antibodies to AChR. The marketing

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authorisation holder claims that the medicine is therapeutically equivalent to eculizumab and ravulizumab.

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Advice

The National Health Care Institute recommends that you include zilucoplan on List 1B of the GVS for treating adult patients with *refractory* generalised myasthenia gravis (gMG) who test positive for antibodies to AChR. Because of the therapeutic equivalence with ravulizumab and eculizumab, including zilucoplan should not lead to additional costs above those associated with treatment using eculizumab or ravulizumab.

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In addition, we recommend that you place zilucoplan on List 2 of the GVS with the following further conditions:

Exclusively for an insured person for whom the medicinal product has been prescribed by a university medical centre for generalised myasthenia gravis (gMG) after approval by the indications committee.

Given the pricing developments discussed below, the National Health Care Institute recommends that you should start negotiations about the price of zilucoplan.

We have explained below how we reached this package advisory report and refer you to the other attached reports for details.

Outcome of the substantive assessment

Assessment of interchangeability

After eculizumab and ravulizumab, zilucoplan is the third C5 inhibitor for which reimbursement has been requested for refractory gMG. The National Health Care Institute recently issued a positive recommendation to your predecessor for efgartigimod alfa, but that medicinal product is (at the time of writing) not yet reimbursed. Based on the criteria for interchangeability, the National Health Care Institute has concluded that zilucoplan is *not* interchangeable with other medicinal products that have been included in the GVS. This is because eculizumab, ravulizumab and efgartigimod alfa are inpatient medicines. On those grounds, zilucoplan is not eligible for inclusion on List 1A. The National Health Care Institute then assessed whether zilucoplan is eligible for inclusion on List 1B.

Therapeutic value

The efficacy and safety of zilucoplan in adult patients with gMG that are positive for anti-AChR antibodies have been investigated in the RAISE study, a randomised, double-blind, placebo-controlled, multicentre phase III trial. The REGAIN and CHAMPION-MG studies were used for comparison with eculizumab and ravulizumab, using an indirect comparison method as no studies using a direct comparison are available.

The National Health Care Institute believes it is sufficiently probable that there are no relevant differences between the favourable and unfavourable effects of zilucoplan, eculizumab and ravulizumab in patients with refractory gMG with antibodies to AChR. The National Health Care Institute concludes that zilucoplan complies with established medical science and medical practice and thus is equivalent in value to eculizumab and ravulizumab.

Budget impact analysis (BIA)

The National Health Care Institute estimates that 12 refractory gMG patients with AChR antibodies will be treated per year with zilucoplan by year 3 after inclusion in the package. The total costs per patient per year are €276,333. This results in macro costs of €3 million in the third year. When substitution of ravulizumab and eculizumab in specialist medical care is also taken into account, the budget impact in year 3 is a saving of €0.5 million. The calculations in the BIA used list prices. Given that pricing agreements have been made by the Ministry of VWS for reimbursing ravulizumab, the savings will be less in reality and there may even be additional costs instead. Furthermore, the National Health Care Institute notes that biosimilars of eculizumab licensed for the indication gMG may also enter the market in a few years, possibly allowing further price cuts to be achieved.

The National Health Care Institute expects that zilucoplan will be an attractive alternative to the complement inhibitors, if it is reimbursed, because of zilucoplan's benefits in terms of ease of use (an injection instead of intravenous administration at the hospital). The extent to which the extramural medicine zilucoplan will replace the inpatient medicines eculizumab and ravulizumab is unclear. Moreover, there is not a level playing field (see 'Reimbursement framework'). Given these considerations, the National Health Care Institute advises that you should start price negotiations. For further uncertainties regarding the budgetary impact, please refer to the attached report.

Cost-effectiveness

Given the equivalence, an evaluation of the cost-effectiveness of zilucoplan is not necessary. It is however not known whether the medicinal products to which it has been compared (i.e. ravulizumab and eculizumab) are themselves cost-effective.

The cost-effectiveness of the standard treatment is unknown

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. If the standard treatment is a non-cost-effective treatment that is already included in the basic package, the new treatment will also not be cost-effective at the same price. This undesirable situation has been identified by the National Health Care Institute, 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.

Reimbursement framework

Unlike eculizumab, ravulizumab and efgartigimod alfa, zilucoplan is designated in the demarcation letter¹ as an extramural medicine. Based on your ministry's current policy, there is no way of deviating from that at the moment. The National Health Care Institute notes that there can potentially be negative consequences of having an agreement to reimburse just some of these medicines by the extramural pathway. That is because this could mean that the playing field is not

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¹ Ministry of Health, Welfare and Sport (2014) *Afbakening aanspraak Farmaceutische Zorg en aanspraak Geneeskundige Zorg met betrekking tot geneesmiddelen* (Demarcation of entitlement to Pharmaceutical Care and entitlement to Medical Care with regard to medicinal products). Reference number: 183496-115412-GMT

level, with a financially driven preference for one of the medicines that will not necessarily yield lower costs for society. It is in fact possible that pricing agreements could mean that the costs of the inpatient medicines could be lower than for those that are reimbursed extramurally (through the GVS).

Appropriate care

An indications committee that determines which patients in the Netherlands are eligible for eculizumab or ravulizumab has been set up. The National Health Care Institute proposes including zilucoplan in the existing orphan drug arrangements for eculizumab. Discussions have already been started about this with the professional group.

Should you need any further information, please do not hesitate to contact us. The assessment reports (GVS report, pharmacotherapeutic report and budget impact analysis) have been added as appendices.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

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