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Date 11 July 2023
Re: GVS advice on 'Extension of reimbursement conditions of CGRP inhibitors Aimovig® (erenumab), Emgality® (galcanezumab) and Ajovy® (fremanezumab)'

Our reference
2023026788

Dear Mr Kuipers,

In your letter of 27 February 2023 (reference CIBG-23-0541), you requested the National Health Care Institute's advice on extending the reimbursement conditions for the use of the subcutaneous CGRP inhibitors Aimovig® (erenumab), Emgality® (galcanezumab) and Ajovy® (fremanezumab) in prevention of episodic migraine (EM), as specified by the Dutch Society of Neurology (NVN). You referred to its view that these CGRP inhibitors qualify as prophylaxis of EM in adult patients with at least 4 migraine days per month as the final treatment option; i.e. after prior therapy with 5 categories of migraine prophylactics failed. The National Health Care Institute assessed extension of the reimbursement conditions accordingly, taking into consideration the advice from its Scientific Advisory Board (WAR). The attached reports contain its observations and considerations.

Background

- On 17 September 2021, the National Health Care Institute informed you that these 3 CGRP inhibitors had added therapeutic value compared with placebo in patients with therapy-resistant chronic migraine (CM), who do not experience adequate therapeutic benefit from treatment with topiramate/valproate and botulin toxin A. These CGRP inhibitors therefore meet 'the Dutch established medical science and medical practice standard'. The National Health Care Institute advised you to include them in a group of interchangeable medicines in List 1A of the Medicine Reimbursement System (GVS), and to add specific conditions for their reimbursement. Subsequently, healthcare insurers and neurologists agreed on mandatory *appropriate-use arrangements* (*start and stop criteria*) as provisions for reimbursement; see advice letter dated 17 September 2021 (ref. 2021017995) and the attached pharmacotherapeutic report (p. 13 – 14). These CGRP inhibitors are being reimbursed for therapy-resistant CM accordingly.

Current request

The three marketing authorisation holders of these CGRP inhibitors now jointly request extension of the above-mentioned reimbursement conditions for therapy-

resistant EM. Their request meets the recommendation of the Dutch Neurological Association (NVN) to also use CGRP inhibitors as prophylaxis of therapy-resistant EM in adult patients with at least 4 monthly migraine days (MMD) as the final treatment option after treatment failure with the current 5 categories of migraine prophylactic agents, which are listed in the NVN guideline *'Pharmaceutical treatment of migraine and medication-overuse headache'* (2017).

Therapeutic value

In clinical studies, the use of a CGRP-inhibitor had a clinically relevant effect in 25% of patients with therapy-resistant chronic migraine when compared to placebo, i.e. halving the number of monthly migraine days. This may also apply to the number of days that acute (migraine-specific) medication is required. Overall, each individual patient with therapy-resistant EM has an equal (25%) chance of having a clinically relevant effect when using a CGRP inhibitor. This effect will however not occur in all these patients. As already applicable for therapy-resistant CM, also for therapy-resistant EM additional stopping criteria will be important to ensure their effective use. A beneficial effect of CGRP inhibitors on the reduction of monthly migraine days continues with long-term use (1 to 5 years). Use of a CGRP inhibitor may also have a positive and clinically relevant effect on the quality of life of patients with therapy-resistant EM.
In the short term, the use of a CGRP inhibitor does not cause a higher number of serious side effects or a higher discontinuation rate due to side effects, when compared to placebo. A longer-term study of up to 1 year also shows that CGRP inhibitors are well-tolerated.
Based on these observations, the National Health Care Institute concluded that subcutaneous CGRP inhibitors meet 'the Dutch established medical science and medical practice standard' for the treatment of adult patients with therapeutic EM. Based on its assessment of the clinical data, the National Health Care Institute concludes that they have added therapeutic value when compared with placebo in the prophylaxis of therapy-resistant EM with at least 4 monthly migraine days, following treatment failure of the 5 categories of migraine prophylactics listed in the aforementioned NVN Guideline.

Budget impact analysis (BIA)

Based on the assumptions about amongst others patient numbers and market penetration, reimbursement of these CGRP inhibitors for prophylaxis of EM will increase the Dutch pharmaceutical expenses with €10.3 million (scenario 1; minimum) to €20.3 million (scenario 2; maximum) in the third year after extension of their current reimbursement conditions. Scenario 1 is based on the percentage of patients who had a clinically relevant, positive effect from treatment with a CGRP inhibitor in the clinical studies, which were reviewed. In line with their strict, mandatory stop criteria a 'high' number of patients discontinued treatment after 3 – 6 months because of an insufficient treatment effect. Scenario 2 is based on the assumption that in Dutch clinical practice, a significantly higher percentage of patients will be treated (much) longer than in the strictly monitored study setting. Hence, also a 'lower' number of patients will discontinue treatment after 3 – 6 months.
The difference between these scenarios relates to the major uncertainty about the number of patients with EM who will still use these CGRP inhibitors after 6 months. A recent analysis by the National Health Care Institute of last year's reimbursement data regarding their use for CM indicated that it is most likely that the number of patients who will use a CGRP inhibitor for more than 6 months will

indeed be significantly higher than was observed in clinical trials. This is not in line with the appropriate-use arrangements that currently apply to CM, which were also the guiding principle in the BIA for CM. Since the same arrangements will also apply to EM, it is assumed that patients with EM will also use CGRP-inhibitors for more than 6 months. Scenario 2 is based on this assumption.

Cost-effectiveness
Even after specific and repeated written requests, the marketing authorisation holders did not provide crucial scenario analyses and essential, available data which the National Health Care Institute considered indispensable for a reliable and valid assessment of the cost-effectiveness of their CGRP-inhibitors. The current pharmaco-economic analysis is therefore not transparent. Its quality and representativeness do not meet the high standards of the National Health Care Institute. Hence, it cannot draw valid and reliable conclusions about the cost-effectiveness of these CGRP inhibitors for the treatment of patients with therapy-resistant EM. The current pharmaco-economic analysis is therefore not usable for policy decision-making.

Advice
Although the National Health Care Institute determined that the CGRP inhibitors are therapeutically effective for prophylaxis of EM, it is not feasible to draw valid and reliable conclusions on their cost-effectiveness. The National Health Care Institute, unanimously supported by its Scientific Advisory Board, is therefore unfortunately not able to advise you with the necessary carefulness about extension of the current List 2 reimbursement conditions for the use of the subcutaneous CGRP inhibitors Aimovig (erenumab), Emgality (galcanezumab) and Ajovy (fremanezumab) for prophylaxis of EM.

Yours sincerely,

Peter Siebers
Acting Chairperson of the Executive Board