Erenumab (Aimovig®) for the prophylaxis of adults with migraine

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 27 June 2019

Zorginstituut Nederland carried out an assessment of the medicinal product erenumab (Aimovig®) and came to the following conclusion.

In a letter dated 12 November 2018 (CIBG-18-072 11), the Minister of Health, Welfare and Sport (VWS) asked *Zorginstituut Nederland* to perform a substantive assessment of whether the medicinal product erenumab (Aimovig®) is interchangeable with any product included in the insured package. The *Zorginstituut* has completed its assessment. Their considerations are to be found in the GVS report that was sent to the Minister.

Registered indication
The full registered indication is as follows: "Erenumab is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month."

Erenumab is available as a subcutaneous solution for injection. The dose is one subcutaneous injection of 70 mg every 4 weeks. Some patients may benefit from a dose of 140 mg (two subcutaneous injections of 70 mg) every 4 weeks.

Background
Erenumab belongs to a new class of migraine products, the calcitonin gene-related peptide (CGRP) inhibitors. It is a human IgG2 monoclonal antibody that binds to the CGRP receptor. Raised blood levels of CGRP have been linked to migraine attacks.
Other registered representatives of this class of migraine products, with a similar indication, are fremanezumab (Ajovi®) and galcanezumab (Emgality®). The latter products have not yet been assessed by the *Zorginstituut* for inclusion in the Medicine Reimbursement System (GVS).

GVS assessment
The manufacturer is asking for inclusion on List 1B of the GVS. Reimbursement is being requested for 2 subgroups within the registered indication of erenumab. These are adult patients with:

- Chronic migraine, without medication overuse, as 1st line treatment;

- Episodic migraine with at least 4 migraine days per month, with insufficient response – or a contraindication or intolerance – to at least two other preventive medicinal treatments (candesartan and one beta-blocker (metoprolol or propranolol)).

Scientific advice from the Dutch Neurologists' Association (NVN), suggests to use erenumab instead of topiramate for both episodic migraine and chronic migraine, because of its more favourable safety profile. For this reason, in assessing erenumab, the *Zorginstituut* regards usual treatment with the orally administered topiramate as the comparative treatment.

It is therefore a missed opportunity that the manufacturer did not carry out any study comparing the effect of erenumab directly with that of topiramate. The

Zorginstituut therefore indirectly compared older studies using topiramate with newer studies with erenumab. The comparison was hampered by the fact that these studies all had different set-ups, and the patients were not entirely comparable either. The *Zorginstituut* concludes that the therapeutic value of erenumab is equal to that of topiramate. No difference was found in the number of days that patients suffered from migraine; it was the same for erenumab and topiramate. Nor was a difference found in the chance of suffering severe side effects or in the number of patients who stopped treatment due to side effects. In fact, if the *Zorginstituut* corrects for the study differences, in the short term, no chance of a difference was demonstrated in the number of patients stopping treatment due to side effects. Furthermore, possible long-term side effects of erenumab are not known.

Advice on placement in the GVS

The therapeutic value of erenenumab is equal to that of topiramate. Based on the criteria for interchangeability, erenumab is not eligible for inclusion on List 1A. Nor is erenumab eligible for inclusion on List 1B. In the event of an identical therapeutic value, the inclusion on List 1B would only be acceptable if it does not involve additional costs to the pharmacy budget. The additional costs are, however, considerable, being estimated at circa €73.5 million.
This budget impact analysis did not take into account possible costs of substituting topiramate. This is because it is not clear whether substitution will take place, or whether in practice a shift in treatments will take place. The comment can be made that the total reimbursement for topiramate in 2017 was less than €1 million. Moreover, topiramate is also prescribed for epilepsy. The effect of possible substitution costs on the total sum of more than €73 million is therefore negligible.

Other considerations

The *Zorginstituut* proposes, with due heed to the Minister's response, to take the initiative and invite the professional group to join them in exploring the possibility of creating a subgroup for which evidence of the medicine’s added value can be found. Considerations for this initiative are as follows:

- Due to the high prevalence and the impact on quality of life, migraine in people under the age of 50 years is no. 3 on the WHO's top-ten and the Global Burden of Disease Study 2015 (GBD2015) of disorders limiting quality of life. In the newest GBD studies, it seems that throughout the world (including the Netherlands), the disease is currently no. 2 in disorders with the highest burden of disease;
- According to the clinicians, 60% of the patients who are eligible benefit insufficiently from current migraine prophylactics;
- Unlike the current therapies used for the prophylaxis of migraine, erenumab and the other CRGP antagonists have a mechanism of action that specifically focuses on the pathophysiology of migraine;
- Controlled studies show that erenumab is circa twice as effective as placebo in reducing the number of migraine days per month or in realising a ≥50% reduction in the number of migraine days;
- Erenumab is also effective in patients who did not respond to previous preventive therapies and in patients with chronic migraine;
- Erenumab was well-tolerated in clinical studies, though its long-term effects are not yet properly known.

Based on the above considerations, for migraine prophylaxis, erenumab seems to be a supplement to products currently available, in particular for patients who could not be satisfactorily treated – or who did not tolerate – the products currently available.

As part of this initiative, the *Zorginstituut* wants to involve the other oral CRGP antagonists that have by now been registered for the prophylaxis of migraine.

Once it has clarity about the feasibility of this, the *Zorginstituut* will send the Minister a proposal for inclusion in the GVS.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.