Cost-effectiveness of erenumab (Aimovig®) for the prophylaxis of migraine in adults

The NCPE has issued a recommendation regarding the cost-effectiveness of erenumab (Aimovig®) for the prophylaxis of chronic migraine and episodic migraine in adults who have at least four migraine days per month where two or more prophylactic treatments have been unsuccessful.

Following assessment of the Applicant's submission, the NCPE recommends that erenumab, for the treatment of chronic migraine, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*. Cost-effectiveness of erenumab for episodic migraine is more uncertain and the NCPE recommends that reimbursement not be considered at this time*.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Novartis Ireland Limited) economic dossier on the cost effectiveness of erenumab. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*

National Centre for Pharmacoeconomics **September 2019**

Summary

In January 2019, Novartis Ireland Ltd. submitted a dossier presenting the comparative clinical effectiveness and cost effectiveness of erenumab (Aimovig®) for the prophylaxis of migraine in adults who have at least four migraine days per month. In their submission, Novartis Ireland Ltd. presented erenumab as prophylaxis treatment for a subgroup of the licensed population (i.e. patients for whom at least two prophylactic treatments have been unsuccessful). In addition, the submission incorporates two sub-types of migraine based on the frequency of headache symptoms. These are episodic migraine, with a patient suffering from less than 15 headache days per month, and chronic migraine, with a patient suffering from 15 or more headache days per month.

Erenumab was compared with best supportive care in patients with episodic and chronic migraine. Best supportive care was defined as acute medication and healthcare resource use in line with the monthly migraine day (MMD) frequency experienced. In a scenario analysis of patients with chronic migraine, erenumab was compared with onabotulinum toxin A.

Erenumab is a fully humanised monoclonal antibody which selectively binds the calcitonin gene-related peptide (CGRP) receptor blocking CGRP binding. The product is available in Ireland as a 70mg pre-filled pen for subcutaneous injection. The recommended dose is 70mg every four weeks, while some patients may benefit from 140mg every four weeks.

1. Comparative effectiveness of erenumab

The clinical evidence for erenumab is based on a program of clinical trials, examining the benefit of the drug in chronic and episodic migraine separately.

The 20120295 trial (Tepper et al, 2017), which was a phase II, double-blinded placebo-controlled trial, included patients with chronic migraine (n=667). Patients were excluded if they had failed therapy with more than three options previously. The patients were randomised to placebo (n=286) or 70mg (n=191) or 140mg (n=190) of erenumab once every four weeks for a period of twelve weeks. The primary outcome was the change in MMDs

from baseline at twelve weeks; secondary outcomes included the percentage of patients with at least a 50% reduction in MMD from baseline. The MMD at baseline were 18.2, 17.9 and 17.8 days for the placebo, 70mg and 140mg groups respectively. Erenumab 70mg and 140mg reduced MMD from baseline to the same extent when compared to placebo at the twelve week point (-6.6 days vs placebo -4.2 days; difference -2.5; 95% CI -3.5, -1.4; p<0.001). A higher proportion of patients achieved a 50% reduction in MMD with erenumab 70mg (39.9%) and 140mg (41.2%) than with placebo (23.5%) at week twelve.

For episodic migraine, four double-blinded placebo-controlled studies were presented. Patients enrolled had four to 14 MMDs. Study 20120178 (Sun et al, 2016. Phase II ongoing; n=483) randomised patients whom had failed more than two prophylactic therapies to receive placebo (n=160), erenumab 7mg (n=108), 21mg (n=108) and 70mg (n=107) every four weeks for three doses with a study period of twelve weeks. Following treatment with 70mg, the mean least squares of the difference in MMD (vs. placebo) was -1.1 (95% CI -2.1 to -0.2: p=0.021). ARISE (Dodick et al., 2017. Phase III; (n=577) enrolled patients whom had failed more than two prophylactic treatments and randomised them to placebo (n=291) or 70mg (n=286) every four weeks with outcomes at twelve weeks. The mean least squares of the difference in MMD versus placebo was -1.0 (95% CI -1.6 to -0.5; p<0.001). LIBERTY (Reuter et al., 2018. Phase III; n=246) randomised patients, whom had failed two to four prophylactic treatments, to placebo (n=125) or 140mg of erenumab (n=121) every four weeks during the twelve-week study period. The mean least squares of the difference in MMD versus placebo was -1.6 (95% CI -2.7 to -0.5; p=0.004). STRIVE (Goadsby et al., 2017. Phase III; n=955) randomised patients to placebo (n=319), erenumab 70mg (n=317) and erenumab 140mg (n=319) every four weeks for twenty-four weeks. Patients were excluded if they had had no therapeutic response to two prophylactic treatments. An amendment to the trial protocol was implemented during the enrolment period to allow patients to concomitantly use one prophylactic treatment during the trial. The mean least squares of the difference in MMD versus placebo was -1.4 (95% CI -1.9 to -0.9; p<0.001) for the 70mg group in STRIVE and -1.9 (95% CI -2.3 to -1.4; p<0.001) for the 140mg group.

A recent meta-analysis (Lattanzi, 2019) of the five clinical studies detailed above reported a 1.30 reduction (95% CI -1.66 to -0.95) in MMDs for the 70mg dose and a -1.87 reduction

(95% CI -2.33 to -1.41) for the 140mg dose. A considerable placebo effect is noted in these trials. There is limited efficacy data pertaining to patients with refractory migraine (those who have failed three or more prophylactic treatments).

In chronic migraine, onabotulinum toxin A is a relevant comparator, although due to limited access in Ireland, it can be considered a theoretical comparator. There is no direct evidence comparing onabotulinum toxin A to erenumab and therefore estimates of relative efficacy were derived from an indirect treatment comparison. The studies informing this indirect comparison included the 20120295 trial (for erenumab) and PREEMPT 1 and PREEMPT 2 (for onabotulinum toxin A). The results from this comparison indicated that the number of patients experiencing a 50% reduction in monthly headache days was numerically higher with erenumab. The results from this indirect comparison were not significant. In addition, it should be noted that these were unmatched analyses.

2. Safety of erenumab

In the five clinical trials included in this summary, 1.6% of patients discontinued erenumab due to an adverse event compared to 1.2% in the placebo groups; relative risk = 1.12, 95% CI 0.57-2.18, p=0.744 (Lattanzi, 2019). Most events were mild or moderate including injection site reactions, constipation and pruritis. The potential vascular effects of inhibition of CGRP receptors have not been evident thus far, though larger cohorts and pharmacovigilance are required to monitor this risk. Erenumab should be avoided in pregnancy and there may be concerns regarding treatment in those of child bearing age without further data. There was no rebound effect noted on stopping the medication.

3. Cost effectiveness of erenumab

Methods

The cost-effectiveness of erenumab, for the prophylaxis of migraine in adults who have at least four migraine days per month, was evaluated using a cost-utility model. The model comprised a 12-week decision tree followed by a longer-term Markov model. The patient population considered is a subgroup of the licensed population i.e. patients for whom at

least two prophylactic treatments have been unsuccessful. The patient population includes those with both chronic migraine and episodic migraine.

At the end of the 12 week decision-tree model, patients were deemed to be either responders or non-responders. In the Markov model, patients discontinue treatment with erenumab due to non-response, adverse events or lessening of response. The model allows patients to be evaluated for treatment discontinuation due to their migraines becoming stable and controlled. The model assumes that patients retain some or all of the benefits they derived from erenumab for the remainder of the model 10-year horizon.

The source of treatment effects for erenumab compared with best supportive care were derived from the pivotal trials for chronic and episodic migraine (20120295, STRIVE, ARISE, LIBERTY and 20120178); with the placebo arms of these trials being used to estimate best supportive care. For the scenario analysis where erenumab is compared with onabotulinum toxin A in chronic migraine patients the source of treatment effects is the indirect treatment comparison.

The utility values were derived from migraine-specific instruments to capture quality of life estimates, which were collected within the pivotal trials for chronic and episodic migraine (20120295 and STRIVE). These data were mapped to EQ-5D-3L values. Treatment costs (drug and drug administration) and disease management costs were included. Costs associated with adverse events were not included. Both costs and utilities were discounted at an annual rate of 5%.

Results

There are uncertainties around the ratio of patients who have chronic and episodic migraine and at what dose erenumab will be used in clinical practice in Ireland. Therefore, the Review Group present the results for the treatment of chronic and episodic migraine separately. Also, an escalating dose scenario is presented.

Applicant Proposed Base Case Analysis

CHRONIC MIGRAINE

Deterministic analyses

When erenumab 70mg every four weeks is compared to best supportive care, the incremental cost-effectiveness ratio (ICER) is €24,780 per QALY (incremental cost €7,577; incremental QALYs 0.3058). When erenumab 140mg every four weeks is compared to best supportive care, the ICER is €42,302 per QALY (€17,916; 0.4235).

When erenumab 70mg every four weeks is compared to onabotulinum toxin A the ICER is €30,644 per QALY (€5,820; 0.1899). The ICER comparing erenumab 140mg every four weeks with onabotulinum toxin A was €66,565 per QALY (€15,054; 0.2262).

Probabilistic Analyses

When erenumab 70mg every four weeks is compared to best supportive care the ICER, is €24,294 per QALY (€7,432; 0.31). At willingness to pay thresholds of €20,000 per QALY and €45,000 per QALY, the probabilities of cost effectiveness are 29% and 80% respectively. When erenumab 140mg every four weeks is compared to best supportive care the ICER is €41,448 per QALY (€17,433; 0.42). At willingness to pay thresholds of €20,000 per QALY and €45,000 per QALY, the probabilities of cost effectiveness are 6% and 51% respectively.

EPISODIC MIGRAINE

Deterministic Analyses

When erenumab 70mg every four weeks is compared to best supportive care, the ICER is €36,445 per QALY (€5,482; 0.1504). When erenumab 140mg every four weeks is compared to best supportive care, the ICER is €96,391 per QALY (€16,755; 0.1738).

Probabilistic Analyses

When erenumab 70mg every four weeks is compared to best supportive care, the ICER is €36,705 per QALY (€5,453; 0.15). At willingness to pay thresholds of €20,000 per QALY and €45,000 per QALY, the probabilities of cost effectiveness are 12% and 59% respectively. When erenumab 140mg every four weeks is compared to best supportive care, the ICER is

€96,754 per QALY (€16,910; 0.17). At willingness to pay thresholds of €20,000 per QALY and €45,000 per QALY, the probabilities of cost effectiveness are 1% and 5% respectively.

NCPE Preferred Base Case Analysis

The Review Group have made a number of changes to the base case assumptions:

- On review of Irish College of General Practitioners guidelines, we believe that, if reimbursed, the population would comprise patients for whom at least three prophylactic treatments have failed.
- In the population with chronic migraine, we consider those patients who experience at least a 30% reduction in MMD from baseline to be responders (in line with NICE Guidance TA260). The Applicant's assumption, of at least a 50% reduction in MMD from baseline, in the population with episodic migraine remains.
- In the absence of evidence to the contrary, the number of MMDs should revert to baseline levels upon treatment discontinuation.
- In line with standard practises, the model time should increase to 60 years (i.e. lifetime).

For the population with chronic migraine, the resultant ICERs are €44,164 per QALY (€10,767; 0.2438) for erenumab 70mg every four weeks and €71,073 per QALY (€24,234; incremental QALYs 0.3410) for erenumab 140mg every four weeks.

For the population with episodic migraine, the resultant ICERs are €298,066 per QALY (€4,523; 0.0152) for erenumab 70mg every four weeks and €144,605 per QALY (€15,353; 0.1062) for erenumab 140mg every four weeks.

Scenario Analysis

The Review Group have conducted two scenario analyses on the NCPE preferred base case analysis.

- Given uncertainty in the true value, the positive discontinuation rate of 20% (assumed by the Applicant) was decreased to 10%. For the population with chronic migraine, the resultant ICERs are €52,230 per QALY for erenumab 70mg every four

weeks and €82,303 per QALY for erenumab 140mg every four weeks. For the population with episodic migraine, resultant ICERs are €302,902 per QALY for erenumab 70mg every four weeks and €146,258 per QALY for erenumab 140mg every four weeks.

- When a dose escalating scenario is incorporated (i.e. the dose of erunumab is increased from 70 mg to 140mg every four weeks (for a further 12 weeks) in patients who experienced at least a 30 to 50% response) resultant ICERs are €42,458 per QALY and €127,165 per QALY for the populations with chronic migraine and episodic migraine respectively.

4. Budget impact

The price to wholesaler for erenumab is €425 for a dose of 70mg every four weeks. This results in an annual reimbursement cost per patient (inclusive of pharmacy fees, 5.5% mandatory rebate and VAT) of €7,804.06. The Applicant submission states that the 140mg dose will be provided at the 70mg price. There is considerable uncertainty regarding the number of patients eligible for this treatment. The Applicant derived the eligible population from Irish survey and prescribing data. The eligible population is patients whom have four or more MMDs, whom have failed two prophylactic treatments and to which a market share is applied. A calculated eligible population of 744 patients is given for year one increasing to 1,861 in year five. The Applicant estimated a gross drug budget impact of €2.9 million in 2020 increasing to €7.6 million in 2024 with a 5-year cumulative gross budget impact of €27.3 million. The net drug budget impact varies little from the gross budget impact due to the low cost of best supportive care. The Applicant estimated 5-year cumulative net budget impact is €25.9 million.

The Review Group consider that this is likely a conservative estimate given the uncertainty in the market share estimate and the reservoir of patients who have failed two treatments and who may seek referral to neurology services due to the availability of a new therapeutic option.

5. Patient submission

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

Clinical trial evidence suggests erenumab reduces MMDs compared to placebo in the pivotal trials. However, there are uncertainties around the dose and responder threshold that will be used in clinical practice. In addition, it is unknown if the benefits of erenumab will be maintained by patients who discontinue treatment for any reason.

According to the Review Group's preferred analysis, erenumab 70mg every four weeks is cost effective, at the €45,000 per QALY threshold, for the treatment of chronic migraine. However, cost effectiveness is sensitive to the positive discontinuation rate. Erenumab is not cost effective, at a dose of 140mg every four weeks, for the treatment of chronic migraine. Erenumab, at either dose, is not cost effective for the treatment of episodic migraine.

The NCPE consider that erenumab, for the treatment of chronic migraine, may be considered for reimbursement if cost-effectiveness for both doses can be achieved. We recommend that adequate controls are in place to ensure that the drug is prescribed only for those patients with chronic migraine, who have failed three or more prophylactic treatments.

Cost-effectiveness of erenumab for episodic migraine is more uncertain and the NCPE recommends that reimbursement not be considered at this time. *

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*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.