NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Erenumab for preventing migraine

1 Recommendations

1.1 Erenumab is not recommended, within its marketing authorisation, for preventing migraine in adults who have at least 4 migraine days per month.

1.2 This recommendation is not intended to affect treatment with erenumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment options for preventing chronic (15 headache days a month or more) or episodic (less than 15 headache days a month) migraine include beta-blockers, antidepressants and epilepsy medications. If chronic migraine does not respond to at least 3 preventive drug treatments, botulinum toxin type A or best supportive care (treatment for the migraine symptoms) is offered. If episodic migraine does not respond to at least 3 preventive drug treatments, best supportive care is offered.

For people whose migraine has not responded to at least 3 oral preventive treatments, the clinical trial evidence shows that erenumab 140 mg works better than best supportive care for preventing chronic or episodic migraine. There is only indirect evidence comparing erenumab

with botulinum toxin type A in chronic migraine, which showed that it is very uncertain whether erenumab is more clinically effective than botulinum toxin type A.

For chronic migraine, the cost-effectiveness estimates vary depending on how effective erenumab is compared with botulinum toxin type A. Assuming that erenumab works only as well as botulinum toxin type A, the cost-effectiveness estimates are much higher than what NICE normally considers an acceptable use of NHS resources.

For episodic migraine, the company's evidence on erenumab's cost effectiveness is not good enough. This is because the cost-effectiveness estimates do not include the revised commercial arrangement or the preferred assumptions. The evidence on erenumab for people with high-frequency episodic migraine (that is,10 to 14 migraine days per month) is not considered because expert opinion confirmed this is not a clinically distinct subgroup.

Therefore, erenumab is not recommended for preventing migraine in adults who have at least 4 migraine days per month.

2 Information about erenumab

Marketing authorisation indication	Erenumab (Aimovig, Novartis) is indicated for 'prophylaxis of migraine in adults who have at least 4 migraine days per month'.
Dosage in the marketing authorisation	The recommended dose is 70 mg erenumab every 4 weeks. Some patients may benefit from a dose of 140 mg every 4 weeks. Erenumab is administered as a subcutaneous injection. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter.
Price	£386.50 per dose (70 mg or 140 mg; company's submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Novartis and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

The condition and current treatment

Migraine significantly affects health-related quality of life

3.1 The patient experts described the effect of migraine on their quality of life and how it affects their ability to work and take part in social activities. People with migraine can often miss out on family time and find it difficult to plan future activities. The severity and frequency of the condition can fluctuate over time and can be poorly understood in the workplace. The patient experts explained that symptoms can start in the days leading up to a migraine and that recovery can take a few days, so people with chronic migraine may have few symptom-free days. Chronic migraine is defined as 15 or more headache days a month, with at least 8 of those having features of migraine. Episodic migraine is defined as less than 15 headache days a month. The burden on quality of life can be similar to that of chronic migraine. The committee concluded that migraine, particularly chronic migraine, is a debilitating condition that substantially affects health-related quality of life and employment and is associated with an increase in the prevalence of psychiatric illness.

Well-tolerated treatments are needed

3.2 The committee understood that current oral treatment options for preventing migraine include drugs that are used to treat other conditions, such as beta-blockers, antidepressants and epilepsy medications. The patient experts explained that these treatments can have significant side effects, can be poorly tolerated and may not work for some people. The committee was aware that NICE's technology appraisal guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine recommends botulinum toxin type A for people with

chronic migraine whose condition has not responded to at least 3 previous oral preventive drug therapies and is appropriately managed for medication overuse. Clinical experts stated that although botulinum toxin type A is recommended by NICE, there are lengthy waiting lists and it is not always available in some areas of the country. The committee concluded that effective, well-tolerated treatment options are needed.

Current clinical management

At least 3 oral preventive treatments are tried before more specialist treatment is considered

3.3 The clinical experts explained that the aim of treatment is to reduce the frequency, severity or duration of migraine and improve quality of life. In chronic migraine, a 30% reduction in migraine frequency is considered a clinically meaningful response to treatment. In episodic migraine, a 50% reduction is considered a clinically meaningful response. If there is an insufficient or partial clinical response (that is, less than 30% reduction in chronic migraine symptoms and less than 50% reduction in episodic migraine symptoms), or the person is not able to have an adequate dosage for long enough or has adverse events, treatment is stopped and another oral preventive treatment is tried. The clinical experts explained that it is important for people to try a range of oral preventive treatments before considering more specialist treatment, such as botulinum toxin type A (for chronic migraine) or erenumab. The committee therefore concluded that a clinically meaningful response was a 30% reduction (for chronic migraine) or a 50% reduction (for episodic migraine) in migraine frequency. An insufficient response to at least 3 oral preventive treatments represents usual NHS practice before more specialist treatment is considered.

Clinical evidence

The most relevant comparators are best supportive care for episodic migraine and botulinum toxin type A for chronic migraine

3.4 The company's submission focused on people with migraine for whom at least 3 previous preventive treatments had failed (defined as insufficient or partial response, insufficient dosage or adverse events). This was because the company considered this group to reflect people most in need of treatment options and for whom erenumab would likely be used in practice. The company presented evidence for erenumab's clinical effectiveness compared with placebo for episodic migraine and compared with placebo and botulinum toxin type A for chronic migraine. The company considered that placebo was representative of best supportive care, because it comprised acute treatments that people would have for their migraine symptoms when preventive treatments had not worked. The clinical experts agreed that erenumab would likely be offered to people with migraine for whom at least 3 previous preventive treatments had failed. The committee suggested that some people may be able to have a fourth oral preventive treatment, given that it was important to try a range of oral preventive treatments before more specialist treatment is considered (see section 3.3). After consultation, clinical experts explained that most people will have either botulinum toxin type A or best supportive care. Only some people may have a fourth oral preventive treatment and this is unlikely to have a clinically meaningful benefit. The committee therefore did not consider that a fourth oral preventive treatment would be a relevant comparator. The committee concluded that best supportive care was the most appropriate comparator in episodic migraine. For people who have chronic migraine who have tried 3 oral preventive treatments that haven't worked, the committee recalled comments from patient and clinical experts that these people are most in need of effective therapy. They would be offered botulinum toxin type A at this point in the treatment pathway. The committee concluded that botulinum toxin type A or best supportive care were the relevant comparators in chronic

migraine. But it considered that most people would have botulinum toxin A rather than best supportive care after trying 3 oral preventive treatments.

The evidence does not fully reflect the most relevant subgroup of people who may be eligible for erenumab in clinical practice

3.5 The evidence was from 4 randomised controlled trials that compared 2 different dosages of erenumab (70 mg and 140 mg) with placebo: study 295 in chronic migraine, and STRIVE, ARISE and LIBERTY in episodic migraine. The committee noted that the company's evidence was for a subgroup of people for whom at least 3 previous treatments had failed (see section 3.3). However, people whose migraine had no therapeutic response (defined as no reduction in headache frequency, duration or severity) to a number of previous preventive treatments (more than 3 in study 295, more than 2 in STRIVE and ARISE) were excluded from the trials. In LIBERTY, people for whom more than 4 previous treatments had failed were excluded. The committee was concerned that the people excluded from the trials were likely to represent the people most in need of treatment and were therefore the most clinically important subgroup. The committee concluded that the trials excluded the population with the most refractory migraine who may benefit from the drug in clinical practice.

Erenumab 140 mg is clinically effective for chronic migraine compared with best supportive care but less so at 70 mg

3.6 Study 295 compared erenumab's effectiveness with placebo in 667 people with chronic migraine. The company presented the results of a post-hoc subgroup analysis of erenumab's effectiveness in people for whom at least 3 previous preventive treatments had failed, defined as insufficient or partial response, insufficient dosage or adverse events (excluding people whose condition had no therapeutic response to more than 3 treatments). Results showed that erenumab 140 mg reduced the number of monthly migraine days from baseline to week 12 by 4.1 days more on average than placebo (95% confidence interval [CI] −5.8 to −2.3).

The 70 mg dosage reduced monthly migraine days by 2.5 days more on average than placebo (95% CI −4.3 to −0.8). The proportion of people with at least a 50% reduction in monthly migraine days was 38.5% for the 140 mg dosage, 34.8% for the 70 mg dosage, and 15.3% for placebo. The results were statistically significant. The committee recognised that erenumab 140 mg also improved other outcomes compared with placebo, including the severity of migraine pain and the number of headache days each month. The committee noted that erenumab 140 mg reduced monthly migraine days compared with placebo more than the 70 mg dosage compared with placebo. The committee also noted that in this population at least a 30% reduction in migraine frequency was considered a clinically meaningful response (see section 3.3). Therefore, the clinical evidence did not fully reflect the most relevant outcomes. It concluded that erenumab 140 mg was clinically effective in chronic migraine when compared with best supportive care, but less so at the 70 mg dosage.

Erenumab 140 mg may be clinically effective for episodic migraine compared with best supportive care but erenumab 70 mg is not

3.7 STRIVE, ARISE and LIBERTY compared erenumab with placebo in a total of 1,778 people with episodic migraine. A post-hoc subgroup analysis was done to show erenumab's effectiveness in people for whom at least 3 previous treatments had failed. In STRIVE and ARISE this was defined as insufficient or partial response, insufficient dosage or adverse events (excluding people whose condition had no therapeutic response to more than 2 treatments). In LIBERTY, this was defined as insufficient, partial or no response, insufficient dosage or adverse events (excluding people who had more than 4 treatments). The proportion of people with at least a 50% reduction in monthly migraine days was greater for erenumab than for placebo (results are academic in confidence and cannot be reported here). Erenumab was also more effective than placebo in reducing the number of monthly migraine days from baseline to week 12. The results were statistically significant for the 140 mg dose in STRIVE but not in LIBERTY (ARISE only studied the 70 mg dose). But the committee noted

that in STRIVE, monthly migraine days increased in the placebo group. This was not seen in the full trial population or in the subgroup in the other trials, suggesting that this could be a chance effect in a small subgroup and therefore increased uncertainty in the effect shown. The committee also noted that none of the results for the 70 mg dosage were statistically significant. The committee concluded that erenumab 140 mg may be clinically effective for episodic migraine when compared with best supportive care but there was no evidence that the 70 mg dosage was clinically effective.

High-frequency episodic migraine is not a distinct subgroup

3.8 At consultation, the company updated its submission to focus on chronic migraine and high-frequency episodic migraine only. The company defined high-frequency episodic migraine as between 10 and 14 monthly headache days. The committee was aware that the clinical-effectiveness data for the 140 mg dose of erenumab in people for whom at least 3 previous treatments had failed came from the STRIVE and LIBERTY trials. In STRIVE at week 24, people who had treatment with erenumab 140 mg had a statistically significant reduction in monthly migraine days compared with placebo. In LIBERTY, erenumab 140 mg achieved a numerically greater reduction in monthly migraine days from baseline to week 12 compared with placebo. The exact results for this subgroup are academic in confidence and cannot be reported. The ERG noted that high-frequency episodic migraine was defined in the company's trials as between 8 and 14 monthly migraine days and the results may not give adequate effectiveness data for a population with high-frequency episodic migraine, defined as 10 to 14 monthly headache days. The committee was concerned at the small numbers of people included in the subgroup (17 people in the erenumab arm of STRIVE and 76 people in erenumab arm of LIBERTY). It also noted that this was a subgroup derived from a post-hoc subgroup analysis of the population with episodic migraine (see section 3.7). At the second appraisal committee meeting, the clinical experts explained that there is no internationally recognised classification

of high-frequency episodic migraine and that it is not a clearly defined clinical subgroup. Clinical experts noted that the definition of high-frequency episodic migraine is arbitrary and that a person's quality of life is negatively affected irrespective of which type of migraine they have. The nature of the condition means that some people's migraine can be episodic one month or chronic the next according to the definitions. The committee considered that the clinical-effectiveness results for the high-frequency episodic migraine group were highly uncertain. It concluded that high-frequency episodic migraine is not a distinct subgroup and agreed not to consider it further.

The long-term comparative effectiveness of erenumab is unknown

3.9 The duration of the blinded phase in the trials was just 3 months for study 295 (chronic migraine), ARISE and LIBERTY (episodic migraine), and 6 months for STRIVE (episodic migraine). The company provided supporting data for erenumab's long-term effectiveness from 2 open-label extension studies: a phase II trial in episodic migraine and an extension to study 295 in chronic migraine. The results showed that, in people who completed the trials, the improvement in monthly migraine days at 12 weeks was maintained while on treatment for up to 64 weeks for episodic migraine, and for up to 52 weeks for chronic migraine. The committee noted that 87% of people in STRIVE and 74% of people in study 295 completed the follow-up period. The committee was aware that there was no evidence that comparative efficacy was maintained beyond the blinded phase of the trials. It also noted that the efficacy of erenumab in the open-label extension studies was from the full trial populations, with 13% to 26% of people lost to follow up. The committee further noted that the results of the open-label extension phase II trial (of 70 mg erenumab) in episodic migraine were better than the intention-to-treat results from STRIVE and ARISE. It recalled that, in the evidence the company submitted for the subgroup of people for whom at least 3 previous treatments had failed, the benefit of the 70 mg dose was not statistically significantly different to placebo (see section 3.7). The results for the

140 mg dose of erenumab for episodic migraine were not presented by the company. After the second meeting, the company presented additional clinical data on the long-term effectiveness of erenumab for episodic migraine from an open-label trial following a randomised controlled trial. The mean change in monthly migraine days in the open-label trial, from baseline to month 57 (year 4.5), was −5.8 days (standard error 0.3). At this time point 76.5% of the participants' mean monthly migraine days had reduced by 50% or more. The ERG had concerns about the additional clinical data. In particular, the population in the study was different to the company's proposed population for erenumab, which is people whose condition has not responded to at least 3 oral preventive treatments (see sections 3.2 and 3.3). The open-label study did not specify prior treatment failure and most people (56%) included had not had treatment before. Prior treatment had failed in 36%, but the number of prior treatments was not specified, and included discontinuations because of lack of efficacy, adverse events, or both. Therefore, the committee agreed that the additional clinical data from the open-label study were not directly applicable to the population being considered in the appraisal. The committee concluded that it was unclear whether erenumab works in the long term because there was no evidence that comparative efficacy was maintained in people whose condition has not responded to at least 3 oral preventive treatments.

Indirect treatment comparison

It is very uncertain whether erenumab is more clinically effective than botulinum toxin type A

3.10 There was no direct evidence comparing erenumab with botulinum toxin type A in chronic migraine. So the company did an indirect comparison using data from study 295 for erenumab and PREEMPT1 and PREEMPT2, which compared botulinum toxin type A with placebo. It indirectly compared the proportion of people on:

- erenumab with at least a 50% reduction in monthly migraine days at 12 weeks
- botulinum toxin type A with at least a 50% reduction in monthly headache days at 24 weeks.

The comparison was in the subgroup for whom at least 3 previous treatments had failed (as defined in section 3.3). The difference in outcomes and time points reflected the difference in primary outcomes and timing of assessments between the trials. The resulting odds ratio favoured erenumab but the result was not statistically significant either for the subgroup of people for whom at least 3 previous treatments had failed, or for the full trial populations (presented as supporting data; results are academic in confidence and cannot be reported here). Because the results were not statistically significant (that is, the confidence interval included an odds ratio of 1), erenumab could be more effective or less effective than botulinum toxin type A. The committee noted that the confidence interval around the odds ratio was wide, which meant that there was a high degree of uncertainty associated with the odds ratio favouring erenumab. The committee considered that the company's methods for the indirect treatment comparison were appropriate but noted the differences between the trials for erenumab and botulinum toxin type A. The company used placebo as the common comparator, but it was administered differently in the trials: as a single subcutaneous injection every 4 weeks in the erenumab trial and as intramuscular injections into 31 to 39 different sites on the head and neck in the botulinum toxin type A trials. Given these differences, the committee did not think these should be considered the same, and this could have affected the substantially different placebo responses recorded in the trials. There was a difference in monthly migraine days with erenumab and monthly headache days with botulinum toxin type A. Given that these were separately reported as clinically distinct outcomes the committee did not think that these should be considered as the same. Also, the baseline characteristics of people in the PREEMPT trials in the subgroup who had

3 previous failed treatments were not available to the company and so it was uncertain whether the populations were similar. The committee also considered that the long-term variability in symptom frequency and severity associated with chronic migraine was not adequately captured by the short duration of the indirect treatment comparison. Given the concern over the analysis, the lack of statistically significant results, and the wide confidence intervals, the committee concluded that there was a high degree of uncertainty about whether erenumab is more clinically effective than botulinum toxin type A for chronic migraine.

Adverse events

Erenumab is generally well tolerated in the populations studied

3.11 The rates of serious adverse events in the 4 trials were low, and most of the adverse events were of low to moderate severity. The company considered that erenumab had a safety and tolerability profile comparable with placebo. The committee was aware however that the adverse event data were for the full trial populations and may be different in people for whom 3 previous treatments had failed (including because of intolerability). However, this would be from a much smaller group of people and it would be unlikely that firm conclusions could be drawn. But the committee was also aware that the trials excluded people over 65, anyone with significant comorbidity (for example, cardiovascular disease), and women who could become pregnant, and that no conclusions could be drawn for these groups either. The committee concluded that the adverse events in the trials with erenumab were generally not severe and were comparable with placebo, and erenumab was generally well tolerated in the studied populations.

The company's economic model

The company's updated economic model is appropriate

3.12 The company modelled the assessment period of 12 weeks (24 weeks for botulinum toxin type A) as a decision tree, and the post-assessment

period as a Markov model that included 3 states: on treatment, off treatment and death. The company updated its economic model and modelling assumptions after consultation and after the second committee meeting to include:

- a lifetime time horizon
- only the 140 mg dose of erenumab.

The committee concluded that the company's updated model using a lifetime time horizon was appropriate. It concluded that the 140 mg dose of erenumab was clinically effective in chronic migraine but less so at the 70 mg dose, based on the clinical-effectiveness results (see sections 3.6 and 3.7). It also concluded that it was acceptable to consider only the 140 mg dose in the cost-effectiveness model.

Comparison with botulinum toxin type A

The indirect treatment comparison results are uncertain, so it is appropriate to also consider analyses in which erenumab and botulinum toxin type A have similar effectiveness

3.13 The company's base case used the odds ratio from the indirect treatment comparison to inform the relative effectiveness of erenumab compared with botulinum toxin type A. The committee was aware that the results of the indirect treatment comparison were highly uncertain (see section 3.10). It noted that the relative benefit of erenumab in the company's base case was unchanged over the lifetime time horizon in the model and considered this unlikely (see section 3.14). The committee also noted the additional uncertainty not captured in the confidence intervals of the indirect treatment comparison. This arose from differences in the study populations' baseline characteristics, outcome measures (that is, monthly migraine days for erenumab and monthly headache days for botulinum toxin type A) and treatment assessment time points (see section 3.10). At consultation and after the second appraisal committee meeting the company presented scenarios with the odds ratio for the

comparison with botulinum toxin type A set to 1 (similar efficacy) and scenarios using a midpoint between 1 and the odds ratio of the indirect comparison. The committee agreed with the ERG that the midpoint odds ratio scenario was not methodologically justified because it was an arbitrary figure and not supported by evidence. It did not consider this scenario further. The committee noted consultation comments that long-term real-world evidence on botulinum toxin type A from the NHS in England for the relevant patient population (people for whom at least 3 previous treatments had failed) showed that adherence, efficacy and safety is sustained or improved over a 5-year period. It also noted the clinical experts' consultation comments that it was plausible that botulinum toxin type A and erenumab could be considered to have equal efficacy. However, given the long-term and promising real-world data for botulinum toxin type A, the committee considered that the relative effectiveness of erenumab compared with botulinum toxin type A was not certain in the long term. Also, it recalled its concerns and the uncertainty with the indirect treatment comparison (see section 3.10). Because of the uncertainty in the results of the indirect treatment comparison, the committee considered it appropriate to also consider cost-effectiveness analyses in which erenumab and botulinum toxin type A were assumed to have similar effectiveness (that is, using an odds ratio of 1).

Modelling long-term treatment effectiveness

While people stay on treatment, it is reasonable to assume that the treatment effect does not wane over time

3.14 The company's model assumed that the treatment effect stayed constant while people were on treatment. The committee was aware however that in other chronic conditions the effects of monoclonal antibodies can wane over time. It noted that the company had provided a scenario during clarification that incorporated a treatment waning effect, whereby health state costs and utilities for erenumab and botulinum toxin type A were linearly reduced over 10 years until they were in line with best supportive

care. The ERG had also modelled this and another scenario whereby treatment effect waned over a 5-year period. At consultation the company provided an additional treatment waning scenario whereby treatment waning started at 5 years and waned over a 10-year period. The committee was not presented with any evidence to suggest that erenumab would follow this type of waning pattern. After the second meeting, the company commented that in the ERG's 5 and 10-year waning scenarios, health state costs and health state utilities reduced for patients whose migraine responded to treatment. However, treatment was not stopped as efficacy waned; therefore, treatment costs continued to accrue over the long term. The company considered these as extreme scenarios because treatment should be stopped if people no longer have a clinically meaningful benefit (see section 3.16). The company therefore submitted an alternative scenario that used an additional discontinuation rate instead of a waning assumption, along with longer-term clinical data from an open-label extension study in episodic migraine. The committee agreed that treatment effect waning and treatment discontinuation are 2 separate issues, and adjusting the discontinuation probabilities does not reflect the uncertainty of potential waning (see section 3.15). The long-term clinical data from the extension study showed that low numbers of people withdrew from erenumab treatment because of a lack of efficacy. The committee was aware of conflicting clinical expert opinion as to whether treatment resistance could occur with erenumab. At the second committee meeting the clinical expert suggested that erenumab's mechanism of action as a calcitonin gene-related peptide receptor meant that it may not be associated with a treatment waning effect. However, the committee also noted that a clinical expert at consultation thought that development of treatment resistance was possible. The committee noted that in the erenumab clinical trials, the number of people who developed neutralising antibodies to erenumab was low (approximately 0% to 3%). To date there is no evidence of the impact of anti-erenumab antibody development on efficacy and safety. The committee understood that if a person did develop anti-erenumab antibodies, waning is unlikely to be

linear over time because efficacy would be lost quickly. Based on the evidence available, the committee considered that it was reasonable to assume that the treatment effect does not wane over time.

The company's additional treatment discontinuation scenario is not appropriate

3.15 After the second meeting, the company submitted another scenario analysis that used an additional discontinuation rate as an alternative to treatment waning (see section 3.14). In this scenario, an assumed annual discontinuation rate of 10% because of loss of efficacy was applied in addition to the 2.38% all-cause discontinuation rate already in the company's base case. This additional loss of efficacy discontinuation rate was applied to both the erenumab and botulinum toxin type A treatment arms in the model. The ERG agreed that loss of efficacy may result in treatment discontinuation, but the company's scenario did not reflect the gradual loss of effectiveness that would likely occur before treatment was stopped. This was because people were taken off treatment without any loss of effectiveness in this company scenario. The committee considered that the longer-term data for erenumab submitted by the company after the second meeting (see section 3.9) did not support this level of treatment discontinuation because of loss of efficacy. The data showed that only 5.6% of people taking the 140 mg dose of erenumab stopped treatment, and none of them because of loss of efficacy. Approximately half of these people had asked to stop treatment, but the reasons for stopping were unknown. The committee concluded that the company's additional treatment discontinuation scenario was not appropriate.

Applying a negative stopping rule is appropriate

3.16 The company's model assumed that treatment would be stopped for people who did not respond to erenumab at 3 months. This negative stopping rule was applied to people having less than a 30% reduction in monthly migraine days. At consultation, clinical experts noted that applying a rule using a 50% reduction in monthly migraine days would be

a more accurate reflection of the efficacy of treatments in everyday clinical practice. However, the committee considered the 30% threshold for the chronic group to be appropriate and consistent with NICE's technology appraisal guidance on botulinum toxin type A and the British Association for the Study of Headache guidelines. The committee concluded that it was appropriate to include a negative stopping rule at 3 months in the economic model if there was no response to treatment. No response was defined as those with less than a 30% reduction in monthly migraine days at the 12-week assessment.

The company's positive stopping rule scenarios are not appropriate

3.17 The clinical experts explained that in practice, if migraine responds to treatment, some people may try a treatment break. The committee also noted the clinical experts' written comments that some people may stay on treatment indefinitely. The committee recalled that the company's base case modelling reflected a constant treatment effect over a lifetime time horizon. At consultation the company presented 2 positive stopping scenarios, which assumed that people staying on treatment would be reassessed after 64.5 weeks. After that, 20% of people would stop treatment, while the remainder would resume treatment and be reassessed at 76.5-week intervals. In the first scenario, people who stop treatment would continue to benefit from erenumab for the lifetime time horizon of the model without incurring the costs. The committee was aware that there was no evidence to indicate the duration of treatment benefit (see section 3.14), or maintenance of constant benefit, once treatment had been stopped. The patient expert explained that once treatment with erenumab was stopped the benefit was maintained for only a short time before the migraine returned. In the second scenario, people who stop treatment would return to monthly migraine days based on the placebo arm of the trial. The committee did not consider this scenario appropriate either because erenumab would need to be restarted for these people and the company's model did not allow people to return to treatment once the positive stopping rule was applied. The committee

therefore concluded that the positive stopping scenarios were not appropriate for consideration.

Utilities

Utility values used in the model are highly uncertain

3.18 The company collected quality-of-life data in study 295 (chronic migraine), STRIVE and ARISE (episodic migraine) using the Migraine-Specific Quality of Life Questionnaire (MSQ) and in LIBERTY (episodic migraine) using the EQ-5D-5L. The utility values used in the model were generated from mapping MSQ results to EQ-5D-3L using the Gillard et al. 2012 algorithm. The company explained that the EQ-5D-5L data collected in LIBERTY were not sensitive to changes in quality of life with migraine because the questionnaire was given on appointment days, and asked people about their quality of life on that day. If a patient was having a migraine that day, they would likely rearrange their appointment. So the company considered that the EQ-5D-5L data were collected when the person did not have migraine, and were therefore not appropriate to use in the model. It considered the MSQ to be more appropriate because it had a 4-week recall period. The clinical experts explained that in clinical practice they use the HIT6 and MIDAS tools, not the MSQ, to measure quality of life, so it was not known whether MSQ was the best available measure of quality of life. The committee agreed that the rationale for using MSQ instead of direct EQ-5D-5L data was plausible. However, the committee considered that the actual utility values generated from mapping the MSQ data to EQ-5D-3L may be underestimates, given that they were low (average values ranged from 0.466 to 0.784 across the different health states). However, it recognised that the baseline values for people with chronic migraine represented people having on average about 15 migraine days a month. Given the before and after effects described by the patient experts (see section 3.1) the low utility value of 0.466 could accurately represent quality of life. The committee was also aware that the MSQ data had been mapped to EQ-5D-3L in NICE's technology appraisal

guidance on botulinum toxin type A and that the utility values used were broadly similar. The committee understood that the MSQ data were based on the full trial population, and not just on those for whom at least 3 previous treatments had failed. Also, there were separate mapping algorithms for chronic and episodic migraine but because of small patient numbers these had been applied at the individual patient level based on the number of migraine or headache days at baseline, which created more uncertainty. The committee noted that the utility data were a key driver of the cost-effectiveness estimates and it was concerned about the reliability of the values given the uncertainty of using data from a broader population and mapping this to EQ-5D-3L. On balance, the committee concluded that the utility values used in the model may be reasonable but were uncertain.

Applying a mode of administration utility decrement to botulinum toxin type A is not appropriate

3.19 The company provided scenario analyses which incorporated a utility decrement associated with the mode of administration of botulinum toxin type A. The company suggested that treatment with botulinum toxin type A leads to an increased burden on people compared with treatment with erenumab because of the number of injections needed in the head and neck. At consultation clinical experts noted that erenumab could have a reduced burden on people compared with botulinum toxin type A. However, other comments received during consultation suggested that long-term real-world evidence showed an improvement in quality of life with botulinum toxin type A compared with best supportive care. The company's scenario used a vignette-based time trade off utility valuation study, done in the UK, to derive mode of administration decrements for migraine prophylaxis treatments relative to erenumab. The decrements were applied additively to each monthly migraine day-specific utility value throughout the model. The committee noted that when the utility decrement scenario was applied the total quality-adjusted life years (QALYs) for botulinum toxin type A were lower than for best supportive

care. It considered that this scenario was not clinically plausible. The committee concluded that applying a mode of administration utility decrement to botulinum toxin type A was not appropriate.

Costs

All relevant costs for implementing erenumab in practice are captured in the model

3.20 The clinical experts explained that erenumab would initially be used in a secondary care specialist headache clinic. It recognised the advantages of a self-injectable treatment but given the novel nature of erenumab and the need for starting and stopping rules to ensure it was used appropriately, treatment would need to be started by doctors experienced in treating migraine. The committee considered that for erenumab to be available for the most refractory cases of migraine, and to meet the monitoring requirements, additional resources would likely be needed, and that the cost of setting up these additional services should be accounted for in the model. To inform its assumptions about resource use involving healthcare professionals, the company had used results from a National Health and Wellness Survey involving people across Europe (including the UK), which aimed to characterise migraine burden from the patients' perspective. However, the company assumed that the results, which were grouped into categories based on the number of headache days per month, approximated resource use per migraine day. Consultation comments from clinical experts noted that erenumab treatment would be started in a specialist headache clinic, but the person would be trained to self-administer treatment at home. Consultation comments suggested that self-administration is important because it gives people a sense of control. Further comments from clinical experts suggested that using erenumab in practice is unlikely to affect referrals to specialist services because this was not the case when botulinum toxin type A became available, and these people are already being seen in specialist clinics. At consultation the company updated its economic

model to include the appropriate triptan injection price, which the committee accepted. The committee was satisfied that all relevant costs were captured in the modelling.

Cost-effectiveness estimates

The company's updated cost-effectiveness analyses are appropriate for decision making

3.21 At consultation and after the second meeting the company provided updated cost-effectiveness analyses for consideration. At consultation the updated company's base case included a patient population with chronic migraine and high-frequency episodic migraine only. The committee recalled that the high-frequency episodic migraine population was not a distinct group (see section 3.8) and therefore agreed that it should not consider the cost-effectiveness analyses for this population further. After the second committee meeting, the company's updated base case and scenario analyses considered only chronic migraine and included the following assumptions and scenarios:

- A revised commercial arrangement which included a confidential simple discount in addition to a complex patient access scheme (that is, erenumab is given free of charge for a period of time).
- erenumab compared with botulinum toxin type A and best supportive care (see section 3.4)
- a negative stopping rule using less than a 30% response to treatment (see section 3.16)
- an odds ratio from the indirect treatment comparison, a midpoint indirect treatment comparison odds ratio and an odds ratio of 1 for the comparison with botulinum toxin type A (see section 3.13)
- a range of treatment waning scenarios, including no treatment waning (company base case), ERG treatment waning scenarios of 5 and 10 years, and a company waning scenario of 10 years (starting from year 5; see section 3.14)

- an alternative scenario that applied an additional 10% annual discount rate because of a lack of efficacy instead of a treatment waning effect (see section 3.15).

All of the company's incremental cost-effectiveness ratios (ICERs) after the second committee meeting incorporated a confidential commercial arrangement and were considered confidential by the company. Therefore, they cannot be reported in this document. The ICERs ranged from below £30,000 per QALY gained to substantially over £30,000 per QALY gained. The committee noted that the ERG was able to reproduce the company's cost-effectiveness estimates provided after the second meeting, but the ERG did not provide any additional exploratory analysis.

Erenumab is not cost effective for chronic migraine compared with botulinum toxin type A and best supportive care after 3 preventive treatments have failed

3.22 The committee recalled that:

- the treatment effect does not wane over time (see section 3.14)
- it was not appropriate to include an additional discontinuation rate along with the company's original 2.38% rate for all-cause discontinuation rate every 12 weeks (see section 3.15)
- given the uncertainty in the results of the indirect treatment comparison, it was appropriate to consider the odds ratio from the indirect treatment comparison and an odds ratio of 1 when erenumab and botulinum toxin type A are assumed to have similar effectiveness (see section 3.13).

The committee was aware that the ICERs were highly sensitive to the assumption about the effectiveness of erenumab compared with botulinum toxin type A. It preferred a fully incremental analysis, that is, a combined single analysis in which best supportive care is compared with botulinum toxin type A, which in turn is then compared with erenumab. When the odds ratio from the indirect treatment comparison was used, best supportive care and erenumab 'extendedly dominated' botulinum toxin type A (that is, botulinum toxin type A was less effective and had a

higher ICER than erenumab), leaving the relevant comparison between best supportive care and erenumab. The ICER for erenumab compared with best supportive care was below £30,000 per QALY gained. When an odds ratio of 1 (assuming equal effectiveness) was used, the ICER for erenumab compared with botulinum toxin type A was substantially above £30,000 per QALY gained. The committee considered both ICERs plausible. However, it considered that the ICER based on the odds ratio from the indirect treatment comparison was more uncertain because of the:

- differences between the trials for erenumab and botulinum toxin type A used in the indirect treatment comparison analysis (see section 3.10)
- long-term real-world data on the efficacy and safety was available for the comparator botulinum toxin type A but not available for erenumab. (see section 3.13).

The committee considered the substantial impact on the ICER when assuming equal effectiveness between erenumab and botulinum toxin type A. It noted that the ICER was substantially above the £20,000 to £30,000 per QALY gained range usually considered a cost-effective use of NHS resources. It concluded that, on balance, erenumab compared with botulinum toxin type A and best supportive care was not a cost-effective use of NHS resources for preventing chronic migraine in adults after 3 preventive treatments have failed.

Erenumab is not cost effective in episodic migraine compared with best supportive care after 3 preventive treatments have failed

3.23 The committee noted that the company did not submit any updated cost-effectiveness analyses for episodic migraine at consultation or after the second committee meeting. The committee recalled that it had concluded in the appraisal consultation document that erenumab was not cost effective in episodic migraine compared with best supportive care after 3 preventive treatments (the ICER for erenumab compared with best supportive care was £40,662 per QALY gained). It also noted that the

analyses for these ICERs did not include all of its preferred assumptions or the revised commercial arrangement (see section 3.21). The company had submitted an updated cost-effectiveness analysis for the population with high-frequency episodic migraine. The committee recalled that it had concluded that high-frequency episodic migraine was not a distinct group and that it should not consider the cost-effectiveness analysis for this population further (see section 3.8). Because the committee was not presented with any analyses for the population with episodic migraine that included all of its preferred assumptions and the revised confidential commercial arrangement (see section 3.21), it concluded that it could not recommend erenumab for episodic migraine after 3 preventive treatments have failed.

Other factors

There are no equalities issues that can be addressed in the guidance

3.24 No equalities issues were identified by the company. The clinical and patient submissions highlighted that migraine can be classed as a disability under the Equality Act 2010. Because migraine is most common in people of working age and affects more women than men, women may be further disadvantaged in the workplace. It was also noted that there may be unequal access to specialist headache clinics. The committee considered these issues but concluded that there were no specific adjustments needed to the NICE methods in this instance.

There are no health-related benefits that are not captured in the analyses

3.25 The company explained that erenumab was a first-in-class therapy and therefore a step-change in the management of migraine. However, the committee considered that all relevant aspects of erenumab were captured in the economic modelling and there were no other factors to consider that could enable it to accept a higher maximum acceptable ICER.

Conclusion

Erenumab for chronic migraine is not recommended for use in the NHS

3.26 The committee considered the evidence that erenumab was clinically effective (at 140 mg) in chronic migraine when compared with best supportive care and when response was measured as a 50% or greater reduction in monthly migraine days (see section 3.6). However, it considered that a 30% reduction in monthly migraine days was more clinically relevant (see section 3.3). It considered that there was a high degree of uncertainty about whether erenumab was more clinically effective than botulinum toxin type A (see section 3.10) and agreed that it was appropriate to assume equal effectiveness (see section 3.13). The committee considered the substantial impact on the ICER when assuming equal effectiveness between erenumab and botulinum toxin type A and that the ICER was considerably higher than the £20,000 to £30,000 per QALY gained range usually considered a cost-effective use of NHS resources. Given the substantial uncertainty in the evidence for the clinical and cost effectiveness of erenumab, the committee concluded, that on balance, erenumab compared with botulinum toxin type A and best supportive care was not a cost-effective use of NHS resources for preventing chronic migraine in adults. Therefore, it could not recommend erenumab for use in the NHS for preventing chronic migraine in adults who have at least 4 migraine days a month.

Erenumab for episodic migraine is not recommended for use in the NHS

3.27 In episodic migraine, the committee had concluded that the evidence showed that erenumab 140 mg may be clinically effective when compared with best supportive care. It considered that the evidence to support the effectiveness of erenumab in high-frequency episodic migraine was uncertain and did not consider it further because it is not a distinct subgroup (see section 3.8). The company did not present an updated base case for erenumab for preventing episodic migraine at consultation or after the second meeting (see section 3.21). Therefore, the committee

was unable to recommend erenumab for use in the NHS for preventing episodic migraines in adults who have at least 4 migraine days per month.

4 Review of guidance

4.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Gary McVeigh
Chair, appraisal committee
September 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Omar Moreea, Alan Moore

Technical leads

Victoria Kelly, Nicola Hay

Technical advisers

Joanne Ekeledo, Stephanie Callaghan

Project managers

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