

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Erenumab for preventing migraine

1 Recommendations

1.1 Erenumab is recommended as an option for preventing migraine in adults, only if:

- they have 4 or more migraine days a month
- at least 3 preventive drug treatments have failed
- the 140 mg dose of erenumab is used and
- the company provides it according to the commercial arrangement (see section 2).

1.2 Stop erenumab after 12 weeks of treatment if:

- in episodic migraine (less than 15 headache days a month) the frequency does not reduce by at least 50%
- in chronic migraine (15 headache days a month or more with at least 8 of those having features of migraine) the frequency does not reduce by at least 30%.

1.3 These recommendations are not intended to affect treatment with erenumab that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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

Treatments for preventing chronic or episodic migraine include beta-blockers, antidepressants and antiepileptic drugs. 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 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 no direct evidence comparing erenumab with botulinum toxin type A in chronic migraine, but an indirect comparison suggests that erenumab has some benefit. It is plausible that erenumab may work better than botulinum toxin type A.

The cost-effectiveness estimates are within what NICE usually considers an acceptable use of NHS resources. So erenumab is recommended for preventing migraine in adults who have at least 4 migraine days per month.

2 Information about erenumab

Marketing authorisation indication

- 2.1 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

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The list price of erenumab is £386.50 per 70 mg or 140 mg injection (excluding VAT, BNF online accessed November 2020). The company has a commercial arrangement (simple discount patient access scheme).

This makes erenumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) 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 antiepileptic drugs. 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 the response is lower than this (an insufficient or partial clinical response), 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. It concluded that best supportive care was the most appropriate comparator in episodic migraine. For people with chronic migraine who have tried 3 oral preventive treatments that have not 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 type A rather than best supportive care after trying 3 oral preventive treatments.

The evidence may not fully reflect the 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 evidence may not fully reflect the people who may be eligible for erenumab in clinical practice and it would take this into account.

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. The analysis excluded 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. It 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 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 erenumab 140 mg had a statistically significant reduction in monthly migraine days compared with placebo. In LIBERTY, people who had erenumab 140 mg had 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 by 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 2 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 2 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 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 had not responded to at least 3 oral preventive treatments.

Treatment with a second anti-CGRP drug is not supported by the evidence

3.10 The committee was aware the scope did not include other medicines in the anti-calcitonin gene-related peptide (CGRP) class as potential comparators. Therefore erenumab was not formally compared with them. The committee was not presented with any evidence to support subsequent treatment with other anti-CGRPs, if the initial clinically meaningful response to erenumab treatment is lost. It noted that there was no clinical evidence to support any difference in efficacy between the

different anti-CGRP drugs. Because the drugs target the same pathway it is plausible that their effectiveness is similar. The committee also noted that treatment preferences are not outlined in the [British Association for the Study of Headache's guidelines](#). Therefore the committee considered it reasonable that the least expensive drug would be used unless an alternative was more suitable for the person. The committee concluded that treatment with another anti-CGRP drug, after failure of a previous anti-CGRP drug, was not supported by evidence.

The clinical evidence for having erenumab after botulinum toxin type A or when botulinum toxin type A is contraindicated is uncertain

3.11 After a previous version of the final appraisal document was released, an [appeal](#) was brought against the decision by the British Association for the Study of Headache and the Association of British Neurologists. One of the appeal points was upheld by the appeal panel. This was that the committee unreasonably failed to consider the cost effectiveness of erenumab compared with best supportive care in those whose chronic migraine had failed to benefit from the comparator drug. Before the appeal, the company had not provided any evidence on the efficacy of erenumab after the use of botulinum toxin type A. It had also not provided any evidence for an alternative treatment sequence when erenumab is used beyond third line and when botulinum toxin type A is contraindicated. After the appeal, the company presented evidence from study 295 on erenumab's treatment effect in 2 post-hoc subgroups:

- people with chronic migraine, for whom at least 4 previous treatments, including botulinum toxin type A, had failed
- people with chronic migraine for whom 3 or more previous preventive treatments had failed, and who had not previously had botulinum toxin type A.

The latter subgroup was used as a proxy for those for whom botulinum toxin type A was contraindicated. In both these subgroups, erenumab reduced monthly migraine days more on average than placebo. Also, a

higher percentage of each population had a 30% reduction in monthly migraine days on erenumab compared with placebo (the values cannot be shown here, because they are considered confidential by the company). The ERG questioned the validity of not having botulinum toxin type A treatment as a proxy for botulinum toxin type A being contraindicated, because there are other reasons for not having botulinum toxin type A. The ERG also noted that these post-hoc subgroups were very small, so a meaningful analysis of them may not have been possible. The company and the British Association for the Study of Headache provided some observational data on the use of erenumab in English centres, which supported the study 295 data because a 30% or more reduction in monthly migraine days was seen for some people at week 12. The committee concluded that because of the small subgroups, and the post-hoc analysis of these, there was uncertainty around the clinical evidence. It took this into account in decision making.

Indirect treatment comparison

The indirect treatment comparison does not show a treatment effect for erenumab over botulinum toxin type A

3.12 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 favouring erenumab was wide, which meant that there was a high degree of uncertainty associated with it. 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. The committee was concerned about the analysis, given the lack of statistically significant results and the wide confidence intervals. It concluded that, based on the indirect treatment comparison

alone, it was uncertain 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

3.13 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 has 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 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 a 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 noted that the safety profiles for erenumab 140 mg and 70 mg were similar. It provided evidence from UK neurologists, who considered that they would likely start people with difficult-to-treat migraine on the 140 mg dose, rather than the 70 mg dose. The committee recognised that sometimes it would be more appropriate for a person to have treatment with the lower dose.

The company's economic model

The company's updated economic model is appropriate

3.14 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 erenumab and botulinum toxin type A are assumed to have similar effectiveness

3.15 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 3.12). 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 3.17). The committee also noted the additional uncertainty in the indirect treatment comparison, which was not captured in the confidence intervals. 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 times (see section 3.12). 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) or 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 was available. This was for the relevant population (people for whom at least 3 previous treatments had failed) and 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 3.12). Because of the uncertainty in the results of the indirect treatment comparison, at the time of the third committee meeting 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).

Including a treatment effect for erenumab compared with botulinum toxin type A is acceptable

- 3.16 In the company's indirect treatment comparison, to determine the relative efficacy of erenumab 140 mg compared with botulinum toxin type A, there was some uncertainty about whether erenumab may be more effective. The difference in monthly migraine days, which was not statistically significant, favoured erenumab over botulinum toxin type A. The company used these indirect treatment comparison estimates in a scenario analysis for the fourth appraisal committee meeting (the odds ratio used was considered confidential by the company so cannot be shown here). This was in line with the modelling done in [NICE's technology appraisal guidance on galcanezumab](#). In this, a treatment effect for galcanezumab compared with botulinum toxin type A was used in the final decision-

making model (instead of assuming equivalence). The committee recalled that according to clinical opinion, anti-CGRP drugs are more effective than botulinum toxin type A. Also, the committee was aware that in [NICE's technology appraisal guidance for fremanezumab](#) and galcanezumab, the companies provided indirect treatment comparison point estimates that favoured the anti-CGRP drug over botulinum toxin type A. However, this was associated with uncertainty. The committee was aware that the commercial arrangement for erenumab had been improved. The company provided threshold analysis showing that even a marginal benefit of erenumab over botulinum toxin type A reduced the cost-effectiveness estimates for erenumab for chronic migraine. The committee was aware that, for galcanezumab in the same population, it was able to accept the indirect treatment comparison results. This was because they showed a positive effect for galcanezumab compared with botulinum toxin type A in terms of monthly migraine days. The evidence for erenumab was similar, so the committee agreed that this treatment effect should be taken into account in its decision making.

Modelling long-term treatment effectiveness

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

3.17 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. In this, 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 were reduced for people 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 3.19). 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 waning effect and treatment discontinuation are 2 separate issues, and adjusting the discontinuation probabilities does not reflect the uncertainty of potential waning (see section 3.18). 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 CGRP inhibitor 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

3.18 After the second meeting, the company submitted another scenario analysis that used an additional discontinuation rate as an alternative to treatment waning (see section 3.17). In this scenario, an 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 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

3.19 The company's model assumed that treatment would be stopped for people who did not respond to erenumab at 3 months (a negative stopping rule). The clinical experts had noted that applying a rule using a 50% reduction in monthly migraine days would accurately reflect the efficacy of episodic migraine treatments in clinical practice. Similarly, a 30% reduction in monthly migraine days would be appropriate for chronic migraine (see section 3.3). The committee considered the 30% threshold for the chronic migraine 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's 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 less than a 30% reduction (for chronic migraine) or 50% reduction (for episodic migraine) in monthly migraine days at the 12-week assessment.

The company's positive stopping rule scenarios are not appropriate

3.20 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 show the duration of treatment benefit (see section 3.17), or maintenance of constant benefit, once treatment had been stopped. The patient expert explained that once erenumab treatment 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 this once the positive stopping rule was applied. The committee therefore concluded that the positive stopping scenarios were not appropriate for consideration.

It is acceptable to account for a loss of the placebo effect when migraine responds to best supportive care

3.21 In the company's modelling at the time of the third appraisal committee meeting, the treatment effect for people whose migraine responded to best supportive care was maintained for the lifetime time horizon of the model. Everyone who stopped best supportive care maintained the improvement in monthly migraine days. For the fourth appraisal committee meeting, the company did a scenario analysis in which people whose migraine responded to best supportive care reverted to baseline monthly migraine days at the end of year 1 (a sudden and full loss of placebo effect). Everyone stopping treatment was assumed to return to baseline monthly migraine days. The company considered this to be a slightly more conservative approach than that taken in [NICE's technology appraisal guidance on galcanezumab](#) and [fremanezumab](#). When applying this assumption, the cost-effectiveness estimates for erenumab compared with best supportive care improved. The committee accepted this approach and used it for decision making.

Utilities

Utility values used in the model are highly uncertain

3.22 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 person 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 of migraine 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. 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

3.23 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.

It is acceptable to use differential utilities in the modelling

3.24 The company's original modelling used equal utilities for a health state, regardless of treatment received. The committee recognised that there was some evidence of a treatment effect for erenumab beyond a decrease in monthly migraine days. NICE asked the company for any evidence it had to support the use of differential utilities, capturing treatment benefit beyond a decrease in monthly migraine days, which it had not provided before. The company initially submitted analyses based on a regression model, but the ERG had major concerns about the company's approach. It noted that the regression model was flawed and should not be used. This was because the estimated differential utility (using a 'treatment' covariate where baseline observations were categorised as best supportive care) partly included the placebo effect. In response, the company amended its approach to address the ERG's

concerns. It used separate regression models, including one where baseline quality-of-life data were included with monthly migraine days as the only covariate. Post-baseline quality-of-life data were included in a second regression model with monthly migraine days and treatment as covariates. In this way, separate regression models were used to generate 'off-treatment' utility values and 'on-treatment' utility values, with values differing between erenumab 140 mg and placebo for a given frequency of monthly migraine days. The ERG thought that the company's updated regression models had been implemented correctly and the company's face validity checks were reasonable. However, the ERG preferred the approach taken by the company in its 16 October analyses for the source of differential utility values by intervention and model state. The ERG carried out some scenario analyses with alternative approaches. It found that the exact approach to implement a differential treatment utility was unlikely to be a main driver of the cost effectiveness of erenumab 140 mg. In [NICE's technology appraisal guidance on galcanezumab](#), the committee accepted the use of differential utilities for a health state depending on the treatment used. The committee was satisfied that it had seen enough evidence to support the use of differential utilities for erenumab. It considered that, regardless of the exact implementation approach taken, it was acceptable to use differential utilities in the modelling.

It is appropriate to adjust health state utilities for age in the model

3.25 [NICE's guide to the methods of technology appraisal](#) states that adjustments to utility values, for example for age or comorbidities, may sometimes be needed. When extrapolating health-related quality-of-life data over long time horizons, it is often considered appropriate to adjust for age. This reflects the natural decline in health-related quality of life over time, and ensures utilities do not exceed general population values at a given age. For the fourth appraisal committee meeting, the company did a scenario analysis to use age-adjusted utilities in its modelling. It used a common methodology with utility values weighted based on age

decrements for the UK general population (Ara and Brazier, 2011). The committee noted that this adjustment did not have a large effect on the cost-effectiveness estimates and considered it appropriate to include in its decision making.

Costs

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

3.26 The clinical experts explained that erenumab would initially be used in a secondary care specialist headache clinic. The committee recognised the advantages of a self-injectable treatment. But given the need for starting and stopping rules to ensure erenumab 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. Also, 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. After the appeal, the company incorporated an anti-CGRP administration cost (a 30-minute appointment with a nurse in hospital) in its modelling. This was applied for 10% of patients having erenumab. This was in line with the modelling in previous appraisals of anti-CGRP drugs for migraine. 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

3.27 At consultation the updated company's base case included populations 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 appeal, the company provided updated cost-effectiveness analyses for chronic and episodic migraine, and included the following assumptions and scenarios:

- a revised commercial arrangement (confidential simple discount only)
- evidence for erenumab compared with botulinum toxin type A and best supportive care (chronic migraine) or best supportive care only (episodic migraine; see section 3.4)
- differential utilities for erenumab 140 mg compared with placebo
- a negative stopping rule (see section 3.19)
- a scenario including administration costs for 10% of people having erenumab (see section 3.26)
- a scenario including age-adjusted utilities (see section 3.25)
- a scenario with loss of placebo effect after 1 year for people whose migraine responded to best supportive care (see section 3.21)

- a scenario with a greater treatment effect for erenumab than for botulinum toxin type A (instead of assuming equivalence) from the indirect treatment comparison (see section 3.16).

All of the company's incremental cost-effectiveness ratios (ICERs) presented at the fourth committee meeting included a confidential commercial arrangement. The ICERs were considered confidential by the company and cannot be reported here. Most of the ICERs were around £20,000 per QALY gained, with many below that. The committee noted that the ERG was able to reproduce the company's cost-effectiveness estimates, for both the chronic migraine and episodic migraine populations. The committee concluded that the company's updated cost-effectiveness analyses were appropriate for decision making.

Erenumab is cost effective for chronic migraine and for episodic migraine after 3 preventive treatments have failed

3.28 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).
- The treatment effect does not wane over time (see section 3.17).
- It was not appropriate to include an additional discontinuation rate along with the company's original 2.38% rate for all-cause discontinuation every 12 weeks (see section 3.18).
- It was appropriate to include a treatment effect favouring erenumab over botulinum toxin type A in chronic migraine, because evidence supporting this from an indirect treatment comparison was provided. Also, threshold analysis showed that even a marginal treatment effect made erenumab much more cost effective than when erenumab and botulinum toxin type A were assumed to have equal effectiveness (see section 3.16).
- It was appropriate to use differential utilities in the analysis. This was because of the evidence supporting a treatment benefit for erenumab

compared with placebo beyond a reduction in monthly migraine days. It was also because of the company's corrected regression modelling with off-treatment and on-treatment utilities, with values differing for erenumab 140 mg and placebo for a given frequency of monthly migraine days (see section 3.24).

- The model should use a standard method of adjusting utilities for age over a long time horizon (see section 3.25).
- Administration costs for erenumab should be applied for 10% of people having it (see section 3.26).
- The modelling should account for a loss of the placebo effect in people whose migraine responded to best supportive care (see section 3.21).

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. The committee took its preferences into account after the fourth meeting, including the updated confidential commercial arrangement for erenumab and the confidential Commercial Medicines Unit price for botulinum toxin type A. It agreed that most of the plausible cost-effectiveness estimates were below £20,000 per QALY gained. The committee concluded that erenumab was cost effective for chronic migraine and for episodic migraine after 3 preventive treatments have failed.

Other factors

No adjustments are needed for equality

- 3.29 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 and botulinum toxin

type A. The committee considered these issues and noted that unequal access was not associated with a protected characteristic. So, it concluded that no specific adjustments were needed to NICE's methods in this case.

All relevant aspects of erenumab are captured in the economic modelling

3.30 Erenumab was considered innovative when first discussed by the committee. In its original submission, the company explained that erenumab was a first-in-class therapy and therefore a step-change in the management of migraine. But now, 2 other anti-CGRP drugs have been recommended for use in the NHS to treat migraine. The committee accepted the use of differential utilities (capturing erenumab's benefit beyond a reduction in monthly migraine days), and a treatment benefit of erenumab compared with botulinum toxin type A for chronic migraine after at least 3 previous treatments have failed. So it considered that all relevant aspects of erenumab were captured in the economic modelling.

Conclusion

Erenumab is recommended for chronic migraine after 3 or more preventive treatments have failed

3.31 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), and treatment should be stopped if this is not achieved. It considered that there was a high degree of uncertainty about whether erenumab was more clinically effective than botulinum toxin type A (see section 3.12). But after the company provided further evidence from an indirect treatment comparison, it agreed that it was appropriate to assume a treatment benefit of erenumab over

botulinum toxin type A (see section 3.16). The committee considered the substantial effect of this assumption on the ICER, which was within the range usually considered a cost-effective use of NHS resources.

Therefore, it recommended erenumab for preventing chronic migraine in adults after at least 3 preventive treatments have failed. This includes people with chronic migraine when botulinum toxin type A treatment has failed or is contraindicated. The committee was aware that numbers in these groups would reduce over time because of the introduction of anti-CGRP drugs. Erenumab should be stopped if migraine frequency does not reduce by at least 30% after 12 weeks of treatment.

Erenumab is recommended for episodic migraine after 3 or more preventive treatments have failed

3.32 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, that is, when response was measured as a 50% or greater reduction in monthly migraine days (see section 3.7). Treatment should be stopped if this is not achieved. 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 presented updated analyses for erenumab for preventing episodic migraine for the fourth committee meeting. The clinical evidence supported a treatment benefit, and cost-effectiveness results were within what NICE usually considers an acceptable use of NHS resources. Therefore, the committee recommended erenumab for use in the NHS for preventing episodic migraine in adults after at least 3 oral preventive treatments have failed. Erenumab should be stopped if migraine frequency does not reduce by at least 50% after 12 weeks of treatment.

4 Implementation

4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information](#)

[Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has migraine and the doctor responsible for their care thinks that erenumab is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Review of guidance

- 5.1 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
December 2020

6 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.

Anna Brett, Omar Moreea, Alan Moore, Amy Crossley

Technical leads

Victoria Kelly, Nicola Hay, Caron Jones

Technical advisers

Joanne Ekeledo, Stephanie Callaghan, Gavin Kenny

Project managers

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