NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Erenumab for preventing migraine

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using erenumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using erenumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 31 January 2019

Second appraisal committee meeting: 14 February 2019

Details of membership of the appraisal committee are given in section 4.

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 migraine include beta-blockers, antidepressants and epilepsy medications. If chronic migraine does not respond to at least 3 preventive drug treatments, another oral preventive treatment or botulinum toxin type A are offered. If episodic migraine does not respond to at least 3 preventive drug treatments, another oral preventive treatment is usually offered. The company proposes that erenumab is an option when at least 3 previous treatments have failed, for preventing chronic or episodic migraine.

For people who have had at least 3 previous treatments, the clinical trial evidence shows that erenumab 140 mg works better than best supportive care for preventing chronic migraine. Erenumab 70 mg also works better than best supportive care, but not as well as erenumab 140 mg. For preventing episodic migraine, the 140 mg dosage may work better than best supportive care, but the 70 mg dosage does not. There is no evidence directly comparing erenumab with botulinum toxin type A in chronic migraine or another oral preventive treatment in chronic or episodic migraine. Also, there is uncertainty about whether erenumab works in the long term.

For chronic migraine, the cost-effectiveness estimates for erenumab are higher than what NICE normally considers acceptable when there is substantial uncertainty. For episodic migraine the estimates are much higher than what NICE considers a cost-effective use of resources. So erenumab is not recommended for preventing chronic or episodic migraine.

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 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 apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 4) 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 make plans. The condition can fluctuate over time; it is unpredictable 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, but for people with 10 to 14 headache days a month (high frequency episodic migraine), 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 significantly affects health-related quality of life.

Well-tolerated treatments are needed

3.2 The committee understood that current 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 and can be ineffective for some people. The committee was aware that people with chronic migraine whose condition has not responded to at least 3 previous preventive drug therapies and is appropriately managed for medication overuse also have the option of botulinum toxin type A (NICE's technology appraisal guidance 260). The committee concluded that effective, well-tolerated treatment options are needed.

Current clinical management

At least 3 oral preventive treatments would be 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 would be considered a clinically relevant 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. If there was insufficient response at least 3 oral preventive treatments would be tried before more specialist treatment is considered.

Clinical evidence

The evidence does not include all relevant comparators

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 patients most in need of treatment options and for whom erenumab would likely be used in practice. It presented evidence for erenumab's clinical effectiveness compared with placebo for episodic migraine and compared with botulinum toxin type A and placebo for chronic migraine. The company considered that placebo was representative of best supportive care, because it comprised acute treatments that patients 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. However, they noted that some patients could be eligible for 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). The committee considered that a fourth oral preventive treatment would also be a relevant comparator for erenumab, but was aware that the company had not provided any evidence for this

comparison. The committee concluded that botulinum toxin type A or another oral preventive treatment were the relevant comparators in chronic migraine, and that another oral preventive treatment or best supportive care were the relevant comparators in episodic migraine.

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 3.4). But, people whose condition 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 prior 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. Also, people with medication overuse were excluded from the episodic migraine trials. The committee was aware that medication overuse is common in refractory migraine and was likely to be seen in people who could be eligible for erenumab. The committee concluded that the trial exclusion criteria suggested the evidence presented did not fully reflect the most relevant subgroup of people who may be eligible for erenumab in clinical practice.

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

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 noted that erenumab 140 mg reduced monthly migraine days compared with placebo more than the 70 mg dosage compared with placebo, but the reductions with both dosages were modest. Also, for chronic migraine best supportive care was not a relevant comparator because people would have the option of botulinum toxin type A if at least 3 previous treatments had failed (see section 3.3) or another oral preventive treatment (see section 3.4). 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 patients 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 dosage 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 the reductions in monthly migraine days were modest. None of the results for the 70 mg dosage were statistically significant. The committee was aware that no evidence was presented for erenumab's effectiveness compared with another oral preventive treatment, which was a relevant comparator (see section 3.4). It therefore concluded that erenumab 140 mg may be clinically effective for episodic migraine when compared with best supportive care but that there was no evidence that the 70 mg dosage was clinically effective.

The long-term effectiveness of erenumab is uncertain

3.8 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 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 company clarified that most of these people remained on treatment at these time points. However, the committee noted that there was no evidence that comparative efficacy was

maintained, and that the long-term evidence was limited because it did not go beyond about a year. It also noted that the people in the open-label extension studies were from the full trial populations. The committee noted 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, and that this could not extrapolate to long-term effectiveness in the subgroup given that 70 mg had not been shown to be effective in the subgroup with episodic migraine (see section 3.7). The committee concluded that there was no evidence for the long-term effectiveness of erenumab in the subgroup of interest. The committee therefore concluded that erenumab's long-term effectiveness compared with best supportive care was uncertain.

Indirect treatment comparison

There is no robust evidence that erenumab is more clinically effective than botulinum toxin type A

3.9 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 with the proportion of people on botulinum toxin type A with at least a 50% reduction in monthly headache days at 24 weeks, in the subgroup for whom at least 3 previous treatments had failed (as defined in section 3.4). 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 in the subgroup of patients for whom at least 3 previous treatments had failed, or in the full trial populations presented as supporting data (results are academic in confidence and cannot be reported here). The committee considered that the company's methods

for the indirect treatment comparison were appropriate, but noted that the difference in monthly migraine days with erenumab was compared with the difference in monthly headache days with botulinum toxin type A. Given that these were separately reported outcomes the committee did not think that these should be considered the same outcome. 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. Given the potential for bias in the analysis, the lack of statistically significant results and the wide confidence intervals, the committee would like to see a scenario in the economic modelling in which erenumab and botulinum toxin type A are considered to have similar effectiveness (that is, using a hazard ratio of 1). The committee concluded there was no robust evidence that erenumab is more clinically effective than botulinum toxin type A for chronic migraine.

Adverse events

Erenumab is generally well tolerated in the populations studied

3.10 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 years, those 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 that erenumab was generally well tolerated in the studied populations.

The company's economic model

The structure of the company's economic model is appropriate but a lifetime time horizon should be used

3.11 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. For the chronic migraine population, it modelled clinical effectiveness using the main outcomes (reduction in monthly migraine days and proportion of patients with at least 50% reduction) from study 295 for the comparison with placebo, and from the results of the indirect treatment comparison for the comparison with botulinum toxin type A. For the episodic migraine population the company used the pooled results from STRIVE, ARISE and LIBERTY. The committee noted that the company used a time horizon of 10 years whereas the ERG used a lifetime time horizon. The company considered that a 10-year time horizon fully captured the costs and benefits of erenumab. However, the committee considered that 10 years was an arbitrary time horizon. It also noted that a proportion of modelled patients remained on treatment at 10 years and beyond. Therefore the committee preferred a lifetime time horizon because it would fully capture the costs and benefits for people having erenumab or best supportive care. It therefore concluded that the model structure was appropriate but that a lifetime time horizon should be used, in line with the NICE reference case.

Modelling long-term treatment effectiveness

While people remain on treatment, it is unknown whether the treatment effect wanes over time and so a range of assumptions are considered

3.12 The company's model assumed that the treatment effect remained constant while patients were on treatment. The committee was aware

however that in other chronic conditions such as rheumatoid arthritis, the effects of monoclonal antibodies can wane over time. It accepted that there was no evidence on the long-term effectiveness of erenumab beyond about 1 year (see section 3.8) and therefore no evidence to show whether erenumab's treatment effect waned over time or continued indefinitely. It noted that the company had provided a scenario during clarification that incorporated a treatment waning effect, whereby costs and utilities for erenumab and botulinum toxin type A were linearly reduced over 10 years until they aligned with best supportive care. The ERG had also modelled this and another scenario whereby treatment effect waned over a 5 year period. On balance, the committee considered that the treatment effect was unlikely to be maintained indefinitely and so a constant treatment effect was implausible. In the absence of evidence it therefore agreed to consider the 10-year and 5-year effect waning scenarios in its decision making.

When people stop treatment, there is no evidence that benefit continues

3.13 The company's model assumed that patients whose condition was responding to treatment would remain on treatment indefinitely. The clinical experts explained that in practice if a person's migraine was responding to treatment they would be unlikely to remain on treatment indefinitely, and a treatment break would be trialled. The committee noted the company did not include this in its base case, but had included a 'positive discontinuation' scenario which assumed that patients remaining on treatment would be reassessed after 64.5 weeks. After that, 20% of patients would stop treatment while the remaining patients resumed treatment and would be reassessed at 76.5 week intervals thereafter. The ERG had also presented this scenario although it assumed that the benefit was maintained indefinitely after stopping treatment and noted that there was no evidence for this. The patient expert reported that once treatment was stopped the benefit was maintained for only a short time before the migraine returned. The committee therefore concluded that this positive discontinuation scenario was not appropriate for consideration

because there was no evidence that treatment benefit would continue once treatment had stopped.

Utilities

Utility values used in the model are highly uncertain

3.14 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 patients 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 patient did not have migraine, and was therefore not appropriate for using 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 be an accurate representation of quality of life. The committee was also aware that the MSQ data had been mapped to EQ-5D-3L in the botulinum

toxin type A appraisal 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 are uncertain.

Costs

All relevant costs for implementing erenumab in practice are not captured in the model

3.15 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 patients 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. The

company had also used the oral triptan price for triptan injections, which the committee agreed was inappropriate. The committee considered that the costs included in the model did not adequately capture the additional resources needed to provide erenumab in specialist clinics in England and so underestimated the resources needed to implement erenumab in practice.

Cost-effectiveness estimates

The 2 erenumab dosages should be considered separately in both the chronic and episodic populations

3.16 The company's base case presented the cost-effectiveness results for a blended dose, which assumed that half of the whole population would have the 70 mg dosage and half would have the 140 mg dosage (assuming that 66% of people had chronic migraine and 34% had episodic migraine). The committee was aware that the summary of product characteristics recommended a 70 mg dosage but that some patients would benefit from 140 mg, and that the company suggested that patients for whom at least 3 previous treatments had failed (defined as insufficient or partial response, insufficient dosage or adverse events), would likely be the group who would benefit from the higher dose. It noted that in practice no one would have a blended dose and concluded that it was more appropriate to consider the 2 doses separately. It also considered that it was more meaningful to consider the chronic and episodic migraine populations separately because these were well understood definitions (see section 3.1).

Given the uncertainty in the clinical evidence and utility values, an acceptable ICER would be around £20,000 per QALY gained

3.17 The committee noted the substantial uncertainty in the model inputs, specifically:

- The trial evidence did not fully reflect the relevant subgroup of patients (see section 3.5).

- There was no evidence of erenumab's effectiveness compared with another oral preventive treatment (see section 3.6 and section 3.7).
- The subgroup analysis of the trial data was post hoc (see section 3.6 and section 3.7).
- The most relevant outcome for chronic migraine (at least a 30% reduction in migraine frequency) was not reflected (see section 3.3 and section 3.6).
- There were limited data on long-term effectiveness that did not include the subgroup of interest (see section 3.8).
- There was no robust evidence of erenumab's effectiveness compared with botulinum toxin type A (see section 3.9).
- Uncertain utility values (see section 3.14).
- All relevant costs were not captured (see section 3.15).

Therefore, it agreed that an acceptable probabilistic incremental cost-effectiveness ratio (ICER) would be around £20,000 per quality-adjusted life year (QALY) gained (see NICE's guide to the methods of technology appraisal).

Erenumab is unlikely to be cost effective for chronic migraine compared with botulinum toxin type A after 3 preventive treatments have failed

3.18 The company's base-case ICER for the 140 mg dosage, in a deterministic pairwise analysis compared with botulinum toxin type A, was £17,832 per QALY gained for the population with chronic migraine. The ERG presented deterministic incremental analyses that included the 70 mg and 140 mg dosages as separate treatments compared with botulinum toxin type A. The committee noted that the ERG had corrected modelling errors, used the appropriate costs for triptan injections and altered the monthly migraine day distributions after stopping treatment for people whose migraine had not responded, which had a negligible effect on the company's base case and which the committee had accepted. The ERG's base case for the 140 mg dosage, using a lifetime time horizon which the committee preferred (see section 3.11), was an ICER of £15,641 per

QALY gained (70 mg was dominated, that is, it was more costly and less effective). However, the committee was aware that these estimates assumed a 50% response rate and that treatment effect was constant while patients remained on treatment. The committee had considered a 30% response rate to be most relevant (see section 3.3) and a treatment waning effect to be likely (see section 3.12), and so considered the ERG's scenarios using the following assumptions:

- Waning of treatment effect over 10 years increased the ICER to £26,351 per QALY gained.
- Waning of treatment effect over 5 years increased the ICER to £36,659 per QALY gained.
- Assuming a constant treatment effect, using a 30% response rate, increased the ICER to £18,862 per QALY gained.

The 70 mg dosage was dominated in all scenarios. For the 140 mg dosage, the committee concluded that the most plausible ICER was above £18,862 per QALY gained (although this would increase when a treatment waning assumption was applied) to £36,659 per QALY gained compared with botulinum toxin type A (although this would increase when a 30% reduction in migraine frequency was assumed, that is, a clinically meaningful response). The committee had also concluded that there was no evidence that erenumab was more effective than botulinum toxin type A (see section 3.9) and that assuming equal effectiveness would increase the ICER further. Considering the potential cumulative effect of these scenarios, the committee concluded that the ICER for erenumab was likely to be higher than around £20,000 per QALY gained compared with botulinum toxin type A for chronic migraine when at least 3 previous treatments had failed. Also, the committee concluded that it had seen no cost-effectiveness evidence comparing erenumab with another oral preventive treatment.

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

3.19 The company's base-case ICER for the 140 mg dosage, in a pairwise analysis compared with best supportive care, was £40,662 per QALY gained for the population with episodic migraine. The committee noted that the ERG had corrected modelling errors, used the appropriate costs for triptan injections and altered the monthly migraine day distributions after stopping treatment for people whose migraine did not respond, which had a negligible effect on the company's base case and which the committee had accepted. The ERG's base case (using incremental analysis), using a lifetime time horizon which the committee preferred (see section 3.11), was £10,207 per QALY gained for the 70 mg dosage compared with best supportive care, and the 140 mg dosage was dominated (by the 70 mg dosage). It considered the ERG's scenarios assuming a treatment waning effect:

- Waning of treatment effect over 10 years increased the ICER to £74,349 per QALY gained for the 70 mg dosage compared with best supportive care and £97,527 per QALY gained for the 140 mg dosage compared with the 70 mg dosage.
- Waning of treatment effect over 5 years increased the ICER to £94,984 per QALY gained for the 70 mg dosage compared with best supportive care and £310,725 per QALY gained for the 140 mg dosage compared with the 70 mg dosage.

The committee noted that the results for the 70 mg dosage did not reflect the clinical data, which showed little evidence that erenumab 70 mg was effective in episodic migraine for patients for whom at least 3 previous preventive treatments had failed (see section 3.7). The ERG explained that these results were a feature of the modelled treatment response in people whose condition did not respond to treatment (those with less than 50% reduction in monthly migraine days), and not of treatment effectiveness. The committee therefore concluded that there were no

robust cost-effectiveness estimates that could be used to decide on the cost effectiveness of erenumab 70 mg in episodic migraine. It also concluded that the 140 mg dosage was not cost effective in episodic migraine because the ICERs were much higher than what is usually considered a cost-effective use of NHS resources. Also, the committee concluded that it had seen no cost-effectiveness evidence comparing erenumab with another oral preventive treatment.

Other factors

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

3.20 No equality 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 concluded that these were not issues that could be addressed by NICE guidance.

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

3.21 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 is not recommended for use in the NHS

3.22 The committee considered the evidence that erenumab was clinically effective (at 140 mg and 70 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 chronic migraine was more clinically relevant (see section 3.3). It did not consider there was sufficient evidence to conclude that erenumab was more effective than botulinum toxin type A (see section 3.9). 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 but that the 70 mg dosage was not (see section 3.7). It had not seen any evidence for the effectiveness of erenumab for either chronic or episodic migraine when compared with another oral preventive treatment, which it had concluded was also a relevant comparator (see section 3.4). It considered that there was no evidence of erenumab's long-term effectiveness in the subgroup of patients for whom 3 previous preventive treatments had failed (see section 3.8), and the health utility estimates were highly uncertain (see section 3.14). The committee concluded that the cost-effectiveness estimates were higher than what NICE normally considers a cost-effective use of resources when there is substantial uncertainty in the evidence. Therefore it could not recommend erenumab for use in the NHS.

Professor Gary McVeigh
Chair, appraisal committee
December 2018

4 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
Technical lead

Victoria Kelly
Technical adviser

Gemma Barnacle, Kate Moore
Project managers

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