

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Fremanezumab 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 fremanezumab 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 fremanezumab 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: 6 December 2019

Please email NICE (tacommd@nice.org.uk) if you wish to comment but are unable to do so during the consultation period because of your condition. You may be able to have extra time to comment.

Second appraisal committee meeting: to be confirmed

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Fremanezumab 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 fremanezumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

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

For people whose migraine has not responded to at least 3 oral preventive treatments, clinical trial evidence shows that fremanezumab works better than best supportive care in both episodic and chronic migraine. But there is only indirect evidence comparing fremanezumab with botulinum toxin type A in chronic migraine. This shows that it is very uncertain whether fremanezumab is more clinically effective than botulinum toxin type A.

The cost-effectiveness results are highly sensitive to assumptions about treatment effectiveness after stopping treatment, which are not supported by evidence and are highly uncertain. The most likely estimates of cost effectiveness for fremanezumab for both episodic and chronic migraine

are higher than what NICE normally considers an acceptable use of NHS resources. Therefore, fremanezumab is not recommended.

2 Information about fremanezumab

Marketing authorisation indication	Fremanezumab (Ajovy, Teva Pharmaceuticals) is indicated for 'prophylaxis of migraine in adults who have at least 4 migraine days per month'.
Dosage in the marketing authorisation	2 dosing options are available: 225 mg once a month or 675 mg every 3 months (quarterly). Fremanezumab is administered as a subcutaneous injection. The treatment benefit should be assessed within 3 months after starting treatment. Any decision to continue treatment should be taken on an individual patient basis. Evaluating the need to continue treatment is recommended regularly afterwards.
Price	£450.00 per 225 mg injection (£1,350 per 675 mg) excluding VAT; British national formulary online, accessed October 2019. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Teva UK Limited, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that none of the issues were fully resolved during the technical engagement stage. It discussed the following issues, which were outstanding after the technical engagement stage (see technical report, issues 1 to 7):

- treatment stopping rules
- the model time horizon and post-discontinuation treatment effectiveness
- model utility values
- the high-frequency episodic migraine subgroup
- resource use and costs
- the network meta-analysis in chronic migraine and

- using fremanezumab after botulinum toxin type A (a new issue since technical engagement).

The condition

Migraine has a substantial effect on health-related quality of life

3.1 Migraine attacks usually last between 4 and 72 hours and involve throbbing head pain of moderate to severe intensity. The patient experts explained that they are often accompanied by nausea, vomiting, sensitivity to light, sensitivity to sound or other sensory stimuli, numbness, and speech issues. Migraine can adversely affect quality of life, affecting people's ability to do their usual activities, including work. Some people with migraine have severe depression and suicidal thoughts. The patient experts also described invisible losses such as loss of concentration and confusion. These can slow personal and professional development so that people feel they have unachieved potential. 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. A clinical expert explained that the severity of the condition can vary over time. The committee concluded that migraine, particularly chronic migraine, is a debilitating condition that substantially affects both physical and psychological aspects of quality of life and employment.

Treatment pathway and comparators

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

3.2 The clinical experts explained that the aim of treatment is to reduce the frequency, severity or duration of migraine and improve quality of life. The committee was aware that 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 clinical response is less than this, 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 fremanezumab. A clinical expert noted that at least 5 different oral preventive treatments were available for migraine but noted that not all of these would necessarily be tried before offering fremanezumab. The clinical experts agreed that fremanezumab would mostly be offered after 3 failed oral preventive treatments, noting that there was no clear evidence of benefit using oral preventives after third line. The committee understood that some clinicians may choose to offer a fourth or fifth oral preventive before offering more specialist treatments. It concluded that an adequate trial of at least 3 oral preventive treatments represents usual NHS practice before more specialist treatment is considered. It further concluded that a clinically meaningful response was a 30% reduction (for chronic migraine) or a 50% reduction (for episodic migraine) in migraine frequency.

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

3.3 The company's submission focused on people with migraine for whom at least 3 previous preventive treatments had failed (defined as lack of a clinically meaningful response, intolerance to the treatment or the treatment was contraindicated or unsuitable). The company considered that fremanezumab would likely be used in NHS clinical practice at this point because of the unmet need for additional treatment options after 3 preventive treatments had failed. The company presented evidence for fremanezumab'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 fremanezumab would likely be offered to people with migraine for whom at least 3 previous preventive treatments had failed (see section 3.2). The committee recalled advice from a clinical expert that, in usual NHS practice, some specialists may offer further oral preventive treatments after 3 previous treatments have failed. The committee acknowledged that there was no supporting evidence for a fourth oral preventive treatment, and that experts had different opinions about whether more than 3 preventive treatments would be tried. The committee agreed that there was uncertainty about the most appropriate comparator in episodic migraine and that this would add to the uncertainty about the cost effectiveness estimates. So it considered that best supportive care was the most appropriate comparator in episodic migraine. The committee recalled patient and clinical expert comments that people with chronic migraine for whom 3 oral preventive treatments have failed are most in need of effective therapy. It recognised that best supportive care would be ineffective in preventing the frequency or severity of migraine and increased the risk of medication overuse headache. It also acknowledged that there is a lack of evidence, and a diversity of opinion among experts, on the role and benefit of a fourth oral preventive treatment. The committee concluded that botulinum toxin type A or best supportive care were relevant comparators in chronic migraine, and that some specialists might offer a fourth oral preventive treatment. But it considered that most people would be offered botulinum toxin type A after trying 3 oral preventive treatments.

Clinical evidence

The FOCUS trial provides the most relevant clinical evidence for the population of interest

3.4 The company's systematic literature review identified 3 double-blind randomised controlled trials evaluating fremanezumab:

- FOCUS: in people whose migraine had inadequately responded to 2 to 4 previous classes of preventive treatment
- HALO EM: in people with episodic migraine when fewer than 3 classes of preventive treatment had failed
- HALO CM: in people with chronic migraine when fewer than 3 classes of preventive treatment had failed.

All trials compared fremanezumab (dosage of 675 mg every 3 months [quarterly] or 225 mg monthly) with placebo in adults 18 to 70 years across multiple international centres. The HALO and FOCUS trials were 16 weeks long, including a 4-week run-in period and a 12-week treatment period. Long-term safety and efficacy data were collected in the HALO extension study, which included people from HALO EM and HALO CM for a further 12 months. The committee recalled that fremanezumab would be considered as a treatment option after 3 oral preventive treatments had failed (see sections 3.2 and 3.3). It concluded that the subgroup of people from FOCUS for whom 3 preventive treatments had failed provided the most relevant data for the population of interest.

FOCUS does not fully reflect the people who may be eligible for fremanezumab in clinical practice

3.5 The committee considered whether inadequate treatment response, as defined in FOCUS, reflected what would be considered treatment failure in clinical practice. FOCUS defined an inadequate treatment response as a lack of clinically meaningful improvement after at least 3 months of therapy, intolerance to the treatment or the treatment was contraindicated or unsuitable. The clinical experts explained that a contraindication would not necessarily represent a treatment failure. The committee noted that some patients may have had a clinically meaningful response to an oral preventive treatment before stopping because of adverse events. It also noted that valproic acid was considered differently to other preventive treatments in FOCUS and was regarded as being in a class of its own. Therefore, a person whose migraine had an inadequate response to

valproic acid, topiramate and propranolol would be included in the subgroup analysis (3 or more preventive treatment failures) even though this represents a failure of 2 treatment classes. The committee was concerned that because of this a substantial proportion of people in the subgroup may not have had 3 or more failed preventive treatments. The committee concluded that the subgroup whose treatment with 3 or 4 treatment classes was considered to have failed in FOCUS may not fully reflect those eligible for fremanezumab in clinical practice.

Differences in the fremanezumab dosage between the trials and the marketing authorisation are unlikely to affect the generalisability of the results

3.6 The committee understood that in both FOCUS and HALO EM, the 225 mg monthly fremanezumab treatment group had a 675 mg loading dose. It considered whether this loading dose could bias the clinical effectiveness results for this group. The clinical experts explained that the loading dose, consisting of 3 injections, was given to maintain the blinding of treatment allocation. The company noted that a loading dose was not included in fremanezumab's marketing authorisation because the 675 mg quarterly and 225 mg monthly dosages have equal efficacy. It also noted that having no loading dose simplified dosing, therefore benefitting patients and clinicians. The committee concluded that differences in dosing between the FOCUS and HALO EM trials and the marketing authorisation would not likely affect the generalisability of the results to clinical practice.

Fremanezumab is clinically effective compared with placebo for episodic and chronic migraine

3.7 The company presented clinical effectiveness results from FOCUS for the subgroup of people for whom 3 or 4 preventive migraine therapies failed to produce clinically meaningful improvement, were not tolerated, or were contraindicated or unsuitable. The baseline to week 12 subgroup results from FOCUS showed:

- fremanezumab reduced the number of monthly migraine days more than placebo for episodic and chronic migraine
- more people on fremanezumab had a reduction of at least 50% in the average monthly number of migraine days compared with placebo for episodic migraine
- more people on fremanezumab had a reduction of at least 30% in the average monthly number of migraine days compared with placebo for chronic migraine
- fremanezumab reduced the monthly number of days with acute headache medication more than placebo for both episodic and chronic migraine.

The committee recalled that the company's subgroup analysis from FOCUS may not fully reflect the population of interest (see section 3.5), but agreed that this subgroup provided the most relevant clinical evidence. It also noted that the results were taken from a post-hoc subgroup analysis, which it agreed reduced the robustness of the findings. It concluded that the subgroup results showed that fremanezumab is an effective treatment compared with placebo for people with episodic or chronic migraine when 3 or 4 preventive treatments have failed.

High-frequency episodic migraine is not a clinically distinct subgroup

3.8 The company defined high-frequency episodic migraine as between 8 and 14 monthly headache days. The ERG noted that the company's high-frequency episodic migraine definition was not in line with other definitions in the literature (10 to 14 and 11 to 14 monthly headache days), highlighting that there was no consensus on the definition. 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. They also noted that the definition of high-frequency episodic migraine is arbitrary and a person's quality of life is negatively affected irrespective of which type of migraine they have. The committee

concluded that high-frequency episodic migraine is not a distinct subgroup and agreed not to consider it further.

The long-term comparative effectiveness of fremanezumab is unknown

3.9 The duration of the blinded phase in the trials was 12 weeks for FOCUS, HALO EM and HALO CM. The company provided supporting data for fremanezumab's long-term effectiveness from the uncontrolled open-label HALO extension study. The committee recalled that the population in the HALO studies was less relevant than the population in FOCUS to the population of interest (see section 3.4), but acknowledged that no long-term evidence was available from FOCUS. People who had fremanezumab in HALO EM and HALO CM had the option to continue on a stable dose in the extension study, whereas those who had placebo could opt to be randomly assigned to either 675 mg fremanezumab quarterly or 225 mg monthly (with a 675 mg loading dose). The committee recognised that although the HALO extension study provided some longer-term clinical effectiveness evidence for people having fremanezumab, comparative effectiveness could not be estimated because the extension study did not include a placebo group. The committee recognised that because not everyone in the trials continued to the extension phase there was an additional risk of bias. This was because it considered that people not experiencing benefit were more likely to drop out. The company said that the results suggested that treatment effectiveness was maintained long term with no evidence of waning. It noted similar results for people who previously had fremanezumab in HALO EM and HALO CM to those who had previously had placebo, and consistency in results between the 2 fremanezumab dosages (675 mg quarterly and 225 mg monthly). These results were considered academic in confidence by the company and cannot be reported here. The committee concluded that it was unclear whether fremanezumab 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.

Indirect treatment comparison

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

3.10 There was no direct evidence comparing fremanezumab with botulinum toxin type A for chronic migraine. So the company did an indirect comparison using data from:

- FOCUS for fremanezumab
- study 295, which compared erenumab and placebo
- PREEMPT1 and PREEMPT2, which compared botulinum toxin type A with placebo.

The company noted that data from study 295 were included only to strengthen the network and not to include erenumab as an additional comparator. The comparison was in the subgroup for whom 3 or 4 previous treatments had failed (as defined in section 3.2). It compared the reduction in monthly migraine days in people on fremanezumab or botulinum toxin type A. It also compared the proportion of people on fremanezumab 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. Differences in outcomes and time points reflected the differences in primary outcomes and timing of assessments between the FOCUS and PREEMPT trials. The results of the comparison numerically favoured fremanezumab, but these findings were not statistically significant in people for whom at least 3 preventive treatments had failed (results are academic in confidence and cannot be reported here). Because the results were not statistically significant, fremanezumab could be more effective or less effective than botulinum toxin type A. The company used placebo as the common comparator, but it was administered differently:

- as either a single subcutaneous injection every month or 3 subcutaneous injections every quarter in the fremanezumab trial

- as intramuscular injections into 31 to 39 different sites on the head and neck in the botulinum toxin type A trials.

The committee thought that this could have been the cause of the substantially different placebo responses recorded in the trials. It also considered the difference between monthly migraine days with fremanezumab and monthly headache days with botulinum toxin type A. The clinical experts explained that headache days and migraine days both affected quality of life but stated that changes in monthly migraine days were of greater importance because migraines are more severe. The committee thought that because these were separately reported as clinically distinct outcomes they should not be considered the same. The clinical experts acknowledged that there was real-world evidence supporting the effectiveness, tolerability and safety of botulinum toxin type A from a UK perspective. The committee acknowledged this and recognised the same was not available for fremanezumab. Given the concern over the analysis and the lack of statistically significant results, the committee concluded that there was a high degree of uncertainty about whether fremanezumab was more clinically effective than botulinum toxin type A for chronic migraine. It agreed it was appropriate to consider a scenario in which equivalent efficacy was assumed and another in which the results of the network meta-analysis were incorporated.

Quality of life

The Migraine-Specific Quality of Life questionnaire is more sensitive to changes in quality of life caused by migraine than the EQ-5D-5L

3.11 Health-related quality-of-life data were collected in FOCUS using the Migraine-Specific Quality of Life Questionnaire (MSQ) and the EQ-5D-5L. The company considered that the EQ-5D-5L data were not sensitive to changes in quality of life with migraine because the questionnaire was given on appointment days. This meant that it only captured quality-of-life data for people who were able to attend appointments. If a person was having a migraine that day, they would likely rearrange their appointment

and the effect of that migraine on quality of life would not be captured. The clinical experts explained that in clinical practice they use the HIT6 and MIDAS tools to measure quality of life, so it was not known whether MSQ was the best available measure of quality of life. The company highlighted that the MSQ included a 4-week recall period, which ensured the effect of migraine on quality of life was captured. The committee concluded that the rationale for using MSQ data was reasonable because the EQ-5D-5L was not sufficiently sensitive to changes in quality of life caused by migraine.

The company's economic model

The company's economic model is appropriate for decision making

3.12 The company modelled the assessment period of 12 weeks (24 weeks for botulinum toxin type A) as a decision tree, and the post-assessment period as a Markov model. Episodic and chronic migraine were analysed separately, with each analysis using a dedicated set of input parameters. In the decision tree phase people were grouped into:

- those whose migraine responded (response was defined as a 50% reduction for episodic migraine or a 30% reduction for chronic migraine in monthly migraine days from baseline) who remained on treatment
- those whose migraine did not respond who stopped treatment.

The Markov phase was used to model the distribution of monthly migraine days in each health state: no response (on treatment); response (on treatment); discontinue (off treatment). The committee concluded that the structure of the company's economic model was appropriate for decision making.

Modelling long-term treatment effectiveness

A lifetime time horizon is necessary to capture all relevant costs and benefits associated with fremanezumab

3.13 The company's base-case model included a time horizon of 10 years. The company explained that it expected all meaningful differences in costs and quality-adjusted life-years (QALYs) between treatments to be captured within this time horizon. It also noted that because there are no long-term natural history data, any long-term modelling beyond 10 years would be highly uncertain. The ERG highlighted that a time horizon of 10 years was problematic for predicting long-term safety and efficacy. However, it agreed with the company that extending the time horizon increased the uncertainty in extrapolating short-term evidence, and because of this it considered 10 years to be a reasonable time horizon. The committee understood that extending the time horizon could increase the uncertainty. But it noted that arbitrarily capping the time horizon could also increase uncertainty because long-term costs and benefits were not captured. It acknowledged that although the average age of the subgroup from FOCUS was over 40 years, people much younger than this would have treatment in clinical practice. Therefore, it agreed this should be taken account of in the model time horizon. The committee concluded that it preferred a lifetime time horizon of at least 30 years to ensure that all relevant costs and benefits associated with fremanezumab were captured.

The fremanezumab all-cause discontinuation rate is higher than expected and could affect the cost-effectiveness results

3.14 The company's model included a separate health state for people who stopped treatment. The discontinuation rate applied after each model cycle (4 weeks) was based on the number of people on fremanezumab who dropped out of the HALO extension study. The committee considered that the all-cause discontinuation rate was relatively high for what it understood to be a clinically effective and well tolerated treatment. The ERG noted that the discontinuation rate in the HALO extension study was

higher than that seen in the extension studies of another anti-calcitonin gene-related peptide (CGRP), erenumab. The clinical experts noted that the additional injections given in the HALO trials to preserve the blinding of treatment allocation could explain why more people dropped out. The patient experts highlighted that most people would tolerate injections if the treatment was effective. The committee agreed that additional injections alone were unlikely to explain the higher than expected discontinuation rates. It also noted that because treatment allocation was not blinded in the HALO open-label extension study from which the discontinuation rate was calculated, additional sham injections would not be necessary. It acknowledged that because treatment costs stop after discontinuation, an inflated discontinuation rate would affect the cost-effectiveness results. The committee concluded that the discontinuation rate was higher than expected and this could affect the cost-effectiveness results.

The company's post-discontinuation assumptions are overly optimistic

3.15 In the company's model, people reverted to the migraine frequency of best supportive care after all-cause discontinuation. The ERG explained that this assumption was overly optimistic because the migraine frequency of people having best supportive care was determined by the response to placebo in the clinical trials. It noted that this response was similar to that of people on fremanezumab. The committee noted that a placebo effect would not be seen in clinical practice when no treatment is given. It also considered it unrealistic that a substantial treatment effect would be maintained indefinitely for people who are no longer having treatment. The clinical experts highlighted that there was no long-term evidence in people who have discontinued treatment, but agreed that it seemed implausible that a substantial treatment benefit would be maintained. The committee agreed that this assumption was overly optimistic because an implausibly large benefit was maintained and costs were stopped. To account for this the ERG did a scenario analysis. In this, people reverted to baseline migraine days after fremanezumab all-cause discontinuation, and the treatment effect for people who responded to best supportive care

diminished to baseline over 1 year. The committee agreed that this scenario was more in line with how the clinical experts expected treatment effectiveness could change after stopping treatment. The committee concluded that the company's post-discontinuation assumptions were overly optimistic. It agreed that it would consider the ERG's scenario in which people revert to baseline monthly migraine days after discontinuing fremanezumab or best supportive care.

Applying a negative stopping rule is appropriate

3.16 The company's model included a negative stopping rule. So in the model, people whose migraine did not respond to treatment (a reduction in monthly migraine days from baseline of less than 50% for episodic migraine or less than 30% for chronic migraine) stopped treatment after assessment at 12 weeks (24 weeks for botulinum toxin type A). The committee concluded that it was appropriate to include a negative stopping rule at 12 weeks in the economic model if there was no response to treatment. It accepted the company's approach to modelling this.

Positive stopping rule assumptions are not appropriate because it is implausible that treatment benefit is maintained indefinitely

3.17 The company's model applied a positive stopping rule by assuming 20% of people whose migraine responded to treatment would discontinue every 64 weeks (52-week treatment period and 12-week response assessment). After this period, treatment effect was maintained, but treatment costs were stopped indefinitely. The patient expert explained that, from their own experience, once fremanezumab was stopped the benefit was maintained for only a short time before migraines returned to their pre-treatment frequency and severity. The committee recalled that there was a lack of long-term effectiveness evidence for fremanezumab in the population of interest (see section 3.9). It recognised that there was no evidence but agreed it was unrealistic to assume that the treatment effect would be maintained indefinitely after stopping treatment. It also noted that any report of long-term treatment effectiveness could be affected by

natural variation in the condition. But the committee acknowledged that without long-term natural history data this could not be fully understood. The committee concluded that it was not appropriate to apply a positive stopping rule in the model because it was unrealistic to assume that treatment benefit was maintained indefinitely after stopping treatment.

Utility values in the economic model

The company's approach to calculating model utility values is reasonable but still uncertain

3.18 The utility values used in the model were generated from mapping MSQ results to the EQ-5D-3L using the Gillard et al. (2012) algorithm. The committee understood that the MSQ data were based on the full trial population, and not just on those for whom at least 3 to 4 treatments had failed. It also understood that the patient characteristics could not be included in the mapping algorithm because of data limitations. It agreed that this could limit the robustness of the mapped EQ-5D-3L utility values used in the economic model. It also noted concerns about the reliability of the utility values given the uncertainty of using data from the broader, full trial, population. The ERG explained that the inconsistency in the population used to estimate utility values would not likely have a substantial effect on the results. The committee concluded that the company's approach to calculating model utility values was reasonable but noted that the values were uncertain because of data limitations.

Additional on-treatment utility value benefits should not be included in the model

3.19 After mapping from MSQ to EQ-5D-3L, the company split the EQ-5D utility values into 'on-treatment' and 'off-treatment' groups. Off-treatment health state utility values were estimated using baseline (week 0) MSQ data, on-treatment utility values were estimated from the week 4 and week 12 MSQ data. Off-treatment utility values were applied to best supportive care and on-treatment utility values were used for fremanezumab and botulinum toxin type A strategies until people stopped treatment. The

company highlighted that on-treatment utility value benefits have been shown for people with migraine. It noted that the application of treatment-specific utility values was consistent with previous migraine appraisals. The ERG noted that the company had not provided evidence to support its claim that on-treatment utility value benefits have been shown for people with migraine. The committee agreed that it was uncertain whether health-related quality-of-life benefits beyond those achieved by reducing monthly migraine days were not adequately captured by the MSQ. It also noted that baseline (before treatment) fremanezumab utility values included a benefit over best supportive care, which it agreed was inconsistent with applying an on-treatment utility value benefit. The committee concluded that additional on-treatment utility value benefits were not supported by the evidence and should not be included in the economic model.

Costs in the economic model

Costs used in the economic model are appropriate

3.20 The company based its resource use estimates on data from a European study of migraine burden by Vo et al. (2018). It noted a limitation of the study was that resource use estimates were based on monthly headache days, not migraine days, which it considered could underestimate the migraine cost burden. In the model it assumed that resource use would be equivalent for both fremanezumab dosage schedules; monthly injections of 225 mg or 3 injections of 675 mg every quarter. The ERG noted that this could be a conservative assumption because quarterly administration is likely to be less resource intensive. The ERG also noted that resource use rates were not specific to the population of interest (that is, people who have had 3 failed preventive treatments) but based on the general migraine population. The committee concluded that despite the limitations in the estimates of resource use the costs included in the model were appropriate for decision making.

Some people will need fremanezumab to be administered for them

3.21 The company assumed that fremanezumab could be self-administered by subcutaneous injection. At the technical engagement stage, the clinical experts suggested that most people would be capable of self-administering fremanezumab. However, 1 expert noted that people with physical or mental disabilities, the elderly and those who have a phobia of needles may need help. They also noted that additional services may be needed to train people how to administer treatment. The committee considered it unlikely that everyone having fremanezumab would be capable of self-administering treatment. It agreed that applying administration costs for 10% of people having fremanezumab was reasonable, but acknowledged that this had little effect on the model results. It concluded that it was appropriate to assign administration costs for a proportion of people having fremanezumab because it was unrealistic to assume everyone could self-administer.

Cost-effectiveness estimates

Fremanezumab is not cost effective compared with best supportive care for people with episodic migraine after 3 preventive treatments have failed

3.22 The company's base-case incremental cost-effectiveness ratio (ICER) for fremanezumab compared with best supportive care for episodic migraine was £13,954 per QALY gained. However, the committee noted that the company's base case did not include all of its preferred assumptions, that is:

- minor ERG model corrections
- applying a lifetime (at least a 30-year) model horizon (see section 3.13)
- applying the ERG's post-discontinuation scenario (see section 3.15)
- removing a positive stopping rule (see section 3.17)
- removing additional on-treatment utility benefits (see section 3.19)
- applying fremanezumab administration costs for 10% of people (see section 3.21).

Taking its preferences into account, the committee agreed that the most plausible ICER for fremanezumab compared with best supportive care for episodic migraine was £48,996 per QALY gained. It recalled that it had concluded that people with high-frequency episodic migraine were not a distinct group and that it should not consider the cost-effectiveness analysis for this population further (see section 3.8). It also recalled that there were several uncertainties in the clinical and cost-effectiveness evidence that could affect the robustness of the ICERs. These included:

- the lack of data comparing fremanezumab with a fourth oral preventive treatment (see section 3.3)
- the lack of long-term natural history data and the simplicity of the model (see section 3.13) and
- the sensitivity of the model to the time horizon and the different post-treatment discontinuation scenarios (see sections 3.13 and 3.17).

Taking this into consideration it agreed that the most plausible ICER for episodic migraine was much higher than the £20,000 to £30,000 per QALY gained range usually considered a cost-effective use of NHS resources. Therefore, it concluded that fremanezumab was not a cost-effective use of NHS resources for preventing episodic migraine after 3 preventive treatments have failed.

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

3.23 The company's base-case pairwise ICERs for fremanezumab were £11,825 per QALY gained compared with best supportive care and £16,227 per QALY gained compared with botulinum toxin type A. The committee recalled that the company's base-case analysis for chronic migraine did not include all of its preferred assumptions, that is:

- minor ERG model corrections
- applying a lifetime (at least a 30-year) model horizon (see section 3.13)

- applying the ERG's post-discontinuation scenario (see section 3.15)
- removing a positive stopping rule (see section 3.17)
- removing additional on-treatment utility benefits (see section 3.19)
- applying fremanezumab administration costs for 10% of people (see section 3.21)
- considering a scenario of equal effectiveness of fremanezumab and botulinum toxin type A and then another assuming the comparative effectiveness estimates from the network meta-analysis (see section 3.10).

The committee 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 compared with fremanezumab. Taking its preferences into account, including equal effectiveness of fremanezumab and botulinum toxin type A, fremanezumab was dominated (more costly and less effective) by botulinum toxin type A. When assuming the comparative effectiveness estimates from the network meta-analysis the fully incremental ICER for fremanezumab compared with botulinum toxin type A was £40,297 per QALY gained. It was therefore substantially above the range usually considered a cost-effective use of NHS resources. The committee recalled that botulinum toxin type A was the most relevant comparator for people with chronic migraine (see section 3.3). It noted that best supportive care may be offered to people for whom botulinum toxin type A was not an option or for those who refused it. However, it recalled that most people would tolerate inconvenient and unpleasant injections for a clinically effective treatment (see section 3.14), and agreed that the group for whom botulinum toxin type A is contraindicated was small. It also recalled there were several other factors which meant the ICERs were substantially uncertain (see section 3.22). Therefore, it concluded that fremanezumab was not a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments have failed.

There is no cost-effectiveness evidence after 3 oral preventive therapies and botulinum toxin type A have failed

3.24 The committee noted that fremanezumab is positioned as a treatment option after 3 or more failed preventive treatments. It recognised that this could include people who had previously had botulinum toxin type A. It noted that there was a subgroup of people in FOCUS who had previously had treatment with botulinum toxin type A, but that no cost-effectiveness results had been provided. It concluded that it could not consider the use of fremanezumab after botulinum toxin type A because it had not been presented with cost-effectiveness estimates for this group.

Other factors

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

3.25 The company and clinical and patient experts 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 disadvantaged in the workplace. In addition, there may be unequal access to specialist headache clinics in England. The committee considered these issues but concluded that there were no specific adjustments needed to NICE's methods in this situation.

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

3.26 The company suggested that fremanezumab should be considered as an innovative treatment on the grounds that anti-CGRP therapies represent a step change in the management of migraine. The committee concluded that the modelling had adequately captured the benefits of fremanezumab.

Conclusion

Fremanezumab is not recommended for use in the NHS

3.27 The committee recognised the substantial burden that migraine has on quality of life and day-to-day functioning. It acknowledged that this could

lead to psychosocial issues (see section 3.1). It considered that fremanezumab was a clinically effective treatment compared with placebo based on the short-term comparative evidence it was presented with (see section 3.7). However, the committee considered that there was a high degree of uncertainty about whether fremanezumab was more clinically effective than botulinum toxin type A and agreed that it was appropriate to also consider equal effectiveness (see section 3.10). It also considered there was considerable uncertainty about the long-term comparative evidence on fremanezumab (see section 3.9). The committee recalled that the most relevant comparators were best supportive care for people with episodic migraine and botulinum toxin type A for people with chronic migraine (see section 3.3). All this considered, the fremanezumab ICERs, compared with the ICERs for best supportive care in episodic migraine, and with the ICERs for botulinum toxin type A (fully incremental analysis) in chronic migraine, were substantially higher than the £20,000 to £30,000 per QALY gained usually considered a cost-effective use of NHS resources. Therefore, the committee did not recommend fremanezumab for use in the NHS for preventing episodic or chronic migraine in adults who have at least 4 migraine days per month after 3 preventive treatments have failed.

4 Proposed date for review of guidance

- 4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
November 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

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

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

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.

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.

Thomas Paling

Technical lead

Caron Jones and Nicola Hay

Technical advisers

Kate Moore

Project manager

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