

Fremanezumab for preventing migraine

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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This guidance replaces TA631.

1 Recommendations

1.1 Fremanezumab 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 and
- the company provides it according to the [commercial arrangement](#).

1.2 Stop fremanezumab after 12 weeks of treatment if:

- in episodic migraine (fewer 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 fremanezumab 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 anticonvulsant 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 oral preventive treatments, clinical trial evidence shows that fremanezumab works better than best supportive care in

both episodic and chronic migraine. However, it is unclear if fremanezumab works better than botulinum toxin type A.

For chronic migraine, assuming fremanezumab works better than botulinum toxin type A, the most likely cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. So it is recommended for chronic migraine. For episodic migraine, the estimates of cost effectiveness are even lower, so it is recommended for episodic migraine. Fremanezumab treatment should be stopped if it is not working well enough after 12 weeks.

2 Information about fremanezumab

Marketing authorisation indication

- 2.1 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

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

Price

- 2.3 The price of fremanezumab is £450.00 per 225-mg injection (£1,350 per 675 mg) excluding VAT; BNF online, accessed November 2021. The company has a [commercial arrangement](#). This makes fremanezumab 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 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.

As part of the rapid review of the previous appraisal of fremanezumab (TA631), the appraisal committee considered further evidence submitted by the company for episodic migraine, and a review of this submission by the ERG. See the [committee papers](#) for full details.

The condition

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

3.1 Migraine attacks usually last between 4 hours and 72 hours and involve throbbing head pain of moderate to severe intensity, which can be highly disabling. The patient experts explained that they are often accompanied by nausea, vomiting, sensitivity to light, sensitivity to sound or other sensory stimuli, numbness, confusion, loss of concentration 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. All of 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. 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 that not all of these would be tried before offering fremanezumab. The clinical experts agreed that fremanezumab would usually be offered after 3 failed oral preventive treatments. This was because there was no clear evidence that using oral preventives after this was of benefit, and side effects may outweigh any benefits. 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 and best supportive care 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 committee recalled its discussion about using oral preventive treatments after 3 had failed (see [section 3.2](#)) and agreed that best supportive care was the most appropriate comparator in episodic migraine. It recognised that best supportive care would not reduce the frequency or severity of migraine and would increase the risk of medication overuse headache. It also recalled that botulinum toxin type A is recommended for people with chronic migraine whose condition has not responded to at least 3 prior preventive therapies. However, the committee was also aware that some people who are eligible for botulinum toxin type A are unable to have it or have to wait a long time for it. This is because few UK clinics are offering this treatment, and there are long waiting lists for it. The committee concluded that both botulinum toxin type A and best supportive care were relevant comparators in chronic migraine.

High-frequency episodic migraine is not a clinically distinct subgroup

- 3.4 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.

Clinical evidence

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

3.5 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 2 classes of preventive treatment had failed
- HALO CM: in people with chronic migraine when fewer than 2 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 aged 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 [section 3.2](#) and [section 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

3.6 The committee considered the generalisability of FOCUS to NHS clinical practice. FOCUS excluded people who had the most severe, unremitting headaches, clinically significant comorbidities or clinically significant

psychiatric issues. Therefore, it agreed that people enrolled in FOCUS were on average healthier than people who may be eligible for fremanezumab in clinical practice. The committee also 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. But the company clarified that only about 2% of recorded treatment failures were because of a contraindication. The committee also noted that some people 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 not frequently used in the UK for migraine prevention, although about 1 in 3 people in FOCUS had previously had it. The committee concluded that FOCUS may not fully reflect those eligible for fremanezumab in clinical practice.

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

3.7 The committee understood that people with chronic migraine in the 225 mg monthly fremanezumab treatment group in both FOCUS and HALO CM had a 675 mg loading dose. It considered whether this loading dose could bias the clinical-effectiveness results for this group. 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 benefiting patients and clinicians. The committee concluded that differences in dosing between the FOCUS and HALO CM 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

3.8 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.

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 3.5](#)), 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 in HALO CM). 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 having 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 the long-term benefits of fremanezumab compared with best supportive care remained uncertain.

Fremanezumab may be clinically effective for chronic migraine after 3 preventive treatments and botulinum toxin type A have failed

- 3.10 Clinical experts advised that botulinum toxin type A is ineffective for about 1 in 3 people with chronic migraine, based on real-world studies. The committee recalled that this group of people has high unmet need because of high disease burden and no further treatment options. At consultation, the company submitted additional evidence on the clinical effectiveness of fremanezumab compared with best supportive care for people with chronic migraine after 3 preventive treatments and botulinum toxin type A have failed. The evidence was based on a post-hoc subgroup analysis of FOCUS. The baseline to week 12 results showed improvements in key outcomes (as listed in [section 3.8](#)), which were in line with the results for the subgroup of people for whom 3 or 4 preventive migraine therapies failed (see [section 3.8](#)). They were

considered academic in confidence by the company and cannot be reported here. The ERG highlighted the small population size in this analysis. It noted that the clinical-effectiveness evidence was weak and should be treated with caution. The company also submitted supporting analyses for 2 additional slightly larger populations:

- people for whom 3 or more treatments have failed, one of which was botulinum toxin type A
- all people with chronic migraine for whom botulinum toxin type A has failed, regardless of the number of prior therapies.

The results of these analyses were in line with the main subgroup analysis. The committee noted that the company's analysis was exploratory. But it concluded that fremanezumab appeared to be clinically effective compared with best supportive care for chronic migraine after 3 preventive treatments and botulinum toxin type A have failed.

Indirect treatment comparison

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

3.11 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 was included only to strengthen the network and not to include erenumab as an additional comparator. However, the ERG noted that adding this study does not strengthen or weaken the network in any way and so it was not expected to affect the network meta-

analysis results. 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 with the reduction in monthly headache days in people on 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 the differences in administration may have influenced the placebo responses, which were substantially different 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 changes in monthly migraine days were more important 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 UK real-world evidence supporting the effectiveness, tolerability and safety of botulinum toxin type A. The committee acknowledged this and recognised the same evidence was not available for fremanezumab (as for most new treatment options). 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

3.12 Health-related quality-of-life data was collected in FOCUS using the Migraine-Specific Quality of Life Questionnaire (MSQ) and the EQ-5D-5L. The committee was aware that in NICE's reference case and current position statement on the EQ-5D-5L, the EQ-5D-3L is preferred for base-case analyses. The company considered that the EQ-5D-5L was not sensitive to changes in quality of life with migraine because the questionnaire had to be completed on appointment days. This meant that it only captured quality-of-life data for people who were able to attend appointments. A person having a migraine on the day of their appointment would likely rearrange it 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 Headache Impact Test (HIT6) and Migraine Disability Assessment Test (MIDAS) 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

3.13 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 (defined as a 50% reduction for episodic migraine or a 30% reduction for chronic migraine in monthly migraine days from baseline) and who remained on treatment
- did not respond and 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

3.14 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 in this time horizon. It also noted that because there is 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 a problem 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 into account in the model time horizon. The committee concluded that it preferred a lifetime time horizon to ensure that all relevant costs and benefits associated with fremanezumab were captured. For the rapid review, the company used a lifetime time horizon in its updated model.

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

3.15 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 discontinuation rate (from all causes) 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 ([NICE has published guidance on erenumab for preventing migraine](#)). 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 the HALO extension study from which the discontinuation rate was calculated was an open-label study. This meant that treatment allocation was not blinded, so 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

3.16 The ERG explained that assuming migraine frequency would revert to that of best supportive care after discontinuation from all causes was overly optimistic. This is 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. It also considered it unrealistic that a substantial treatment effect would be maintained indefinitely for people who are no longer having fremanezumab treatment. The clinical experts highlighted that there was no long-term evidence in people who have stopped 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 discontinuation (from all causes), and the treatment effect for people whose migraine 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 stopping fremanezumab, botulinum toxin type A or best supportive care.

Applying a negative stopping rule is appropriate

3.17 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. It agreed that any treatment benefit seen while on treatment (during the initial 12 weeks) would not be maintained after stopping the treatment.

Positive stopping rule assumptions are not appropriate

3.18 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 pretreatment 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. The committee acknowledged that without long-term natural history data, this could not be fully understood. In response to consultation, the company revised its positive stopping rule. The proposed new stopping rule assumed that 15% of people whose migraine responded to treatment would stop every year. It also assumed that once treatment stopped, migraine frequency returned to pretreatment levels within 1 year. The committee was aware that clinical experts considered that successful treatment with fremanezumab would not be continued indefinitely (see [section 3.2](#)). The company did not provide any positive stopping criteria for chronic or episodic migraine. However, the committee noted clinical expert comments at consultation suggesting that people with chronic migraine would stop treatment when their migraines had reduced to 10 migraine days a month for at least 3 months. The committee was aware that no comments were received about positive stopping criteria in episodic migraine. Therefore, taking account of what it had heard from the clinical experts, the committee considered that there are no clear criteria for when people should stop treatment and understood that a positive stopping rule could be challenging to implement in clinical

practice. It recognised that people may not be willing to stop treatment that is beneficial for them. It also recalled that no positive stopping criteria were used in FOCUS. Therefore, the committee concluded that it was not appropriate to apply the company's positive stopping rule in the model. But it acknowledged that treatment may not continue indefinitely after successful treatment and took this into account for decision making.

Utility values in the economic model

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

3.19 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 was based on the full trial population, and not just on those for whom 3 or 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. It noted that the mapping algorithm led to implausibly low utility values for certain patient populations, as confirmed by the clinical experts. The ERG explained that the company did not provide enough detail on how the utility values were extracted and mapped to assess their robustness. 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.

The company's original approach to additional on-treatment utility value benefits should not be included in the model

3.20 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 for people on best supportive care and on-treatment utility values were used for fremanezumab and botulinum toxin type A until people stopped treatment. The company highlighted that on-treatment utility value benefits have been shown for people with migraine. It noted that applying treatment-specific utility values was consistent with the appraisal for botulinum toxin type A for chronic migraine. The ERG noted that the on- and off-treatment utilities were not appropriately generated and applied in the model. It considered the company's approach was overly simplistic and did not account for possible improvements in quality of life related to being included in a clinical trial (placebo effect). It also explained that the on-treatment utilities were not correctly applied in the model because of how the model was structured. The committee recalled that utility values were generated from MSQ data, which measured the impact of migraine on daily social and work-related activities, and emotional functioning. Therefore, it agreed that it was uncertain whether health-related quality-of-life benefits beyond those related to reducing monthly migraine days were not already 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. At the time of the original guidance (TA631; June 2020), the committee concluded that the company's additional on-treatment utility value benefits should not be included in the economic model.

There is a clinical rationale for using differential utilities for on- and off-treatment health states

3.21 Since the publication of the original guidance for this topic (TA631), [NICE has published guidance on galcanezumab for preventing migraine and erenumab for preventing migraine](#). Both are anti-CGRP drugs for migraine in adults, like fremanezumab. In these appraisals, the committee was satisfied that it had seen enough evidence to support using differential utilities for the treatment being appraised. That is, using different utilities for people on and off fremanezumab, as a result of taking into account improvements in utilities beyond a reduction in the monthly migraine days measure. For the rapid review of fremanezumab, the company presented evidence to support using differential utility values in its

economic modelling. It focused on episodic migraine (specifically when 3 preventive treatments had failed) because fremanezumab was not recommended for episodic migraine in TA631. The company's clinical experts advised that there are improvements in utilities beyond a reduction in the monthly migraine days measure, which does not fully capture the duration and severity of migraines, and other factors that influence quality of life. The company reasoned that quality of life is affected by migraine between attacks, not just during them, so quality-of-life impairment could extend beyond monthly migraine days alone. Using differential utilities reflects further treatment benefits, for example improvements in photophobia and disability levels, less severe migraine attacks, and quicker recovery time. The company explained that a migraine-specific quality-of-life questionnaire was used, which found a significant improvement in the different domains for fremanezumab compared with placebo, in the full FOCUS population and the population for whom 3 or more treatments had failed. The committee noted that a reduction in the monthly migraine days measure would not capture the benefits to people with migraine of being able to plan their lives and remain in employment. It acknowledged that better day-to-day functioning overall would lead to increased quality of life and utility values, and that a similar rationale had been accepted by the committee in other appraisals.

The company's new approach to modelling differential utility for people on and off treatment is acceptable

3.22 The company's updated analyses for episodic migraine with 3 or more previous treatment failures used differential utilities, and the committee's preference for a normal distribution as in the [NICE guidance on galcanezumab](#) and [erenumab](#). The company explained that in its regression analysis, fremanezumab treatment was a significant covariate in its preferred post-baseline model, and that its approach accounted for any placebo effect in the data. It did some face validity checks on the revised utility values generated by the new approach. The ERG believed the company's regression analysis seemed reasonable and consistent with previous migraine appraisals. However, the company did not provide a detailed statistical analysis plan. Because fremanezumab appeared to be a significant covariate, the ERG interpretation was that this may

indicate fremanezumab has a utility benefit beyond reducing monthly migraine days alone. The ERG pointed out the similarities between the regression model used in the rapid review and those in the appraisals of galcanezumab and erenumab, which were used to justify the choice to use differential utilities for when people were on and off treatment. The ERG considered that the company's approach in its updated analysis addressed the limitations of previous regression models and used separate models for baseline and post-baseline quality-of-life data. The committee noted that the company should have provided a full statistical analysis plan alongside its updated analyses. It considered that fremanezumab may have a utility benefit beyond fewer monthly migraine days. So the committee concluded it was appropriate to take into account the company's updated analyses using differential utilities for its decision making in the rapid review.

Costs in the economic model

Costs used in the economic model are appropriate

3.23 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 at least 3 failed preventive treatments) but based on the general migraine population. At consultation, the company submitted a revised base-case model, which included updated administration costs for botulinum toxin type A (£125 per administration as per the 2016/17 tariff; the corresponding cost for 2018/19 should be £116 but this has very limited impact on model results), as estimated by NICE and NHS England in their budget impact analysis. 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

3.24 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 disabled people or people with a learning disability, older people 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 concluded that it was 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.

Cost-effectiveness estimates

Because of the uncertainty, an acceptable ICER would be towards the lower end of the range normally considered cost effective for episodic migraine

3.25 [NICE's guide to the methods of technology appraisal](#) notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted a high level of uncertainty, specifically:

- the lack of long-term natural history data and the simplicity of the model (see [section 3.14](#))
- the sensitivity of the model to the time horizon and the different post-treatment discontinuation scenarios (see [section 3.14](#) and [section 3.18](#))

- the sensitivity of the model to alternative utility value assumptions (see [section 3.20](#)).

The committee also considered that the impact of introducing fremanezumab for episodic migraine on NHS resources may be higher than for chronic migraine. This is because episodic migraine is more common than chronic migraine. Therefore, the committee agreed that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) for episodic migraine.

Fremanezumab is cost effective for episodic migraine after 3 preventive treatments have failed

3.26 The committee recalled that it had concluded that people with high-frequency episodic migraine were not a distinct group, so it should not consider the cost-effectiveness analysis for this population further (see [section 3.4](#)). The company's revised base-case ICER for fremanezumab compared with best supportive care for episodic migraine was below the range NICE normally considers an acceptable use of NHS resources. For the rapid review, the company's revised base case included the committee's preferred assumptions from the time of the original guidance (TA631; June 2020):

- model corrections
- applying a lifetime (58 years) model time horizon (see [section 3.14](#))
- applying the ERG's post-discontinuation scenario (see [section 3.16](#))
- applying fremanezumab administration costs for 10% of people (see [section 3.24](#)).
- removing a positive stopping rule (see [section 3.18](#))
- removing additional on-treatment utility benefits (see [section 3.20](#)).

It also included differential utilities for on and off treatment, as well as an updated commercial arrangement. Taking its preferences into account, the committee agreed that the most plausible ICER for fremanezumab compared with best supportive care for episodic migraine after 3 preventive treatments

have failed was below £20,000 per QALY gained, which is less than the lower end of the range NICE normally considers an acceptable use of NHS resources. Therefore, it concluded that fremanezumab was a cost-effective use of NHS resources for preventing episodic migraine after 3 preventive treatments have failed.

Fremanezumab is cost effective for chronic migraine after 3 preventive treatments have failed

3.27 The committee was aware that many uncertainties associated with the episodic migraine evidence also applied to the chronic migraine evidence. However, it was aware that the eligible population and impact on NHS resources would be smaller for chronic migraine than for episodic migraine (see [section 3.25](#)). It also recalled that consultation comments from professional organisations and patient groups specifically highlighted the unmet need for the chronic migraine population. It therefore considered that an acceptable ICER would be within the range normally considered cost effective. The company's revised base-case fully incremental ICERs for fremanezumab compared with both best supportive care and botulinum toxin type A were within this range. The company's revised base case assumed the comparative effectiveness estimates from the network meta-analysis (see [section 3.11](#)) and the committee's preferred assumptions:

- model corrections
- applying a lifetime (58 years) model time horizon (see [section 3.14](#))
- applying the ERG's post-discontinuation scenario (see [section 3.16](#))
- applying fremanezumab administration costs for 10% of people (see [section 3.24](#)).

However, the revised base case did not include these committee preferred assumptions:

- removing a positive stopping rule (see [section 3.18](#))
- removing additional on-treatment utility benefits (see [section 3.20](#))

- considering both a scenario of equal effectiveness of fremanezumab and botulinum toxin type A and a scenario using the results of the network meta-analysis (see section 3.11).

The committee recalled that patient and expert groups told them of variable access and long waiting times for botulinum toxin type A treatment. It also recalled that both botulinum toxin type A and best supportive care were relevant comparators for people with chronic migraine (see [section 3.3](#)). Taking the committee's preferences into account, the ICER for fremanezumab compared with best supportive care was within the range NICE usually considers a cost-effective use of NHS resources. Taking its preferences into account and including equal effectiveness of fremanezumab and botulinum toxin type A, the committee noted that fremanezumab was dominated (more costly and less effective) by botulinum toxin type A. But the committee also noted that the difference in QALYs was very small and related to differences in the timing of the assessment for these 2 treatments (12 weeks for fremanezumab and 24 weeks for botulinum toxin type A) and subsequent discontinuation of the treatments. Therefore, it agreed the QALYs produced by the 2 treatments were likely similar. The committee noted that the total costs of fremanezumab were slightly higher than those of botulinum toxin type A over the lifetime model time horizon. The committee was aware that clinical experts considered that fremanezumab would likely cost less than botulinum toxin type A, but noted that no evidence was provided for this. Therefore, it agreed that the relative costs of the 2 therapies in NHS clinical practice were uncertain. It also considered that a small QALY benefit would be needed to produce an ICER within the range NICE usually considers a cost-effective use of NHS resources. The committee noted the results of 2 surveys done by the Migraine Trust, which showed that most patient and clinical experts consider anti-CGRP drugs to be either as effective as, or more effective than, botulinum toxin type A (see page 17 of the [committee papers for the final appraisal document for TA631](#)). The committee noted the methodological limitations of both surveys, which are considered to be low quality in the hierarchy of evidence. But it considered them as expert opinion, and agreed that it could be plausible that fremanezumab may have a small benefit over botulinum toxin type A. The committee noted that the analysis using clinical-effectiveness estimates from the network meta-analysis produced much bigger QALY benefits than this. When assuming the comparative effectiveness estimates from the network meta-analysis, the ICER for fremanezumab compared with

botulinum toxin type A was within the range NICE usually considers a cost-effective use of NHS resources. Taking all the evidence into consideration, the committee concluded that, although there are still uncertainties with fremanezumab's clinical effectiveness and with the model, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments had failed.

Fremanezumab is cost effective for chronic migraine after botulinum toxin type A has failed

3.28 The committee recalled that for the whole chronic migraine population, including the population for whom botulinum toxin type A had failed, fremanezumab was likely to be a cost-effective use of NHS resources for preventing chronic migraine after 3 preventive treatments had failed (see [section 3.27](#)). The committee considered the company's additional evidence submitted at consultation for people with chronic migraine only after 3 preventive treatments and botulinum toxin type A have failed. The committee concluded that the most plausible ICERs for fremanezumab compared with best supportive care were within the range normally considered a cost-effective use of NHS resources, using both company and committee preferred assumptions.

Other factors

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

3.29 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 no specific adjustments were needed to NICE's methods in this situation. No other equalities issues were raised after the original guidance for this topic was published (June 2020).

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

- 3.30 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. But it also acknowledged that fremanezumab administration may be considered more convenient and less unpleasant than administration of botulinum toxin type A.

Conclusion

Fremanezumab for chronic migraine is recommended for use in the NHS

- 3.31 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](#)). The committee recalled that the most relevant comparators for chronic migraine were botulinum toxin type A and best supportive care (see [section 3.3](#)). It considered that fremanezumab was a clinically effective treatment compared with placebo (see [section 3.8](#)). However, the committee considered that it was uncertain whether fremanezumab was more clinically effective than botulinum toxin type A and agreed that it was appropriate to also consider equal effectiveness (see [section 3.11](#)). It considered the revised base case provided by the company at consultation, which included a confidential simple discount patient access scheme for fremanezumab. The committee noted that the most plausible ICER for fremanezumab compared with best supportive care was within the range NICE usually considers a cost-effective use of NHS resources. Although there was uncertainty around the relative treatment effects of fremanezumab and botulinum toxin type A, the committee considered it likely that fremanezumab was a cost-effective use of NHS resources. Therefore, the committee recommended fremanezumab for use in the NHS for preventing chronic migraine in adults after 3 preventive treatments have failed. This includes the chronic migraine

population for whom treatment with botulinum toxin type A has failed. Treatment with fremanezumab should be stopped if migraine frequency does not reduce by at least 30% after 12 weeks of treatment.

Fremanezumab for episodic migraine is recommended for use in the NHS

3.32 The committee recalled that the most relevant comparator for episodic migraine was best supportive care. It considered that the evidence showed that fremanezumab was clinically effective when compared with best supportive care. It also considered that the evidence in high-frequency episodic migraine was uncertain and did not consider it further because it is not a distinct subgroup. For the rapid review, the company presented new evidence supporting the use of differential utilities on and off treatment, specifically focusing on the population with episodic migraine after 3 preventive treatments have failed. It also submitted an updated commercial arrangement. The committee noted that the company should have provided a statistical analysis plan for the regression carried out. However, all the ICERs for scenarios using the updated model with differential utilities were less than £20,000 per QALY gained, and a scenario without differential utilities resulted in an ICER within the range usually considered an acceptable use of NHS resources. Therefore, the committee recommended fremanezumab for use in the NHS for preventing episodic migraines in adults after 3 preventive treatments have failed. Treatment with fremanezumab should be stopped if migraine frequency does not reduce by at least 50% after 12 weeks of treatment.

4 Implementation

- 4.1 Section 7 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 patient has chronic or episodic migraine for which at least 3 preventive drug treatments have failed, and the doctor responsible for their care thinks that fremanezumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

NICE project team

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

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