NICE National Institute for Health and Care Excellence

NICE guidance

Rimegepant for treating migraine

Technology appraisal guidance
Published: 18 October 2023

www.nice.org.uk/guidance/ta919

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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Rimegepant is recommended as an option for the acute treatment of migraine with or without aura in adults, only if for previous migraines:

- at least 2 triptans were tried and they did not work well enough or
- triptans were contraindicated or not tolerated, and nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol were tried but did not work well enough.

1.2 This recommendation is not intended to affect treatment with rimegepant 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

The company proposed rimegepant for acute treatment after at least 2 triptans have not worked well enough, or if people cannot have triptans (contraindicated or not tolerated), which is narrower than the marketing authorisation.

Clinical trial evidence for acute migraine shows that rimegepant is more likely to reduce pain at 2 hours than placebo.

The most likely cost-effectiveness estimates are below or within what NICE considers to be an acceptable use of NHS resources. So, rimegepant is recommended.

2 Information about rimegepant

Marketing authorisation indication

2.1 Rimegepant (Vydura, Pfizer) is indicated for the 'acute treatment of migraine with or without aura in adults'.

2.2 Rimegepant for preventative treatment is recommended in NICE's technology appraisal guidance on rimegepant for preventing migraine.

Dosage in the marketing authorisation

2.3 The dosage schedule is available in the summary of product characteristics for rimegepant.

Price

2.4 The proposed price of rimegepant is £12.90 per 75 mg tablet (excluding VAT).

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Migraine attacks usually last between 4 hours and 72 hours. They involve throbbing head pain of moderate-to-severe intensity, which can be highly debilitating. The patient experts explained that migraine is an individual condition in terms of triggers and presentation. They noted that migraines are often accompanied by nausea, vomiting, dizziness, and sensitivity to light, sound and smells. Migraine can adversely affect quality of life, including people's ability to do their usual activities, and work. The Migraine Trust commented that a 2023 workplace survey found that 43% of people were affected financially and 74% were affected mentally because of the effect of migraines on work. A patient expert highlighted that migraine has a large emotional and psychological burden on the day-to-day lives of those affected. In response to consultation, NICE received comments from the public, carers and people with migraine. They explained that they can feel isolated, dismissed, and treated as if they are responsible for their condition. They described a migraine as an invisible disability that affects all aspects of life including work, education, finances, mental health, social activities, and family. The Migraine Trust also commented that people with migraine are stigmatised, partly because of the lack of understanding about the condition and effective treatments, and the perceived effect on work productivity. It said that access to a treatment that can be taken at onset of migraine could avoid symptoms fully developing, becoming debilitating, and prevent migraine attacks affecting day-to-day life. Migraine can be classified as either with or without aura. An aura is a warning sign of a migraine, such as flashing lights. Migraine can also be classified based on the frequency of headaches, as:

- episodic (fewer than 15 headache days a month) or
- chronic (15 or more headache days a month, with at least 8 of those having features of migraine).

The patient experts explained that the severity of the condition can vary over time, so the distinction between chronic and episodic is not clear cut. This appraisal considers rimegepant within its marketing authorisation (see section 2.1) for treating acute migraine with or without aura, which includes both chronic and episodic migraines. In the first appraisal consultation document, NICE considered rimegepant for both its indications: preventing and treating migraine. In response to consultation, NICE received comments saying that the committee needed to consider the interplay between the acute and preventative indications and the effect of this on the treatment pathways. Comments explained that this is because the acute and preventative indications have distinct populations with only a small overlap. Comments also highlighted that potentially, people may not take rimegepant as prescribed. For example, some people prescribed it for acute migraine might take it to prevent migraine. The committee acknowledged these comments and considered each indication separately. Rimegepant for preventative treatment was recommended in NICE's technology appraisal guidance on rimegepant for preventing migraine. The committee concluded that migraine is a debilitating condition that substantially affects physical, social, psychological and professional aspects of life.

Clinical management

Treatment pathway

3.2 The aim of acute treatment for migraine is to provide effective and sustained relief of headache and associated symptoms. A patient expert highlighted that many treatments target pain but do not address painless migraines. For example, for many people experiencing migraines, a key symptom is an aura, which is not well managed with existing treatments. Existing acute treatments include oral, nasal and injectable triptans, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol, taken either alone or in combination. Antiemetics are also considered, even when there is no nausea or vomiting. The clinical

experts noted that in clinical practice, people with acute migraine would try at least 2 triptans. They explained that some clinicians may choose to offer up to 7 triptans (including different formulations of the same triptan) before moving onto the next stage in the treatment pathway, referred to as best supportive care (see section 3.3). The clinical experts also explained that when triptans are ineffective and the migraine does not respond, it may be because they are not being used properly. They said that if people have no response to between 2 and 4 triptans, it is unlikely they will have a response to any more triptans. In response to consultation, NICE received comments saying that well-defined guidance statements about triptan use could reduce the prevalence and impact of incorrectly used triptans. The clinical experts explained that when triptans are ineffective, not tolerated, or contraindicated, there is no further standard treatment, and that the person should see a migraine specialist. But there are a limited number of headache centres in the UK and there are long waiting lists. Consultation comments noted that some people try medicines not licensed for migraine, such as opioids. The committee concluded that for acute treatment, at least 2 triptans should be tried before another treatment is considered, unless they are contraindicated or not tolerated.

Comparators

3.3 The company proposed rimegepant as an acute treatment for migraine in adults who had taken at least 2 triptans that had not worked well enough, or when triptans are contraindicated or not tolerated (and the person has already tried NSAIDs and paracetamol, which have not worked well enough). This is narrower than the marketing authorisation. The company considered that this is likely how rimegepant for acute treatment would be used in NHS clinical practice. This is because of the unmet need for a new treatment when triptans are ineffective, and for people who cannot take triptans because of safety or tolerability concerns. The committee noted that many consultation responses highlighted this unmet need, particularly in people aged 65 years and over and people with health conditions such as cardiovascular conditions (see section 3.18). The clinical-effectiveness evidence compared rimegepant with placebo. Clinical experts agreed that after triptans there are no other options available for acute treatment. The company

considered that placebo represented best supportive care, which the committee agreed with. Placebo can be understood to be equivalent to best supportive care from here on. The committee recalled its discussion about triptans for the acute treatment of migraine (see section 3.2) and agreed that placebo was the most appropriate comparator.

Clinical effectiveness

Clinical trials

3.4 The company submission included 3 double-blind, randomised controlled trials (RCTs). The RCTs evaluated rimegepant in adults aged 18 years and over, with 2 to 8 moderate-to-severe migraine attacks per month and fewer than 15 monthly migraine days (MMDs). The RCTs were BHV3000-301 (n=1,084), BHV3000-302 (n=1,072) and BHV3000-303 (n=1,351). The single dose of rimegepant (75 mg) was taken as:

- a tablet in BHV3000-301
- a tablet in BHV3000-302
- an oral dispersible tablet in BHV3000-303.

The 3 trials compared rimegepant with placebo for 11 weeks in multiple centres across the US. The primary outcomes were freedom from pain at 2 hours, and freedom from the person's most bothersome symptoms (for example, aura) at 2 hours. A secondary outcome was pain relief at 2 hours, and this was used in the economic model to inform rimegepant's clinical effectiveness. Long-term safety and efficacy data was collected in the BHV3000-201 study (n=1,800). This was a phase 2/3, single-arm trial, which included people from BHV3000-301, BHV3000-302 and BHV3000-303 for a further 12 months follow up.

Trial population

3.5 The company proposed rimegepant for acute treatment for a narrower population than in the marketing authorisation (see section 3.3). In the 3 RCTs, there was a prespecified subgroup of people who had stopped 2

or more triptans because they had not worked. In the first committee meeting, the company used a post-hoc subgroup analysis as its main source of evidence in the economic model. The company explained that it amended the prespecified subgroup to bring the population closer to the decision problem. In response to consultation, the company clarified that this was done because the prespecified subgroup was very small. It explained that this was because the trial had a strict definition of what it meant for a triptan to have not worked. In the prespecified subgroup, people had to have stopped 2 or more triptan treatments for efficacy reasons. This was after all routes of administration tried, such as nasal, injectable, or oral, had not worked. In the post-hoc subgroup this definition was extended to include people who had stopped treatment because of both efficacy and intolerability, after at least 1 administration route did not work. This post-hoc analysis was made up of 9.3% of people from the 3 pooled RCTs, who had stopped 2 or more triptans. The ERG highlighted that the subgroup analyses had limitations, in particular, that its definition had been amended post hoc for the economic analyses and it was not stratified at randomisation. The ERG preferred to use the modified intention to treat (mITT) population (the full trial population), to inform the efficacy of rimegepant and placebo in the model. This is because it is a larger dataset, which the ERG considered to be more relevant because it included people who cannot take triptans. In the second committee meeting, the ERG and the company agreed that the results for the prespecified and the post-hoc subgroup were similar. Both accepted the mITT population including the BHV3000-310 study in the updated base-case analysis. The committee noted that using a post-hoc subgroup instead of a whole population to provide evidence of rimegepant's clinical effectiveness increased the risk of bias in the evidence. It considered the new information on the subgroup analyses and concluded that the mITT population was the most appropriate trial population. This is because it allowed the use of all trial data, including the BHV3000-310 study (see section 3.6).

Subgroup who cannot have triptans

3.6 The committee recognised that there is an unmet need for people for whom triptans are contraindicated or not tolerated, and who have tried NSAIDs and paracetamol but they have not worked well enough (see

section 3.3). After the second meeting, the committee requested cost-effectiveness analyses to see if rimegepant as an acute treatment could be cost effective in this subgroup. In response to consultation, the company provided clinical trial data from this subgroup, defined as people who cannot have triptans because of cardiovascular conditions and/or have stopped at least 1 triptan because it was not tolerated. The ERG stated that it was unsure how applicable this subgroup analysis was to clinical practice and to the committee's request. This is because the subgroup only needed a person to have stopped 1 triptan because of tolerability, whereas the population that the company proposed for rimegepant is people who had at least 2 triptans and had stopped because of lack of efficacy or intolerability. Also, the committee was aware that in clinical practice, multiple triptans are tried and that intolerance to 1 triptan does not rule out the use of other triptan treatments (see section 3.2). The company considered that the results of the subgroup of people who cannot have triptans were similar to the results of the broader populations (the results are academic in confidence and cannot be reported here). The ERG said that while the freedom from pain at 2 hours outcome was similar, there was a notable difference in pain relief at 2 hours, which is the outcome used to inform efficacy in the model. It also highlighted that there were baseline imbalances for migraine severity, aura and the most bothersome symptom. The committee concluded that the new subgroup analysis had limitations and uncertainties, but it would consider it in its decision making (see section 3.18).

Including study BHV3000-310

3.7 The company also presented evidence from another double-blind RCT, BHV3000-310. This compared rimegepant (75 mg single dose oral dispersible tablet) with placebo in adults from China or Korea with 2 to 8 moderate-to-severe migraine attacks per month and fewer than 15 MMDs. The company initially did not include BHV3000-310 because the trial was not able to extract a subgroup of people who had stopped triptans. So, the results could not be combined into the company's subgroup analysis. The company said that the trial did not reflect the UK population because of cultural differences in reporting pain. The clinical experts were unaware that the perception of pain differed between

people in the UK, China and Korea. They reported that in UK practice, they have seen no evidence that ethnicity affects pain perception. The ERG included BHV3000-310 in its data analyses, as well as the 3 RCTs used in the company's base case. This is because the ERG considered that it provided additional data that was relevant to the decision problem. In particular, the ERG noted that BHV3000-310 used the oral dispersible tablet formulation, which is the formulation approved in rimegepant's marking authorisation but not what was assessed in 2 of the 3 RCTs. The company highlighted that the European regulators concluded that the rimegepant oral dispersible tablet and tablet formulations are bioequivalent. The ERG noted that the BHV3000-310 trial and the 3 pooled RCTs had the same proportion of people reporting severe pain at baseline. This suggests that there was no evidence of cultural differences in pain reporting between these studies. The committee noted that any potential cultural differences in pain reporting are less important in an RCT if the treatment arms within the study are done in the same country, because the relative effects are still informative. The committee concluded that BHV3000-310 should be included in the analyses, and excluding 1 of the 4 RCTs providing evidence of the treatment's effectiveness increased uncertainty. After consultation the company included BHV3000-310 in its base-case analysis.

Trial generalisability

3.8 Rimegepant is indicated for acute migraines with or without aura. This includes people with episodic or chronic migraines (see section 3.1). The clinical trials only included people with 2 to 8 migraines per month. A clinical expert said that the RCTs were not reflective of UK clinical practice because people with chronic migraines were excluded. The ERG had concerns that the trial effectiveness data may not be generalisable to people with chronic migraines because chronic migraines are considered harder to treat. This is because of an increased risk of medication overuse headache. The company reported that it had no further evidence to assess the differences in effectiveness between episodic and chronic migraines. But it did not expect there to be any differences. The company also noted that in the long-term study (BHV3000-201), there were few medication overuse headache events. So, it explained that the concerns about chronic migraines should not

lead to a higher incremental cost-effectiveness ratio (ICER) in this population. The ERG agreed that the generalisability of the trial to people with chronic migraine was unresolvable without comparative evidence. Clinical advice to the ERG was that a large difference in effectiveness between chronic and episodic populations was not expected. But medication overuse headache is a bigger problem for people with chronic migraines, which could mean that their acute migraine attacks are harder to treat. The Association of British Neurologists, and the British Association for the Study of Headache, commented that chronic migraine is more refractory to acute and preventative treatments. The clinical experts explained that it is not appropriate to extrapolate the effects of acute treatment for episodic migraine to chronic migraines, because chronic migraines are more likely to be treatment resistant. They noted that for different migraine treatments, such as botulinum toxin type A, response can be different for people with episodic and chronic migraines. The committee concluded that it may not be appropriate to extrapolate the effects of acute treatment for episodic migraines to chronic migraines, because chronic migraines are potentially more refractory to treatment. But the committee recalled the patient experts explaining that the severity of the condition can vary over time, so the distinction between chronic and episodic is not clear cut (see section 3.1). So, the committee accepted that the trial results are generalisable to both populations.

Clinical evidence results

3.9 The committee's preferred results were pooled from BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310 for the mITT population. The results showed that more people on rimegepant had freedom from pain at 2 hours compared with placebo (the results are academic in confidence and cannot be reported here). Using the secondary outcome selected for the economic model, more people on rimegepant had pain relief at 2 hours compared with placebo (the results are academic in confidence and cannot be reported here). Adverse events were considered mild to moderate by both the company and the ERG, with low rates of severe or serious events. For this reason, adverse events were not included in the economic model. The committee concluded that rimegepant is likely to be more effective than placebo for

acute treatment of migraine.

Economic model

Company's modelling approach

3.10 For the acute treatment of migraine, the company modelled the assessment period of 48 hours as a decision tree, and the post-assessment period as a Markov model. In the decision-tree phase, people were grouped into those whose migraine:

- responded (defined as pain relief at 2 hours) and who remained on treatment
- did not respond and who stopped treatment.

The Markov phase was used to model the distribution of MMDs in each health state: on treatment and stopped treatment. The committee concluded that the structure of the company's economic model was appropriate for decision making.

Modelling response

3.11 The company's economic model assumed that response to a single rimegepant dose would inform subsequent response to rimegepant. This means that if there was no response to the first dose of rimegepant, the model assumed there would never be a response to rimegepant. The summary of product characteristics (see section 2.3) has no such stopping rule. In the first meeting, the committee heard that there is no long-term data to inform how response to a single attack may predict response for future migraine attacks. It concluded that the issue of whether the response to a single rimegepant dose should inform subsequent responses in the model was unresolvable because of a lack of data. Given that this technology has a dual indication and there is potential that people may not take rimegepant as prescribed (see section 3.1), in the second meeting, the committee requested information about the stopping rule of rimegepant as an acute migraine treatment. This is because there is a stopping rule in NICE's technology appraisal guidance

on rimegepant for preventing migraine (stop rimegepant after 12 weeks of treatment if the frequency of migraine attacks does not reduce by at least 50%). In response to consultation, the company explained that this modelling response assumption is a built-in stopping rule in the model. It stated that in clinical practice, rimegepant for acute treatment of migraine is anticipated to align with the trial design. This means that treatment will stop if migraine does not respond after 1 dose. The clinical experts explained that a treatment is generally considered ineffective if 3 migraine attacks have been treated and there is no response. They added that clinicians would not be likely to encourage people to stop treatment after only 1 dose. This was supported by the Association of British Neurologists who said that it is unreasonable to assume that if there is no response after 1 dose, there will never be a response. The Association of British Neurologists further explained that typically a treatment is tried for 2 to 3 migraine attacks to assess effectiveness. To account for possible wastage and to acknowledge that some people may take multiple doses of rimegepant to determine response, the company said that a full pack of rimegepant was costed for people whose migraine did not respond. The ERG noted that these modelled stopping rules are based on what is anticipated to happen in practice. It explained that the decision to stop would instead be based on a discussion between the clinician and person with migraine or their carer. The committee considered that people with migraine and their clinicians should consider stopping treatment if there is no response after 2 to 3 attacks. The committee concluded that although multiple doses of rimegepant would likely be tried in practice before stopping treatment, a formal stopping recommendation is not needed.

Baseline monthly migraine days distribution

3.12 After technical engagement, the company and the ERG agreed that the long-term study BHV3000-201 was an appropriate source to inform the economic model of the baseline MMDs distribution. This is because it included a broader range of migraine attacks per month (2 to 14), than the 3 pooled RCTs (restricted to 2 to 8). This means the study better represented the population in the UK who would have rimegepant as an acute treatment. But the company and the ERG did not agree with the distribution used to model baseline MMDs. The company preferred to

use the observed data from BHV3000-201, which it considered to be the natural distribution of the full range of MMD data seen in the UK population. The ERG preferred to model the data using a Poisson distribution. This is because it aligned with the expected distribution for acute treatment as well as the distribution observed for migraine prevention. The ERG also noted that the observed data was sporadic, which the committee agreed with. The committee concluded that a Poisson distribution of the BHV3000-201 trial data should be used to model baseline MMDs.

Reduced monthly migraine days

3.13 Rimegepant has a marketing authorisation for both acute and preventative treatment of migraine (see section 2.2). At the first committee meeting, the company's model assumed that when rimegepant is taken as needed for acute treatment, there will be a long-term reduction in MMDs. This assumption was based on 1-year follow-up data from the long-term study BHV3000-201, where MMD reductions were seen in people who frequently took rimegepant as needed. The ERG considered these results to be highly uncertain because they were from a post-hoc analysis of an uncontrolled study. It also said there was uncertainty from the lack of a comparator group, the lack of randomisation or blinding, and there being no long-term data. The clinical experts stated that reduced MMDs may be a plausible assumption, if rimegepant was used frequently enough to have a preventative effect. But they explained that if someone was having migraines often enough to have a preventative benefit from acute treatment, then they should be having a preventative treatment. The clinical experts noted that there is uncertainty about how a person's condition would respond to rimegepant if they are already taking a preventative treatment. The committee acknowledged that there is biological plausibility that taking rimegepant as needed may reduce MMDs. But there is not enough clinical evidence to support this. So, at the second meeting, the committee concluded that this assumption should be removed from the model. In response to the second consultation, the company presented additional information to support this assumption (it cannot be reported here because it is considered academic in confidence). The reduction in MMDs at 12 weeks was compared between this new evidence and the BHV3000-201 study.

The company base case excluded the reduction in MMDs assumption but modelled it as a scenario analysis, in which it had a significant effect on the quality of life of people taking rimegepant. The ERG acknowledged this effect but said that the evidence is insufficient to include this assumption. The committee was still uncertain about how the preventative effect would translate to NHS practice. For example, if someone is having migraines often enough to benefit from and need a preventative effect, there is a reasonable likelihood that they will be having 1 of the approved preventative treatments (such as in NICE's technology appraisal guidance on galcanezumab, erenumab and fremanezumab). These treatments have a similar mechanism of action to rimegepant, in that they target the calcitonin gene related peptide (CGRP) receptor. The committee questioned whether someone who is already having a drug targeting CGRP for prevention would then have an additional preventative effect from the acute use of another drug with the same target. The committee acknowledged that this is biologically plausible and considered the additional information. But it concluded that it may be considered as a small, potential uncaptured benefit, and should not be included in the model.

Time horizon

3.14 The ERG, who preferred to remove the reduction in MMDs assumption, reduced the time horizon from 20 years to 2 years. This was because it wanted the time horizon to reflect rimegepant's use as an acute treatment. The ERG considered that in an acute migraine attack, costs and benefits of taking rimegepant would occur immediately, so should be accounted for within 2 years. The company did not consider 2 years an adequate length to capture the costs and benefits of acute treatment. It said that acute migraine attacks are chronic and recur across a person's life, so 20 years would be more appropriate. After the first committee meeting, the company provided evidence suggesting that:

- people have migraine attacks over a period of at least 20 years
- a time horizon of 10 years or more was most appropriate
- some people have acute migraine treatment for at least 5 years.

Also, the company stated that using a time horizon that is different to the model used in NICE's technology appraisal guidance on rimegepant for preventing migraine (20 years), but for the same condition, is illogical and inconsistent. At the second meeting, the ERG acknowledged that the company's evidence suggests that people may have migraine attacks which occur over a period longer than 2 years. So, people may have rimegepant as an acute treatment multiple times for longer than 2 years. But it said that this should not dictate the time horizon, and rimegepant as an acute treatment should be modelled to reflect the differences in costs and health-related quality of life for each specific migraine attack, which are of a short duration. At the second meeting, the committee explained that it was not in any doubt that migraine is a chronic and lifelong disease, and rimegepant is an acute treatment that may be used repeatedly over many years. In response to consultation, the company provided additional evidence to show why it considered a 2-year time horizon an unreasonable approach. An extrapolation of the long-term study BHV3000-201 showed that 31% of people having rimegepant who had stopped at least 2 triptan treatments remained on treatment at 5 years. The company also said that the time horizon should be 20 years because a significant proportion of people who have rimegepant long-term will incur additional costs and benefits of migraine compared with those who stop treatment early. Also, for people having placebo, there are no other treatments available, so they will have the full quality of life impact of their migraines for beyond 2 years. The British Association for the Study of Headache commented that a 2-year time horizon is not reasonable and that 20 years is more appropriate. The Association of British Neurologists commented that although acute treatment might be needed for around 20 years, migraine might only become treatment resistant later in life, so people may only swap to other acute treatments for a few years. The committee explained that the main issue with the duration of the time horizon was because of the impact of the placebo response assumption from the company's model. This caused the cost effectiveness of rimegepant to be considerably different at different time horizons (see section 3.15). The 2-year time horizon agreed in the second meeting was chosen to account for the impact of the placebo effect being removed at 1 year. The ERG highlighted that after model corrections made in response to consultation (see section 3.15), the placebo response no longer had a big impact on the relationship between the time horizon and cost effectiveness in the ERG's results. The committee explained that given the effect on cost effectiveness between using a 2- and

20-year time horizon is now small, a 2-year time horizon was sufficient to capture all the cost and benefit differences of each migraine attack. It concluded that the time horizon has a small impact on the cost-effectiveness results.

Placebo response

3.15 In the second meeting, the committee heard that rimegepant is more cost effective over a longer period almost exclusively because of the response observed in the placebo control arm being removed after 12 months. The committee noted that this assumes that after the first year in the model, there is no potential for the migraine attack to improve at 2 hours when not having active treatment. In response to consultation, 2 model errors were identified by the company and ERG, which explained why the placebo effect assumption was causing the cost effectiveness of rimegepant to be considerably different at different time horizons. This meant that the time horizon no longer had a big impact on the ICER estimates when no loss of placebo response was assumed (see section 3.14). The company's response to consultation stated that the committee's conclusion was implausible because a 2-year time horizon with a placebo response lasting 2 years suggests that the placebo response would be sustained indefinitely. Clinical advice to the company said that a placebo response of 1 year or less is expected for the acute treatment of migraines and that a duration of 3 to 6 months is most likely. The company also provided evidence from the literature which suggested that a placebo response is plausible for people having active treatment but is unlikely for people who are not on treatment. The ERG acknowledged the evidence but considered that in clinical practice, people on placebo will have some form of treatment and may have a response. The company also explained that its base case is conservative because it did not include any costs for placebo, but highlighted that in practice it is not possible to have placebo with no NHS cost. The company provided a scenario analysis including placebo healthcare resource use costs for 2 years for every person in the placebo arm and everyone with no response to rimegepant. The ERG agreed that not including placebo costs was conservative but said that the scenario was inappropriate because the healthcare resource use costs were not also applied to the rimegepant arm. In the second meeting, the committee

noted that all effects associated with the placebo response would likely also be seen in the rimegepant arm so it cannot reasonably be removed from 1 treatment arm but not the other. In response to consultation, the company accepted that a placebo response would be seen in both treatment arms but stated that it could not separate a placebo response for those having rimegepant. The committee explained that RCTs are designed to identify the difference between what happens when somebody has an active treatment compared with someone who under similar circumstances does not have an active treatment. A response, such as reduced pain, in the placebo arm could be more than an expectation effect associated with placebo treatment. For example, it may be because of other medicines people might be taking, such as NSAIDs or paracetamol (see section 3.2). Alternatively, it could be the natural resolution of the condition or other effects of the way that that people were sampled in the trial, which leads to a regression to the mean. The committee noted that the company's evidence was presented as though the placebo response is only an expectation effect. The company clarified that the model does include a natural migraine resolution, so that when the placebo response is removed, the migraines of people in the placebo arm still improve over each 48-hour period. The committee stated that the evidence suggests that there is little potential for there to be any natural resolution at 2 hours in people taking placebo whose migraine does not respond. It then explained that the company's evidence came from double-blind RCTs (see section 3.4). The reason for this is so that people do not know which treatment they are having, otherwise a response to treatment could be captured in a single-arm study. So it cannot be said that a placebo effect was in 1 arm and not the other arm. The company responded that their model included some conservative assumptions, for example, excluding placebo costs, using the mITT population (see section 3.5) and modelling placebo response according to previous preventative migraine appraisals. The committee concluded that there should be no loss of placebo response in the model.

Response trajectory after stopping rimegepant

3.16 In the company's base-case model, it was assumed that people who initially had a response to rimegepant and who then stopped treatment,

went on to have a response to placebo for 12 months. This means that people who stop rimegepant are assumed to have the outcomes of someone having placebo for 1 year. Then their outcomes change to those who do not have a response to placebo. Clinical advice to the ERG explained that only a small proportion of people would have a response to placebo when they stop rimegepant. The ERG said a more realistic scenario is one in which those who stopped rimegepant follow a placebo 'all-comers' trajectory for 12 months. This means a combination of people with symptom response and those without. The clinical experts said that without clinical experience of using rimegepant they were uncertain which trajectory would be followed. The committee concluded that the placebo all-comers trajectory was more appropriate for decision making.

Cost-effectiveness estimates

Company and ERG cost-effectiveness estimates

3.17 The company and ERG opinion differed on the time horizon and placebo response. The company base case used a 20-year time horizon and removed the placebo response after 1 year, and the ERG base case used a 2-year time horizon and had no loss of placebo response (see section 3.14 to section 3.15). The company's probabilistic base-case ICER for rimegepant compared with placebo was £18,444 per quality-adjusted life year (QALY) gained. The ERG's probabilistic base-case ICER for rimegepant compared with placebo was £29,281 per QALY gained.

Committee preferred cost-effectiveness estimate

3.18 The committee's preferred assumptions aligned with the ERG's. These were to:

- use the mITT trial population (see section 3.5)
- include study BHV3000-310 (see section 3.7)
- use a Poisson distribution to model baseline MMDs (see section 3.11)

- use the all-comers placebo trajectory for rimegepant response after stopping (see section 3.15)
- exclude reductions in MMDs from rimegepant taken as needed (see section 3.13)
- use a 2-year time horizon (see section 3.14)
- not remove the placebo response at 1 year (see section 3.15).

The cost-effectiveness estimates after accounting for the committee's preferred assumptions and considering the scenario analyses where alternative populations (see section 3.6) and assumptions were used (see section 3.13 and section 3.15), gave a range of ICER estimates that were between £15,000 and £30,000 per QALY gained. This was below or within what NICE normally considers to be an acceptable use of NHS resources.

Other factors for acute treatment

Equality issues

3.19 The company, clinical and patient experts, and consultation comments highlighted that migraine can be considered a disability under the Equality Act 2010. The committee noted that all relevant benefits associated with migraine as a disability were likely captured in the model. It noted that its decision making took into account any obligations related to the Equality Act 2010. Consultation comments also noted that people over 65 years, or those who have other health conditions such as a cardiovascular condition, are not able to have triptans. The committee was aware that people who cannot have triptans in particular had an unmet need (see section 3.3) and agreed that it was important to see if rimegepant could be cost effective in this group (see section 3.6). One consultation comment said that some existing treatments cannot be used in pregnancy because of gestational and maternal safety considerations around continuous dosing. The company responded that there is no available data on rimegepant's use in pregnancy. The summary of product characteristics for rimegepant states that as a precautionary measure, it is preferable to avoid taking rimegepant during

pregnancy (see section 2.3). The company, clinical and patient experts, and consultation comments highlighted that migraine is more common in people of working age and affects more women than men. But the committee agreed that issues relating to differences in prevalence or incidence of a condition cannot be addressed in a technology evaluation. The clinical experts also said that there are a limited number of headache centres in the UK and there are long waiting lists. So, there may be unequal access to specialist headache clinics in England. The committee considered these issues and noted that unequal access was not associated with a protected characteristic. Consultation comments noted people in more deprived areas of the country are at greater risk of becoming disabled by migraine and of losing their jobs and experiencing severe financial hardship. The committee considered whether its recommendations could affect health inequalities associated with socioeconomic factors. It considered that it had not been presented with evidence that people in more deprived areas are at greater risk of becoming disabled by migraine. It also considered that NICE's methods do not include productivity costs in its analyses. In response to consultation, some comments highlighted that rimegepant is available in the US, Europe, United Arab Emirates, Israel and Scotland. The committee noted that the decision to recommend rimegepant in those places is independent from NICE decision making because they have different health systems to the NHS. The committee said that it had read all consultation comments and acknowledged the equality considerations raised. It factored these considerations into its decision making. The committee concluded that no specific adjustments were needed to NICE's methods in this situation.

Innovation

3.20 The company suggested that rimegepant should be considered as an innovative treatment because it is the first dual-indication treatment approved for both acute and preventative treatment of migraine. It said rimegepant is a 'step change' in managing migraines because it is the first targeted acute migraine treatment. The company highlighted that there have been no new UK-approved acute treatments for migraine in over 20 years and that triptans and NSAIDs are the dominant acute treatments. The company also suggested there is an uncaptured benefit

because the model does not consider medication overuse headache and chronification (the progression from episodic to chronic migraine). The ERG and clinical experts explained that there is a lack of clinical evidence supporting either of these and the extent of any potential benefit is unclear. The committee considered rimegepant to be innovative, but that all benefits relating to this were captured in the model.

Conclusion

3.21 The committee recognised the substantial burden that migraine has on quality of life and day-to-day functioning. It acknowledged that this could affect physical, social, psychological and professional aspects of life (see section 3.1). The committee recalled that the most relevant comparator for acute migraine with or without aura was placebo (see section 3.3). The committee considered different trial populations, including for people when triptans are contraindicated or not tolerated, and when NSAIDs and paracetamol have not worked well enough (see section 3.6). It decided that using the mITT trial population was most appropriate (see section 3.5). The committee also decided that economic analyses should include the BHV3000-310 study (see section 3.7). The committee considered the uncertainty in the generalisability of the trial results and the size of its effects (see section 3.8), and concluded that rimegepant was a clinically-effective treatment compared with placebo (see section 3.9). In the economic model, the committee agreed with the ERG that baseline MMDs should be modelled using a Poisson distribution as the observed data distribution was sporadic (see section 3.12). Based on evidence presented by the company and the clinical experts, the committee acknowledged that it was biologically plausible to suggest that there could be reductions in MMDs when rimegepant was taken as needed. But given the uncertainties and the lack of comparative clinical data, the committee concluded that this assumption should be removed from the model. But it noted that this may be considered as a small, potential, uncaptured benefit (see section 3.13). After exploring the effect that the loss of placebo response at 1 year had on the cost effectiveness of rimegepant using different time horizons, and considering the nature of the response observed in the placebo comparator arm, the committee decided there should be no loss of placebo response in the economic model (see section 3.15). The

committee considered both 2- and 20-year time horizons after the reduction in MMDs assumption was removed, and concluded that the time horizon has a small impact on cost effectiveness (see section 3.14). The cost-effectiveness estimates after accounting for the committee's preferred assumptions and the scenario analyses gave a range of ICER estimates that were between £15,000 and £30,000 per QALY gained. This was below or within what NICE normally considers to be an acceptable use of NHS resources. So, the committee recommended rimegepant as an acute treatment for migraine with or without aura in adults, only if for previous migraines:

- at least 2 triptans were tried and they did not work well enough or
- triptans were contraindicated or not tolerated, and NSAIDs and paracetamol were tried but did not work well enough.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 guidance 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 draft guidance.

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 migraine and the doctor responsible for their care thinks that rimegepant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Megan John
Chair, technology appraisal committee D

NICE project team

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

Cara Gibbons
Technical lead

Rufaro Kausi
Technical adviser

Celia Mayers
Project manager

ISBN: 978-1-4731-5484-1

Accreditation