

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Rimegepant for preventing migraine

1 Recommendations

- 1.1 Rimegepant is recommended as an option for preventing episodic migraine in adults who have at least 4 and fewer than 15 migraine attacks per month, only if at least 3 preventative treatments have not worked.
- 1.2 Stop rimegepant after 12 weeks of treatment if the frequency of migraine attacks does not reduce by at least 50%.
- 1.3 If people with the condition and their clinicians consider rimegepant to be 1 of a range of suitable treatments, after discussing the advantages and disadvantages of all the options, use the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements.
- 1.4 These recommendations are not intended to affect treatment with rimegepant 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

The company proposed rimegepant for preventing episodic migraine after 3 or more treatments have not worked, which is narrower than the marketing authorisation. Usual treatments at this point include erenumab, fremanezumab or galcanezumab, which are injections. Rimegepant is an oral treatment, which may be preferred by some people.

Clinical trial evidence shows that rimegepant reduces monthly migraine days more than placebo. It has not been directly compared in a trial with erenumab, fremanezumab or galcanezumab, but indirect comparisons suggest that it is likely to be similar to or less effective than these.

Rimegepant is cost effective compared with 2 of the 3 usual treatments. So rimegepant is recommended for preventing migraine after 3 or more preventative treatments have not worked.

2 Information about rimegepant

Marketing authorisation indication

- 2.1 Rimegepant (Vydura, Pfizer) is indicated for the 'preventative treatment of episodic migraine in adults who have at least 4 migraine attacks per month'.
- 2.2 Rimegepant for acute treatment is being evaluated in [NICE's technology appraisal guidance on rimegepant for acute migraine](#) (ID1539).

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 external 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 disabling. 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, affecting people's ability to do their usual activities, including 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 patients with migraine, who explained that they can feel isolated, dismissed, and treated as 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 a lack of understanding about the condition and effective treatments, and the perceived effect on work productivity. Migraine can be classified as episodic or chronic, based on the frequency of headaches. Episodic migraine is defined as fewer than 15 headache days a month. Chronic migraine is defined as 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 for preventing episodic migraine. Preventing chronic migraine was not considered because it is not within rimegepant's marketing authorisation. 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

there is a potential for misuse of rimegepant. For example, some people prescribed it for preventing migraine might take it when they have an acute migraine. The committee acknowledged these comments and considered each indication separately. Rimegepant for acute treatment is being evaluated in [NICE's technology appraisal guidance on rimegepant for acute migraine](#) (ID1539). 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 preventative treatment is to reduce the frequency, severity or duration of migraine and improve quality of life. A 50% reduction is considered clinically meaningful in episodic migraine. The committee was aware that there is a range of oral preventative treatments that people with at least 4 migraine days per month would try before moving onto a different type of treatment. These include topiramate, propranolol and amitriptyline. The clinical experts noted that rimegepant would usually be offered after 3 preventative oral treatments had not worked, or the person cannot tolerate them. Available fourth-line treatments on the NHS are the injectable monoclonal antibodies erenumab, fremanezumab and galcanezumab. The committee also noted [NICE's recently published technology appraisal guidance on eptinezumab for preventing migraine](#). But because eptinezumab was not recommended for routine use at the time of its decision making, it was not considered a comparator for rimegepant. Consultation comments said that there is a high unmet need for new treatment options and that existing treatments do not work for many people. Comments noted that some people try medicines not licensed for migraine, such as opioids. The committee concluded that at least 3 oral preventative treatments should be tried before other treatments are considered.

Comparators

3.3 The company proposed rimegepant as a preventative treatment for episodic migraine in adults who have at least 4 and fewer than 15 migraine attacks per month, and whose symptoms have not responded to at least 3 preventative treatments, which is narrower than the marketing authorisation. The company considered that rimegepant would likely be used in NHS clinical practice at this point. The company positioned rimegepant alongside erenumab, fremanezumab and galcanezumab. But the committee noted the licensed indication of the comparators is for migraine days per month. This differs slightly from the rimegepant indication, which is for the number of migraine attacks per month. This is because a migraine attack can last more than 1 day (see [section 3.1](#)) so a person can have more than 4 monthly migraine days (MMDs) but could still have fewer than 4 attacks per month. The committee concluded that erenumab, fremanezumab and galcanezumab are the most appropriate comparators. Also, it concluded that any recommendation would not be based on migraine days per month because this would be outside of rimegepant's licence.

Clinical effectiveness

Clinical trials

3.4 The company's clinical evidence for rimegepant for preventative treatment came from BHV3000-305 (n=741), a phase 2/3, double-blind randomised controlled trial. This evaluated rimegepant in adults aged 18 years and over, with at least a 1-year history of migraine with or without aura. It only included people with 4 to 8 moderate-to-severe migraine attacks per month that last, on average, 4 hours to 72 hours if left untreated. Rimegepant (75 mg administered orally as a tablet on alternate days) was compared with placebo over 12 weeks. The primary outcome was the change in mean MMDs in the last 4 weeks of the trial treatment phase. A key secondary outcome, which was used to inform response in the economic model at 12 weeks, was a reduction of at least 50% from baseline in mean number of moderate-to-severe MMDs in the last 4 weeks of the trial treatment phase.

Clinical trial results

3.5 The company presented results from the trial definition (the proportion with at least a 50% reduction in mean number of moderate-to-severe MMDs compared with baseline MMDs in the last 4 weeks of the trial). It also presented results using the definition from the trials for rimegepant's comparators (see [section 3.3](#); the proportion with a reduction in mean MMDs by at least 50% [any severity] compared with baseline during the whole 12-week treatment period). In both definitions, rimegepant was more effective at reducing MMDs than placebo. Adverse events were considered mild to moderate by both the company and ERG, with low rates of severe or serious events. For this reason, they were not included in the economic model. The committee concluded that rimegepant was more effective at reducing MMDs than placebo.

Network meta-analysis

3.6 There was no direct evidence comparing rimegepant with erenumab, fremanezumab and galcanezumab. So, the company did a network meta-analysis (NMA) using data from separate clinical trials of rimegepant, erenumab, galcanezumab and fremanezumab. After technical engagement, the company and the ERG agreed on an NMA including 14 studies. A random effects NMA adjusted for baseline risk was determined to be the most suitable model to use, given that there were limitations in the evidence (see [section 3.7](#)). The outcomes of the model were similar to those in the trial. The results of the NMA numerically favoured erenumab, fremanezumab and galcanezumab in both outcomes (the results are academic in confidence and cannot be reported here) (see [section 3.4](#)). The committee concluded that rimegepant is likely to be similar to or less effective than erenumab, fremanezumab and galcanezumab at reducing MMDs.

Network meta-analysis limitations

3.7 The ERG explained that the NMA was uncertain. This was because of the limitations of BHV3000-305 (see [section 3.8](#)) and the comparability of the

trials included. The ERG explained that the trials in the indirect treatment comparison had different populations, different methods to handle missing data, and different treatment stopping histories. Also, some studies included people with chronic migraines, which is not in rimegepant's licence for preventative treatment. The company acknowledged that there was a lack of direct clinical trial evidence comparing rimegepant with erenumab, fremanezumab and galcanezumab. The ERG accepted that the company had attempted to reduce the uncertainty and that the outstanding limitations were unresolvable. The Association of British Neurologists and British Association for the Study of Headache commented that direct comparisons between trials cannot be made because of differences in study design and placebo response. In response to consultation, NICE received comments saying that not enough evidence had been collected, and further trials are needed directly comparing rimegepant with erenumab, fremanezumab and galcanezumab. The committee acknowledged that BHV3000-305 excluded the most relevant patient population, which limited the NMA and its applicability to this appraisal. The committee concluded that the NMA limitations were unresolvable, largely because of the issues with BHV3000-305, but that the NMA was suitable for decision making.

Exclusion of treatment history

3.8 The company proposed a narrower population than the licence for rimegepant for preventing migraine (see [section 3.3](#)). The clinical evidence presented by the company did not reflect this population. Eleven out of 14 studies included in the NMA excluded people with a history of no response to prior treatment. Also, BHV3000-305 excluded people with no response to at least 2 preventative treatments. A key concern from a clinical expert, which was also noted in comments from the Association of British Neurologists and the British Association for the Study of Headache, was that a history of no response to prior treatments indicates that the migraine could be treatment resistant. The company stated that this issue was unresolvable. This is because no data was collected to assess how

no response to prior treatment affects rimegepant's efficacy. The company presented evidence from comparator trials suggesting that the rimegepant results may be conservative in a population with refractory migraine (the results are academic in confidence and cannot be reported here). The ERG did not agree with this conclusion, stating that the evidence was uncertain and did not show a substantial difference between refractory or non-refractory migraine. Clinical advice to the ERG suggested that refractory migraine could be more difficult to treat, with a higher risk of treatment not working. The committee concluded that the clinical evidence from the NMA was not aligned with the company's positioning for rimegepant, which is after 3 preventative treatments. The committee took this uncertainty into account in its decision making.

Economic model

Company's modelling approach

3.9 For preventing migraine, the company modelled the assessment period of 12 weeks 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 at least a 50% reduction from baseline in MMDs) 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. Those with treatment response remained on treatment beyond 12 weeks but could stop. The committee concluded that the structure of the company's economic model was appropriate for decision making.

Response probability

3.10 In the first committee meeting, to inform rimegepant's efficacy in the economic model, the company used the BHV3000-305 trial outcome definition of the proportion with at least a 50% reduction in the mean

number of moderate-to-severe MMDs compared with baseline in the last 4 weeks of the trial. The ERG preferred to use the definition used in the NMA, which was the proportion with a reduction in the mean number of MMDs (any severity) by at least 50% compared with baseline during the whole 12-week treatment period. The ERG stated that both rimegepant response probability and the relative effects of rimegepant compared with erenumab, fremanezumab and galcanezumab should be informed by the same definition of response. The company reported that 85% of the experts providing clinical advice to the company agreed that assessment of response should be done at 12 weeks. But a GP and pain specialist preferred an average over 12 weeks. The ERG accepted that in practice, response may be measured at 12 weeks. But for consistency, it should be taken over a 12-week average. This was supported by the Association of British Neurologists, The British Association for the Study of Headache and comparator companies. The committee concluded that there should be consistency across model inputs. In response to consultation, the company accepted the committee's preference and used the average over 12 weeks to inform rimegepant's efficacy in the economic model.

Network meta-analysis results application

3.11 In the original company base case, the results from the NMA were implemented into the model in cycle 3 (weeks 9 to 12). The ERG thought that because response in the NMA was assessed as an average over 12 weeks, the results should be applied earlier than week 12. This was supported by data from the rimegepant and comparator trials, which showed reductions in MMDs in the first few weeks of treatment. In response to technical engagement, the company agreed that benefits could be accrued before week 12 and presented 2 options for implementing the results. Option 1, which was preferred by the company, applied the full 12-week benefit from the original base case at week 4. Option 2 used the benefit observed before week 12 for people with response at week 12, applied at week 4 in the model. This was estimated using an alternative regression to that used in the original base case and

option 1. The company used option 1 in its base-case analysis in the first committee meeting. The ERG had concerns about the MMD data for people without response, so it considered that option 1 had limitations. The ERG preferred option 2 because it allowed for incremental improvements between weeks 1 to 12. This was considered plausible by the Association of British Neurologists, the British Association for the Study of Headache and comparator companies. The committee agreed with the ERG that option 2 was the most appropriate method to apply. In the second committee meeting the company included this preferred assumption in its updated base case.

Baseline EQ-5D

3.12 The company derived utility values for the model by mapping health-related quality of life data collected in the BHV3000-305 trial at baseline and week 12 using the Migraine Specific Questionnaire version 2 to the EQ-5D. Utility values were calculated using a regression model that adjusted for the covariates, treatment arm (rimegepant or placebo) and MMD. The company reported that at baseline, the utility values favoured rimegepant (0.6136, n=348) over placebo (0.5976, n=346). But this difference was not statistically significant (p=0.1436; 95% confidence interval 0.12 to 0.17). The ERG was concerned that the difference in utility values at baseline was non-trivial. This is because if the utility benefit of rimegepant above placebo continues over time, people in the rimegepant arm will have improved utility compared with erenumab, fremanezumab and galcanezumab. To make sure that baseline utility in each treatment arm was as similar as possible, the ERG preferred to include the baseline mapped EQ-5D scores as a covariate in the regression model to calculate the utility values. The committee concluded that at baseline, mapped EQ-5D values for each treatment arm should be the same and agreed with the ERG's approach.

Primary care approach

3.13 The company's submission suggested that rimegepant had potential to be prescribed in primary care. In the first committee meeting, the healthcare resource costs were from a secondary care perspective. The committee concluded that rimegepant could eventually be used in primary care. But it recognised that specialist referral, diagnosis and treatment management would likely be needed before rimegepant could be used in primary care (see [section 3.17](#)). In response to consultation, the company updated the model to include healthcare resource use costs mostly from primary care (a primary care approach). Because there is no commercial arrangement for rimegepant it can be used in all applicable settings. [NICE's health technology evaluation manual 2013](#) states that for medicines mainly prescribed in primary care, prices are based on the drugs tariff. In the second committee meeting, the company's revised base case was updated to include a one-off starting cost and a 3-month follow up cost. This was provided by a GP for rimegepant and a neurologist for the comparators. An additional one-off neurologist referral cost was added to the comparator costs, included as 1 GP visit. The company suggested that the primary care approach was conservative because monitoring would likely continue in primary care for rimegepant and in secondary care for the comparators. Clinical advice to the company was that rimegepant could provide resource use cost savings for patients in the community. The company provided a scenario where all rimegepant care was provided in primary care. The ERG was not convinced by the main resource costs of rimegepant being provided in primary care, particularly after the committee's conclusions that a specialist would be needed. A clinical expert explained that there was no reason why a neurologist would only see a patient once and that it was more likely to be at 6 months then yearly. They further noted that there was also no reason why a GP could not start treatment with rimegepant. The committee explained that they had received feedback from clinical practice that GPs would likely prefer people with migraines to be referred to them from a neurologist to have rimegepant, instead of treatment being started in primary care. They said that rimegepant could possibly be provided by a GP, but it would more

likely happen within a shared care agreement or with advice and guidance from a specialist. This is an arrangement in which GPs and specialists work together so a person can have a complex treatment in primary care. Under these circumstances, rimegepant could be started by a specialist in secondary care then later be prescribed by a GP in primary care. But GPs can decline a shared care agreement, keeping the treatment in secondary care only. The Migraine Trust commented that rimegepant provided in primary care could be an excellent opportunity for people with migraine, even if it has to be started in secondary care. The British Association for the Study of Headache also commented that rimegepant should be available in primary care, but it should be used only after a specialist recommendation to ensure appropriate prescribing as part of the treatment pathway for migraine in the UK. The committee concluded that rimegepant would most likely be started by a specialist because of its proposed position in the treatment pathway.

Cost-effectiveness estimates

Company and ERG cost-effectiveness estimates

3.14 The company and ERG differed on 1 assumption, the healthcare resource use costs of rimegepant. The company base case used a primary care approach (see [section 3.13](#)) and the ERG base case used a secondary care approach. The company and ERG's probabilistic base-case incremental cost-effectiveness ratios (ICERs) for rimegepant compared with erenumab, fremanezumab and galcanezumab showed that rimegepant is less expensive and less effective than 2 of the 3 comparators (the exact ICERs cannot be reported here because of confidential commercial discounts).

Net health benefits

3.15 The committee's preferred assumptions were to:

- use the NMA definition to inform the rimegepant response probability (see [section 3.10](#))

- apply the NMA results using option 2 (see [section 3.11](#))
- ensure the specialist costs in secondary care are included alongside the primary care costs (see [section 3.13](#)).

Using the committee's preferred assumptions, rimegepant was less expensive and less effective than the comparators, resulting in ICERs in the south-west quadrant of the cost-effectiveness plane. Cost effectiveness was assessed by calculating net health benefit. The incremental net health benefit of rimegepant was compared with erenumab, galcanezumab and fremanezumab, at threshold values of £20,000 and £30,000 per quality-adjusted life-year (QALY) gained. After the second appraisal committee meeting, the company revised its list price. This updated price resulted in a positive incremental net health benefit compared with 2 of the 3 the comparators (the exact results cannot be reported here because of confidential commercial discounts). The committee concluded that rimegepant is cost effective compared with 2 of the 3 standard treatments.

Other factors

Equality issues

3.16 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 the decision making took into account any obligations related to the Equality Act 2010. Comments also said that migraine is more common in people of working age and affects more women than men. But it was agreed that issues relating to differences in prevalence or incidence of a condition cannot be addressed in a technology evaluation. Also, one 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 clinical experts 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 that 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 and Israel. 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 they had read all consultation comments and acknowledged the equality considerations raised. It factored these considerations into its decision making. The committee decided that these factors did not affect the conclusions reached in this appraisal and that no specific adjustments were needed to NICE's methods in this situation.

Innovation

- 3.17 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. Also, the company noted that it is the first oral alternative to injectable preventative options, with potential for primary care prescription. A clinical expert supported this and noted that there is a need for oral treatment options. They said rimegepant is a 'step-change' in managing migraines.

Consultation comments said that an oral treatment could reduce specialist waiting times, costs, and referrals. The committee acknowledged that rimegepant could eventually be used in primary care but recognised that it would need specialist involvement (see [section 3.13](#)). The committee acknowledged that having an oral option for fourth-line preventative treatment increases choice and may be preferred by some people.

Conclusion

3.18 The committee recognised the substantial burden that migraine has on quality of life and day to day functioning. It acknowledged that this affects physical, social, psychological, and professional aspects of life (see [section 3.1](#)). The committee recalled that the most relevant comparators for episodic migraine after 3 previous preventative treatments were erenumab, fremanezumab and galcanezumab (see [section 3.3](#)). Although there were unresolvable uncertainties about the clinical evidence (see [sections 3.7 to 3.8](#)), and a lack of evidence for the decision problem population, the committee considered that rimegepant is likely to be a clinically-effective treatment compared with placebo (see [section 3.5](#)). The committee concluded that rimegepant is likely to be similar to or less effective than erenumab, fremanezumab or galcanezumab (see [section 3.6](#)). The committee noted that measuring response over the 12-week assessment period was most appropriate (see [section 3.10](#)). To account for benefits while on treatment, the committee preferred to apply the NMA results in the first cycle using option 2, an alternative regression to the original base case (see [section 3.11](#)). The committee considered rimegepant's use in primary care and concluded that currently it would most likely be started by a specialist (see [section 3.13](#)). The committee recognised that some people may prefer an oral medicine, rather than the other options at this stage of the pathway, which need to be injected. The cost-effectiveness estimates after including the comparators' confidential commercial discounts showed that rimegepant is less expensive and less effective than some of the standard treatments. Most of the cost-effectiveness estimates are within what NICE normally considers to be an

acceptable use of NHS resources. The committee decided that, to reflect the clinical trials and current clinical practice, rimegepant should be stopped after 12 weeks of treatment if the frequency of migraine attacks does not reduce by at least 50%. Also, it agreed that, after people with the condition and their clinicians have discussed the advantages and disadvantages of the available treatments, taking into account the administration costs, dosage, price per dose and commercial arrangements, if more than 1 treatment is suitable, it would be appropriate to choose the least expensive option. So the committee recommended rimegepant for preventing episodic migraine in adults who have at least 4 and fewer than 15 migraine attacks per month, if at least 3 preventative treatments have not worked.

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.

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