NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Rimegepant for treating or preventing migraine

1 Recommendations

1.1 Rimegepant is not recommended, within its marketing authorisation, for acute treatment of migraine with or without aura in adults.

1.2 Rimegepant is not recommended, within its marketing authorisation, for preventing episodic migraine in adults who have at least 4 migraine attacks per month.

1.3 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

Acute treatment

The company proposed rimegepant for acute treatment to be used after 2 or more triptans have not worked, or if people cannot have triptans, which is narrower than the marketing authorisation.

Clinical trial evidence for acute migraine shows that rimegepant is likely to reduce pain at 2 hours more than placebo. The company's evidence for people who have had 2 or more triptans that have not worked, or who cannot have triptans, is uncertain. So more analysis of the evidence is needed. Rimegepant might also reduce monthly migraine days. But there is a lack of comparative long-term evidence to support this.

Because of the clinical uncertainty, the cost-effectiveness estimates are uncertain. Also, the most likely estimates are above what NICE normally considers to be an acceptable use of NHS resources. So rimegepant is not recommended for acute treatment.

Preventing migraine

Standard treatment for preventing migraine after 3 or more treatments includes erenumab, fremanezumab or galcanezumab.

Clinical trial evidence for preventing migraine 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 less effective than these.

The cost-effectiveness estimates suggest that rimegepant costs more and less effective than erenumab, fremanezumab and galcanezumab. The estimates are above what NICE normally considers to be an acceptable use of NHS resources. So rimegepant is not recommended for preventing migraine.

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' and the 'preventative treatment of episodic migraine in adults who have at least 4 migraine attacks per month'.

Dosage in the marketing authorisation

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

Price

2.3 The price of rimegepant is £40.00 per 2 pack of 75 mg tablets (excluding VAT; BNF online accessed January 2023).

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. 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 or chronic. 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. Acute migraine attacks can happen to people with either episodic or chronic 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 and preventing episodic migraine. Preventing chronic migraine was not

considered because it is not within rimegepant's marketing authorisation. The committee concluded that migraine is a debilitating condition that substantially affects both physical, social and psychological aspects of life and employment.

Acute treatment

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 current treatments. Current acute treatments include oral, nasal, and injectable triptans, other nonsteroidal anti-inflammatory drugs, and paracetamol and aspirin, 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 experiencing 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, which is best supportive care (see section 3.3). The clinical experts also explained that when triptans are ineffective and the migraine does not respond, it is often 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 response to any more triptan treatments. The clinical experts explained that when triptans are ineffective, not tolerated, or contraindicated, there is no further standard treatment, and 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. The committee concluded that for acute treatment, at least 2 triptans should be tried before another treatment is considered.

Comparators

3.3 For acute treatment of migraine, the company's submission focused on people with migraine who had taken at least 2 triptans that had not worked, or when triptans are contraindicated or not tolerated. 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 for people who cannot take triptans because of safety or tolerability concerns, or when triptans are ineffective. The clinical-effectiveness evidence compared rimegepant with placebo. The company considered that placebo represented best supportive care. Clinical experts agreed that after triptans there are no other treatment options available. The committee agreed that placebo represented best supportive care. Placebo can be understood to mean 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) evaluating 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). These 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 administered 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 key secondary outcome was pain relief at 2 hours, and this was used in the economic model to inform rimegepant's effectiveness. Long-term safety and efficacy data was collected in the BHV3000-201 study (n=1,800), a phase 2/3, single-arm trial, which included people from BHV3000-301, BHV3000-302, 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 triptan treatments because they had not worked. In the company's submission, a post hoc subgroup analysis was used as its main source of evidence in the economic model. The prespecified subgroup and the post hoc subgroup defined treatment failure differently. 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 company's preferred subgroup analyses had limitations, in particular, that its definition had been amended post hoc for the economic analyses and was not stratified at randomisation. The company explained that they amended the prespecified subgroup to bring the population closer to the decision problem. 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. The committee concluded that there were too many uncertainties in the analysis of the post hoc subgroup, so agreed that the mITT population is more appropriate because it allows use of all trial data, including the BHV3000-310 study (see section 3.6). But the committee had not seen data from the prespecified subgroup so requested these results, as well as more information about how treatment failure was defined in this subgroup (see section 3.33). Also, the committee noted that using a post hoc subgroup instead of a whole population to provide

evidence of rimegepant's effectiveness increased the risk of bias in the evidence.

Including the BHV3000-310 study

3.6 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 did not include BHV3000-310 because the trial was not able to extract a subgroup of people by 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 or 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 RCT trials. 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, suggesting that there is no evidence of cultural differences in pain reporting between these studies. The committee noted that any potential cultural differences in the reporting of pain are less important in an RCT if the treatment arms within the study are done in the same country. So the relative effects could still be applicable. 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.

Trial generalisability

3.7 Rimegepant is indicated for acute migraines with or without aura. This includes people with episodic migraines (defined as fewer than 15 headache days a month) or chronic migraines (defined as 15 or more headache days a month with at least 8 of those having features of migraine). The clinical trials only included people with fewer than 8 migraines per month. A clinical expert said that the RCTs were not reflective of current 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 getting a headache from overusing medicine (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 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 (Botox), 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. However, 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

3.8 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 8.2% more people on rimegepant showed freedom from pain at 2 hours compared with placebo. Using the secondary outcome selected for the economic model, 15.2% more people on rimegepant showed pain relief at 2 hours compared with 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, adverse events were not included in the economic model. The committee concluded that rimegepant is likely to be more effective than placebo for treating acute migraine.

Economic model

Company's modelling approach

3.9 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 model had a time

horizon of 20 years to capture the costs and benefits of repeated acute treatment with rimegepant (see section 3.12). The committee concluded that the structure of the company's economic model was appropriate for decision making, but more explanation of the most appropriate time horizon is needed (see section 3.12).

Modelling response

3.10 The company's economic model for the acute treatment of migraine assumed that response to the 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 2.2) has no such stopping rule. The company said that there is no long-term data to inform how response to a single attack may predict response for future migraine attacks. The ERG confirmed that this was an unresolvable uncertainty because there is no long-term data to support the assumption. The Association of British Neurologists and The British Association for the Study of Headache commented that response to treatment may vary considerably between migraine attacks. They also highlighted that there is a large uncertainty associated with a single dose of rimegepant being used to drive efficacy results over a 20-year time horizon. The clinical experts explained that the general recommendation in clinical practice is that treatment is considered ineffective after no response to 3 migraine attacks. The committee 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.

Baseline monthly migraine days distribution

3.11 After technical engagement, the company and 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 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. It also noted that the observed data is 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

3.12 Rimegepant has a marketing authorisation for both acute and preventative treatment of migraine (see section 2.1). The company's acute model assumed that when rimegepant is taken as needed for acute treatment, there will be a long-term reduction in MMDs. This is because there is biological plausibility that there will be a preventative benefit from rimegepant while having acute treatment. This assumption was modelled over a 20-year time horizon and based on 1 year follow-up data from the long-term study, BHV3000-201. The ERG considered these results to be highly uncertain because they were from a post hoc analysis of an uncontrolled study. The company explained that MMD reductions were seen in BHV3000-201 in people who frequently took rimegepant as needed. The ERG stated that it is appropriate to remove this assumption because of the uncertainty from the lack of a comparator group, the lack of randomisation or blinding, and without long-term data. The clinical experts said that reduced MMDs may be a plausible assumption, if rimegepant was used frequently enough to have a preventative effect. But they acknowledged that there were many factors that could affect this, so it was uncertain. The clinical experts also 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 such as erenumab, fremanezumab or galcanezumab. They 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 was also concerned that the size of the preventative effect was not clear. The committee acknowledged that there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs. However, there is not enough clinical evidence to support this. So the committee concluded that this assumption should be removed from the model, but that it may be considered as a small, potential uncaptured benefit. The ERG, who preferred to remove the reduction in MMD assumption, reduced the time horizon to 2 years from 20 years. This was because the ERG wanted the time horizon to reflect rimegepant's use as an acute treatment. The ERG consider that in an acute migraine attack, costs and benefits of taking rimegepant would occur immediately, so should be accounted for in 2 years. The company did not consider this appropriate and stated that 2 years would be inadequate to capture the benefits of acute treatment. The company noted that most people in the trial remained on treatment longer than 2 years. A neurologist consulted by the company said that there is no justified reason that the reduction of MMDs seen in the data would stop over time, so should be measured over 20 years. The clinical experts agreed with the ERG that a 2-year time horizon is more appropriate. The committee accepted that if the reduction in MMD assumption is removed, the cost and clinical effectiveness of taking rimegepant as an acute treatment should be assessed per migraine attack, as costs and benefits can occur immediately. The committee considered both the 2- and 20-year time horizons, but concluded that the costs and benefits of rimegepant as an acute treatment should be reflected in a shorter time horizon than 5 years and more explanation is needed to determine the most appropriate length (see section 3.32).

Response trajectory after stopping rimegepant

3.13 In the company's base-case model, it was assumed that people who initially had response to rimegepant, who then stopped treatment, went on to have 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 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 most appropriate for decision making.

Cost-effectiveness estimates

Company and ERG cost-effectiveness estimates

3.14 The company and ERG differed on 6 assumptions:

- the trial population used in the model (the company used a subgroup population without response to at least 2 triptans, and the ERG used the mITT population)
- including BHV3000-310
- the distribution of baseline MMDs
- the trajectory of rimegepant response after stopping
- assuming MMD reductions after taking rimegepant as needed
- the model time horizon if MMD reductions are excluded.

The company's probabilistic base-case ICER for rimegepant compared with placebo was £17,359 per quality-adjusted life-year (QALY) gained. The ERG's probabilistic base-case ICER for rimegepant compared with placebo was £43,437 per QALY gained.

Acceptable ICER

3.15 NICE's guide to the methods of technology appraisal notes that above a most plausible 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 the uncertainties informing the cost-effectiveness estimates, including the trial population used in the model (see section 3.5), the generalisability of the trial results to chronic migraines (see section 3.7) and appropriate time horizon to use in the model after reductions in MMD are removed (see section 3.12). Because of these uncertainties, the committee considered the maximum acceptable ICER would be at the lower end of the range normally considered a cost-effective use of NHS resources. The committee's preferred assumptions were:

- to use the mITT trial population (see section 3.5)
- to include study BHV3000-310 (see section 3.6)
- to use a Poisson distribution to model baseline MMDs (see section 3.11)
- to use the all-comer placebo trajectory for rimegepant response after stopping (see section 3.13)
- to exclude reductions in MMDs from rimegepant taken as needed (see section 3.12).

The committee considered both the 2- and 20-year time horizons but concluded that more explanation is needed to determine which is most appropriate (see section 3.12). Using the committee's preferred assumptions, a plausible ICER range of between £30,495 and £43,883 was determined per QALY gained, depending upon the time horizon chosen. The range of cost-effectiveness estimates are above what NICE normally considers to be an acceptable use of NHS resources.

Preventative treatment

Clinical management

Treatment pathway

3.16 The aim of preventative treatment is to reduce the frequency, severity or duration of migraine and improve quality of life. They said a clinically meaningful treatment response in preventing chronic migraine is considered to be a 30% reduction in migraine frequency. 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 concluded that at least 3 oral preventative treatments should be tried before other treatments are considered.

Comparators

3.17 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 intends to position 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 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

3.18 The company's clinical evidence for rimegepant for preventative treatment came from BHV3000-305 (n=741), a phase 2/3, double-blind RCT. 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 used to inform the economic model 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

3.19 In the economic model, to determine response at 12 weeks, the outcome of a reduction in mean MMDs of at least 50% compared with baseline was used. The company presented results from the original trial definition (the proportion with at least a 50% reduction in mean number of moderate-to-severe MMDs compared with baseline during weeks 9 to 12). It also used a definition aligning with the one used in the comparator trials (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. But the absolute results from the definition used in the trial were better than those in the network meta-analysis (NMA) definition. 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

3.20 There was no direct evidence comparing rimegepant with erenumab, fremanezumab and galcanezumab. So the company did an NMA using trial data from rimegepant, erenumab, galcanezumab, fremanezumab. After technical engagement, the company and 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 there were limitations in the evidence (see section 3.21). The outcomes of the model were similar to those in the trial. The results of the NMA numerically favoured the comparators erenumab, fremanezumab and galcanezumab in both outcomes (the results are academic in confidence and cannot be reported here). The committee concluded that rimegepant is less effective at reducing MMDs than erenumab, fremanezumab and galcanezumab.

Network meta-analysis limitations

3.21 The ERG explained that the NMA was uncertain. This was because of the limitations associated with BHV3000-305 (see section 3.22) 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. The committee noted that the BHV3000-305 trial 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 found in BHV3000-305, but that the NMA was suitable for decision making.

Exclusion of treatment history

3.22 The company proposed a narrower population than the licence for rimegepant for preventing migraine (see section 3.17). 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, the BHV3000-305 trial comparing rimegepant to placebo excluded people with no response to at least 2 preventative treatments. A key concern from a clinical expert and also expressed in a comment from the Association of British Neurologists and the Association of British Neurologists 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 a 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

3.23 For the preventative treatment of 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

3.24 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 during weeks 9 to 12. 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. They 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 advice to the company agreed that assessment of response should be done at 12 weeks. But a GP and pain specialist did show preference to the 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. So, the NMA definition should be used to inform rimegepant response probability.

Network meta-analysis results application

3.25 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 that 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 their revised base-case analysis. The ERG considered that the company's option 1 has limitations. This is because the ERG had concerns about the MMD data for people without response. The ERG preferred the option 2 because it allowed for incremental improvements between weeks 1 to 12, which was reported to be 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 most appropriate method to apply the NMA results was to use the benefit observed before week 12 for people with response at week 12, applied at week 4 because it was a closer reflection of what happened in the clinical trials.

Baseline EQ-5D

3.26 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 is 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 approach.

Cost-effectiveness estimates

Company and ERG cost-effectiveness estimates

3.27 The company and ERG differed on 2 assumptions:

- the source of rimegepant response probability
- applying the NMA results.

The company and ERG's probabilistic base-case ICERs for rimegepant compared with erenumab, fremanezumab and galcanezumab showed that rimegepant is more expensive but less effective than the comparators (the exact ICERs cannot be reported here because of confidential commercial discounts).

Acceptable ICER

3.28 NICE's guide to the methods of technology appraisal notes that above a most plausible 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 that the uncertainties informing the cost-effectiveness estimates, including the clinical evidence excluding people who have had 3 or more preventative treatments (see section 3.22) and limitations with the indirect treatment comparisons (see section 3.21). Because of these uncertainties, the committee considered the maximum acceptable ICER would be at the lower end of the range normally considered a cost-effective use of NHS resources.

Net health benefits

3.29 The committee's preferred assumptions were to:

- use the NMA definition to inform the rimegepant response probability (see section 3.24)
- apply the NMA results using option 2 (see section 3.26)

Using the committee's preferred assumptions, cost effectiveness was assessed by calculating net health benefit. This is because rimegepant was more expensive and less effective than the comparators, resulting in negative incremental QALYs. The incremental net health benefit of rimegepant was compared with erenumab, galcanezumab and fremanezumab, at threshold values of £20,000 and £30,000 per QALY gained. This resulted in a negative incremental net health benefit compared with all 3 comparators. The committee concluded that rimegepant is not cost effective compared with erenumab, galcanezumab and fremanezumab.

Other factors for acute and preventative treatment

Equality issues

3.30 The company and clinical and patient experts highlighted that migraine can be considered a disability under the Equality Act (2010). They said that migraine is more common in people of working age and affects more women than men. Also, there may be unequal access to specialist headache clinics in England. 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

3.31 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 an alternative oral formulation to currently available treatments. They said rimegepant is a 'step-change' in managing migraines. The committee acknowledged that rimegepant could eventually be used in primary care but recognised that it would need a referral to a specialist, a specialist diagnosis before use, then treatment to be managed by a specialist. The committee considered rimegepant to be innovative but had noted a possible uncaptured benefit (see section 3.12) and took this into account in its decision making.

Conclusion

Acute treatment

3.32 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 psychological, social and physical problems (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 that there was too much uncertainty about the company's subgroup results amended post hoc. So, 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 3.6). The committee considered that although there was uncertainty in the generalisability of the trial results and the size of its effects (see section 3.7), rimegepant was a clinically-effective treatment compared with placebo (see section 3.8). 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 3.11). 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. However, 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 qualitative benefit (see section 3.12). The committee considered both 2- and 20-year time horizons after the reduction in MMDs assumption was removed but concluded that more explanation was needed to determine the most appropriate time horizon (see section 3.12). The cost-effectiveness estimates after accounting for the committee's preferred assumptions gave an ICER range of between £30,495 and £43,883, depending upon the time horizon chosen. This was above what NICE normally considers to be an acceptable use of NHS resources. So the committee did not recommend rimegepant as an acute treatment for migraine in adults with or without aura.

Further analyses for acute treatment

3.33 The committee requests further clarification and analyses from the company to be made available for the second evaluation committee meeting for rimegepant for acute treatment. These should include:

- clarification of the difference between the prespecified and post hoc subgroups
- prespecified subgroup results from the clinical trials BHV3000-301, BHV3000-302, BHV3000-303, for the population who have had 2 or more triptans that have not worked
- economic analyses using the prespecified subgroup results
- scenario analyses using time horizons of 2, and 5 years
- more explanation about the company's preferred time horizon

- a base case including the committee's preferred assumptions (see section 3.15).

Preventative treatment

3.34 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 psychological and physical problems (see section 3.1). The committee recalled that the most relevant comparators for episodic migraines after 3 previous preventative treatments were erenumab, fremanezumab and galcanezumab (see section 3.17). Although there were unresolvable uncertainties about the clinical evidence (see sections 3.21 to 3.22), 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 3.19). The committee concluded that it is less effective than erenumab, fremanezumab or galcanezumab (see section 3.20). The committee noted that measuring response over the 12-week assessment period was most appropriate (see section 3.24). 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 3.25). The cost-effectiveness estimates after including the comparators' confidential commercial discounts showed that rimegepant is more expensive and less effective than erenumab, fremanezumab and galcanezumab. So the committee did not recommend rimegepant for preventing episodic migraine in adults who have at least 4 migraine attacks per month.

4 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

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