NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Rimegepant for treating migraine

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using rimegepant in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex, or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document, and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using rimegepant in the NHS in England.

For further details, see NICE's guide to the methods of technology appraisal.

The key dates for this evaluation are:

- Closing date for comments: 21 June 2023
- Third evaluation committee meeting: 10 August 2023

Details of membership of the evaluation committee are given in section 4.

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 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 acute treatment after 2 or more triptans have not worked, or if people cannot have triptans. This is narrower than the marketing authorisation. After triptans there are no other treatment options available.

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 above what NICE considers to be an acceptable use of NHS resources. So, rimegepant is not recommended. But because there is an unmet need for people who cannot have triptans, more evidence is needed to see if rimegepant could be cost effective in this group.

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 being evaluated in NICE's technology appraisal guidance on rimegepant for preventing migraine (ID6275).

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 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. 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. 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. 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 acute migraine might take it to prevent migraine. The committee acknowledged these comments and considered each indication separately. Rimegepant for preventative treatment is being evaluated in NICE's technology appraisal guidance on rimegepant for preventing migraine (ID6275). 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, 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 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, 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 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.

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, or when triptans are contraindicated or not tolerated. 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 for people who cannot take triptans because of safety or tolerability concerns, or when triptans are ineffective. The committee noted that many consultation responses highlighted this unmet need, particularly in people aged 65 years and over and people with other health conditions such as cardiovascular conditions (see section 3.18). 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. So, the committee agreed that placebo represented best supportive care. 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 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 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).

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 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

3.7 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 fewer than 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 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 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

3.8 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 more people on rimegepant experienced 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 experienced 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 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.

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 2.3) 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 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. It 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

3.12 Rimegepant has a marketing authorisation for both acute and preventative treatment of migraine (see section 2.2). 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 it is biologically plausible that there will be a preventative benefit from rimegepant while having acute treatment. This assumption was modelled over a 20-year time horizon and was 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 said 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 there being no 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. 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 rimegepant's preventative effect when used as an acute treatment was not clear. The committee acknowledged that there is biological plausibility in the suggestion that taking rimegepant as needed may reduce MMDs. But 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.

Time horizon

3.13 The ERG, who preferred to remove the reduction in MMD assumption, reduced the time horizon from 20 years to 2 years. This was because the ERG 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. In the first committee meeting, the committee considered both the 2- and 20-year time horizons. But it concluded that the costs and benefits of rimegepant as an acute treatment should be captured in a time horizon of less than 5 years, and

that more explanation of the reasons why cost effectiveness increased over longer time horizons was needed to determine the most appropriate length. The committee wanted to understand why the cost effectiveness increased over time, when the expectation was that all costs and benefits should have been captured in shorter time horizons. In response to consultation, the company provided additional evidence to show that people with migraines will experience acute attacks for around 20 years. In response to consultation, the company provided evidence from surveys with GPs and neurologists and said most agreed that the duration of migraine attacks over a lifetime would be longer than 10 years. Also, in the 3 RCTs, the average age of disease onset was 21 years, and the average age of enrolment in the trial was 39 years, which indicates that the average disease duration of migraine is much longer than 2 years. A clinical expert agreed that people would experience migraine attacks for around 20 years. But the clinical expert explained that they expect that the preventative action of rimegepant will minimise the need for acute treatment. This supported conclusions from the first committee meeting, that if someone has migraines often enough to have a preventative benefit from acute treatment, they should be having a preventative treatment (see section 3.12). The company said that the effects of acute migraine last longer than the attack itself, and that poor treatment of attacks over time is associated with progression from episodic to chronic migraine. It explained that this disease progression needs to be considered over a longer time period. The committee asked if the company had considered this in its model, but the company responded that it had not. The ERG acknowledged that the company's evidence shows that people experience migraines for longer than 2 years. So, people would need acute treatment with rimegepant as needed for longer than 2 years. But the ERG said that this should not dictate the time horizon, and rimegepant as an acute treatment should be modelled to reflect the short-term differences in costs and health-related quality of life for each specific migraine episode. A consultation comment agreed with the ERG that 2 years should capture all the costs and benefits of acute migraine treatment, particularly when

modelling is based on the response to a single administration of rimegepant. NICE's guide to the methods of technology appraisal 2013 states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. Also, it explains that a time horizon shorter than a person's lifetime could be justified if there is no differential mortality effect between treatments, and the differences in costs and clinical outcomes relate to a relatively short period. The committee said that it understood that migraine is a chronic and lifelong disease, and rimegepant is an acute treatment that could be used repeatedly over many years. It highlighted that these facts were not in any doubt, and explained that the issue is the mechanism by which the model produces different cost-effectiveness estimates over different time horizons.

Placebo response

3.14 In the first committee meeting, the scenario analyses showed that when the time horizon increased from 2 to 20 years, rimegepant became more cost effective (see section 3.13). In response to consultation, the ERG explained this effect. It said 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. This was based on an assumption in the company model that people having response to placebo no longer have any benefit after 12 months. The removal of the response in the placebo comparator arm meant that in the 20-year time-horizon scenario the comparative effectiveness of rimegepant increased over time. This is because people in the rimegepant arm continue to accrue benefits for up to 20 years, whereas the health outcomes for people in the placebo arm are worse for all subsequent years beyond the first 12 months. As a result, the difference in quality-adjusted life years (QALYs) gained between each treatment arm increases over time. This explains why rimegepant appeared to be more cost effective when a 20-year time horizon was used compared with 2 years. The committee noted that removing the response in the placebo arm 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. The company explained that the removal of response in the placebo arm after 12 months was based on clinical input that said that the length of a placebo effect in the comparator arm would be between 3 and 6 months. It further explained that this was consistent with previous NICE technology appraisal guidance on preventing migraine (for example, NICE's technology appraisal guidance on galcanezumab, erenumab and fremanezumab). The committee noted that this time-horizon issue relates to rimegepant as an acute treatment, not a preventative treatment, so assumptions made in previous preventative migraine treatment appraisals do not necessarily apply. The committee also questioned the nature of the response observed in the placebo arm. It explained that the reduced pain seen in the placebo arm in the first year of the model 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 nonsteroidal anti-inflammatory drugs, paracetamol or aspirin (see section 3.2), or because of natural evolution in the intensity of pain over the first 2 hours of the attack (see section 3.9). The committee noted that all effects associated with the placebo response would likely also be seen in the rimegepant arm and so cannot reasonably be removed from 1 treatment arm but not the other. The committee agreed with the ERG that the costs and benefits of rimegepant as an acute treatment would likely be accounted for in a 2-year time horizon, and concluded that there should be no loss of placebo response at 12 months.

Response trajectory after stopping rimegepant

3.15 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

3.16 Company and ERG opinion differed on the time horizon. The company base case used a 20-year time horizon, and the ERG base case used a 2-year time horizon (see section 3.13). The company's probabilistic base-case ICER for rimegepant compared with placebo was £18,914 per QALY gained. The ERG's probabilistic base-case ICER for rimegepant compared with placebo was £27,621 per QALY gained.

Committee preferred cost-effectiveness estimate

3.17 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 3.6)
- use a Poisson distribution to model baseline MMDs (see section 3.11)
- use the all-comer placebo trajectory for rimegepant response after stopping (see section 3.15)
- exclude reductions in MMDs from rimegepant taken as needed (see section 3.12)
- use a 2-year time horizon (see section 3.13).

The committee's preferred assumptions also included not removing the placebo response at 1 year (see section 3.14). Using these

assumptions, an ICER of £58,486 per QALY gained was set. The cost-effectiveness estimate is above what NICE normally considers to be an acceptable use of NHS resources.

Other factors for acute and preventative treatment

Equality issues

3.18 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. 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 were aware that this group of people in particular had an unmet need (see section 3.3) and agreed that it was important to request more evidence to see if rimegepant could be cost effective in this group (see section 3.21). Also, 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 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 its conclusions and concluded that no specific adjustments were needed to NICE's methods in this situation.

Innovation

3.19 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. They said rimegepant is a 'step change' in managing migraines as it is the first specialist acute migraine treatment. The committee considered rimegepant to be innovative and noted a possible uncaptured benefit (see section 3.12) which it considered in its decision making.

Conclusion

3.20 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 and 3.18). 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 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. 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 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 although migraine is a lifelong disease, a 2-year time horizon is most appropriate because it captures all important differences in the costs and benefits of treating acute migraine attacks (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 the assumption should be removed from the economic model (see section 3.13). The cost-effectiveness estimates after accounting for the committee's preferred assumptions gave an ICER of £58,486 per QALY gained. 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 with or without aura in adults.

Further analyses for acute treatment

3.21 The committee recognised that there is an unmet need when triptans are not tolerated, or contraindicated and there are no further standard treatments. The committee requests further analyses and information to be made available for the third evaluation committee meeting, to see if rimegepant for acute treatment could be cost effective in this group. Analyses should include:

- results from the clinical trials BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310, for people who cannot have triptans
- economic analyses using the clinical evidence for people who cannot have triptans.

The committee also recognised that the company did not include a continuation or stopping rule for acute migraine. But this was included in NICE's technology appraisal guidance on rimegepant for preventing migraine (ID6275). Given the dual indication of rimegepant and the potential for misuse of rimegepant (see section 3.1), the committee requests further information about the stopping rules for rimegepant as an acute treatment.

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

ISBN: [to be added at publication]