The cost-effectiveness of rimegepant (Vydura®) for the treatment of acute migraine with or without aura and the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of rimegepant for the treatment of acute migraine with or without aura and the preventive treatment of episodic migraine in adults. The NCPE recommends that rimegepant be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an appraisal of the Applicant's (Pfizer Healthcare Ireland) Health Technology Assessment of rimegepant. The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

National Centre for Pharmacoeconomics **May 2023**

Summary

On the 7 February 2023 Pfizer Healthcare Ireland submitted an economic dossier on the cost-effectiveness of rimegepant for the treatment of acute migraine with or without aura and the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.

Migraine is the second most prevalent neurological disorder (after tension-type headache) with a female to male ratio of 2:1 and an estimated 1-year prevalence of approximately 14.4 % in the general population. The prevalence peaks between the ages of 35 and 39 years and approximately 75% of affected persons report the onset of migraine before the age of 35 years. The International Classification of Headache Disorders 3rd Edition (ICHD-3) provides diagnostic criteria for the three main categories of migraine: migraine without aura, migraine with aura and chronic migraine. Chronic migraine refers to headaches (suggestive of migraine or tension headaches) on 15 days or more per month for greater than three months and affects approximately 5 to 8% of persons with migraine whereas episodic migraine which is defined as fewer than 15 migraine days per month with or without aura accounts for more than 90% of patients with migraine.

The trigeminovascular system is considered the centre from which nociceptive transmission originates resulting in the perception of migraine pain. Nociceptive transmission originates from the activation and sensitization of first-order trigeminovascular neurons whose cell bodies are in the trigeminal ganglion and their afferent fibers innervate the meninges and it's blood vessels. Ascending transmission from the trigeminal ganglion is projected to the brain stem, activating second-order neurons including the spinal trigeminal nucleus. Signalling molecules involved in the genesis of migraine pain are potent vasodilators and include calcitonin gene-related peptide (CGRP) which is widely distributed in the trigeminovascular system. Recent developments in the drug treatment of migraine has resulted in the introduction of agents that target CGRP or the CGRP receptor. Rimegepant is a second generation gepant which selectively binds with high affinity to the CGRP receptor thereby inhibiting CGRP receptor function. The pharmaceutical formulation is an oral lyophilisate containing rimegepant sulphate, equivalent to 75mg rimegepant. The

recommended dose for acute treatment of migraine is 75mg once daily, as needed. For the prophylaxis of migraine the recommended dose is rimegepant 75mg every other day.

First-line treatment of acute migraine includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac or acetylsalicylic acid or if NSAIDs are contraindicated paracetamol may be used. Antiemetics such as domperidone or metoclopramide may also be used when necessary. Second-line medication, where patients experience three or more consecutive attacks with little or no response to NSAIDs includes the triptans e.g. sumatriptan. For preventive treatment a wide range of therapeutic agents are recommended including beta-blockers, angiotensin II receptor blockers, anti-convulsants, antidepressants in addition to CGRP monoclonal antibodies e.g. erenumab.

The manufacturer anticipates that rimegepant will be used for the treatment of acute migraine in patients who (a) have failed two or more triptans (b) are considered unsuitable (contraindicated) for triptan therapy or (c) are intolerant of triptans. The anticipated place in therapy for treatment of episodic migraine is for adult patients who have at least four migraine attacks per month and have previously failed three or more preventive therapies. These patient populations are narrower than the licensed indication.

1. Comparative effectiveness

Three key phase III multicentre, single-dose, placebo-controlled studies of similar design in addition to an open-label long term safety study, supported rimegepant for the treatment of acute migraine. Two of the phase III trials (BHV3000-301 and BHV3000-302) assessed the safety and efficacy of the rimegepant 75mg oral tablet, which is bioequivalent to the oral lyophilisate. The phase III trial BHV3000-303 assessed the safety and efficacy of rimegepant 75mg oral lyophilisate formulation and is considered to be the pivotal trial due to its use of the marketed orally disintegrating tablet. The phase II/III open-label study BHV3000-201 assessed safety and tolerability of the rimegepant 75mg oral tablet for (a) treatment of acute migraine (as required dosing) up to 12 months duration and (b) treatment of episodic migraine (every other day dosing) up to 12 weeks duration.

The pivotal phase III trial BHV3000-303 compared the efficacy, safety and tolerability of the orally disintegrating tablet formulation of rimegepant 75mg with placebo for the treatment of a single acute migraine attack of moderate or severe pain intensity. This double-blind, randomised, placebo-controlled, multicentre trial included (a) men and women aged 18 years and older with at least a one year history of migraine with or without aura (b) patients whose migraine onset was before 50 years (c) patients who had at least two and not more than eight migraine attacks of moderate to severe intensity per month and (d) participants who had fewer than 15 days per month with migraine or non-migraine headache within the past three months. The co-primary endpoints were freedom from pain and freedom from the most bothersome symptom at two hours post dosing. Some 1351 participants were evaluated for efficacy (rimegepant n=669, placebo n=682). The mean age was 40.2 years, 85% were female and the primary migraine type was migraine without aura (70%). The mean history of moderate to severe attacks per month was 4.6 and untreated attacks lasted a mean of 29.5 hours. The most bothersome symptoms were photophobia (57%), nausea (23%) and phonophobia (19%). In relation to the co-primary outcome measures at two hours post dose rimegepant was superior to placebo for freedom from pain (21% versus 11%, $p<0.0001$) and freedom from the most bothersome symptom (35% versus 27%, $p=0.0009$). Rimegepant was superior to placebo for all secondary endpoints including pain relief and ability to function normally at 60 minutes post dose, freedom from pain and freedom from the most bothersome symptom at 90 minutes post dose, rescue medication use within 24 hours and sustained freedom from pain and pain relief from 2 to 24 hours and 2 to 48 hours post dose. There were limitations with this study including the absence of an active comparator and the single migraine attack study design.

The clinical evidence for the preventive treatment of migraine is taken from the BHV3000-305 study, a pivotal phase II/III randomised, double-blind, placebo-controlled study that evaluated the efficacy of rimegepant 75mg tablet administered every other day for up to 12 weeks. This was followed by a 12 month open-label extension study. A phase IV open-label study is currently underway to assess the long-term safety and tolerability of rimegepant administered daily for the prevention of episodic migraine. In study BHV3000-305 741 adults with at least a one year history of migraine were randomised to oral rimegepant 75mg (n=370) or matching placebo (n=371) every other day for 12 weeks. The mean age of

participants was 41.2 years, 83% were female, the mean number of moderate or severe migraine attacks per month was 7.8 and 23% had a history of chronic migraine. The primary efficacy endpoint was change from the four week observation period in the mean number of migraine days per month in the last four weeks of the double-blind treatment phase (weeks 9-12). Participants who received at least one dose of their assigned study medication and who had 14 days or more of data in the observation period and 14 days or more of data for at least one four week interval during the double-blind treatment phase were analysed for efficacy. Those who received at least one dose of study medication were analysed for safety. Some 695 patients were included in the analysis of efficacy with 348 assigned to rimegepant 75mg every other day and 347 to placebo. The change in the mean number of migraine days per month during weeks 9 to 12 was -4.3 days (95% Confidence Interval (CI) -4.8 to -3.9) with rimegepant and -3.5 days (-4.0 to -3.0) with placebo (least squares mean difference -0.8 days, 95% CI -1.46 to -0.20; p=0099). Rimegepant 75mg also displayed superiority over placebo in relation to the reduction in migraine days per month over the 12 week double blind treatment period (-3.6 days for rimegepant versus -2.7 days for placebo; p=0.0017). The secondary endpoint of rescue medication days per month in the last month of the double-blind treatment phase was not significantly different between the two treatment groups. The NCPE Review Group highlighted the limitations of this preventive treatment of migraine study: the relatively short duration of study i.e. 12 weeks of the double-blind phase, the small sample of participants with chronic migraine, the exclusion of patients with more than 18 headache days during the observation period and the absence of a comparator. The change from baseline in the monthly migraine days for the subjects initially randomised to rimegepant treatment and who continued open-label treatment (every other day and when required) was sustained beyond the first 12 weeks with no evidence of loss of effect over the 12 month open-label period.

2. Safety

The adverse event profile for rimegepant 75mg oral disintegrating tablet was similar to placebo when used for the treatment of acute migraine. The most common on-study adverse events with rimegepant were nausea (2%), urinary tract infection (1%) and dizziness (1%), similar to the placebo group. There was no signal of hepatotoxicity. Use of rimegepant

75mg every other day for preventive treatment of migraine indicated that the adverse event rate was similar to that of placebo over the 12 week treatment period and most adverse events were mild to moderate in severity. Adverse events occurring in at least 2% of patients treated with rimegepant included nasopharyngitis, nausea, urinary tract infection and upper respiratory tract infection. Elevated hepatic transaminases greater than three times the upper limit of normal occurred in 1% of patients in the rimegepant and placebo groups. Therefore, the safety data indicates that oral rimegepant is well tolerated.

3. Cost effectiveness

For acute and preventive treatment of migraine a de novo decision tree plus Markov model was developed to compare the cost-effectiveness of rimegepant with best supportive care. For the treatment of acute migraine, the base case response was defined as pain relief at two hours. Patients who exhibited a response experienced pain trajectories observed in the responders from the treatment arms of studies BHV3000-301, BHV3000-302 and BHV3000-303 while those who did not exhibit a response to either rimegepant or best supportive care were assumed to discontinue treatment. Best supportive care was defined as (a) a triptan combined with a non-steroidal anti-inflammatory drug (NSAID) or an antiemetic or (b) a combination of NSAID and an antiemetic in patients where triptan therapy is contraindicated or unsuitable. Therefore, the first migraine event was used to determine whether patients continued or discontinued treatment in the model. Responders were assumed to continue to respond in the following cycles during subsequent attacks with a proportion of patients receiving rimegepant discontinuing treatment each cycle, as informed from the long-term safety study BHV3000-201. The efficacy of rimegepant is primarily characterized by improved pain trajectories per migraine event among treatment responders, resulting in higher utility values on average across a 48 hour migraine cycle and subsequently additional quality adjusted life hours (QALHs). In relation to utilities, patient level migraine-specific quality of life questionnaire data was mapped to EQ-5D. The time horizon of the acute migraine model was 40 years, the cycle length was 48 hours and the discount rate was 4%.

For preventive treatment of migraine, patients entered the model by initiating treatment

with rimegepant or best supportive care for a 12 week period (assessment period) with treatment response defined as at least a 50% reduction from baseline in monthly migraine days. Best supportive care was defined as the next preventive agent from a list of preventive treatment options not yet attempted. The combination of best supportive care plus a calcitonin gene-related peptide (CGRP) monoclonal antibody was considered as a scenario analysis. Non-responders discontinued treatment at 12 weeks. In the rimegepant treatment arm responders retained the predicted 12-week responder monthly migraine days distribution until treatment discontinuation. Rimegepant and best supportive care response was modelled based on probability observed in the BHV3000-305 study. Probabilities for all other comparators (e.g. CGRP monoclonal antibodies) were based on the relative effects in the network meta-analysis applied to the rimegepant probability from study BHV3000-305. Utilities were generated using patient level migraine-specific quality of life questionnaire data mapped to EQ-5D. Patients entered the model at approximately 41 years of age, the base case time horizon was 40 years with a cycle length of 28 days and a discount rate of 4%. The perspective was that of the Health Service Executive.

For the treatment of acute migraine the base-case (deterministic) incremental cost-effectiveness ratio (ICER) for rimegepant versus best supportive care was estimated at €18,614 per quality adjusted life year i.e. €18,614/QALY. An analysis of costs and QALYs is shown in table 1. Best supportive care was defined as a triptan combined with an NSAID or an anti-emetic and a combination of NSAID plus an anti-emetic in patients where triptan therapy is contraindicated or unsuitable.

Table 1. Cost-effectiveness of rimegepant for the treatment of acute migraine versus best supportive care (BSC).

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Rimegepant	€20,622	11.5121	€7,668	0.4119	18,614
Best supportive	€12,954	11.1001			

care (BSC)					

BSC:Best supportive care ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year

For preventive treatment of migraine the deterministic ICER for rimegepant versus best supportive care was €36,124/QALY (Table 2). Best supportive care was defined as amitriptyline 50mg daily, propranolol 160mg daily, candesartan 16mg daily and topiramate 100mg per day.

Table 2. Cost-effectiveness of rimegepant versus best supportive care (BSC) for preventive migraine treatment

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Rimegepant	€75,541	12.216	€12,172	0.337	36,124
Best supportive care (BSC)	€63,369	11.879			

BSC: Best supportive care ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year

For acute migraine treatment a probabilistic sensitivity analysis (PSA) was conducted and the ICER for rimegepant versus best supportive care was estimated at €18,225/QALY which is consistent with the deterministic ICER of €18,614/QALY. The probability of rimegepant being cost-effective at the €45,000/QALY threshold was 100%. For preventive migraine treatment a PSA was also conducted and the resultant ICER for rimegepant versus best supportive care was €36,127/QALY.

A deterministic sensitivity analysis was also presented. The parameters that impacted the cost-effectiveness of rimegepant versus best supportive care for the treatment of acute migraine included: discounting of costs and outcomes and the time horizon. Any changes to

the parameters explored in the sensitivity analysis did not result in ICERs exceeding the cost-effectiveness threshold. Discontinuation rates did impact the ICER which increased to €27,128/QALY when the discontinuation rate was reduced to 5%. For preventive treatment of migraine the parameters that impacted the ICER value included: discount rates for costs and health outcomes and monthly migraine days related resource use.

4. Budget impact

The price to wholesaler of rimegepant 75mg for a pack size of eight tablets is €200. For the treatment of acute migraine the number of rimegepant tablets used per month will depend on the number of monthly migraine days. In the acute migraine model it is assumed that patients experience 4.7 monthly migraine days and the total cost per patient per year for rimegepant was estimated at €2,103.38. Rimegepant costs for preventive treatment of migraine were based on the recommended dose of 75mg every other day resulting in a total cost of rimegepant per patient per year of €5,298.57.

For acute migraine the Applicant predicted that 144 patients would be treated with rimegepant in year 1 increasing to 3,631 in year 5 under the High Tech Drug Arrangement (HT) resulting in an estimated 5 year gross budget impact of €18,347,194. The net 5 year drug budget impact was estimated at €14,627,063. For episodic migraine the Applicant predicted that 171 patients would be treated with rimegepant in year 1 increasing to 789 in year 5 under the HT resulting in an estimated 5 year gross budget impact of €14,898,981. The net 5 year drug budget impact for episodic migraine was estimated at €14,435,639.

5. Patient Submission

A patient organisation submission was received from the Migraine Association of Ireland.

6. Conclusion

The NCPE recommends that rimegepant (Vydura®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments and that a managed access programme is introduced*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.