SMC2603

rimegepant oral lyophilisate (Vydura®)

Pfizer Limited

04 August 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission

rimegepant (Vydura®) is accepted for restricted use within NHSScotland.

Indication under review: for the preventive treatment of episodic migraine in adults who have at least four migraine attacks per month.

SMC restriction: for patients with episodic migraine who have at least 4 migraine attacks per month, but fewer than 15 headache days per month and who have had prior failure on three or more migraine preventive treatments

In one double-blind, randomised, phase II/III study, there was a significantly greater reduction in the mean number of migraine days per month from the observation period to the last 4 weeks of the 12-week double-blind treatment period in patients treated with rimegepant compared with placebo.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Rimegepant is an oral selective calcitonin gene-related peptide (CGRP) receptor antagonist. The relationship between pharmacodynamic activity and its mechanism of action is unknown. However, it is thought to relieve migraine by blocking CGRP-induced neurogenic vasodilation, returning dilated intracranial arteries to normal by halting the cascade of CGRP-induced neurogenic inflammation which leads to peripheral and central sensitisation and/or by inhibiting the central relay of pain signals. For the prevention of migraine, the recommended dose of rimegepant is 75mg orally taken once every other day. Rimegepant is also licensed for the acute treatment of migraine.[1, 2]

1.2. Disease background

Migraine is the most common type of severe primary headache with no associated underlying pathology. This neurological condition is characterised by recurrent attacks of moderate to severe headache pain and other associated symptoms such as nausea, vomiting, photophobia and phonophobia. When untreated or unsuccessfully treated, a migraine attack generally lasts from 4 to 72 hours. It has a prevalence of 1 in 7 of the population and is more common in females than males due to changes in hormone levels. Migraine can be subdivided into migraine experienced with and without aura. It can also be defined as episodic (occurring on <15 days per month) and chronic (occurring on ≥15 days per month). The symptoms of migraine can have a substantial impact on patients' daily activities and ability to attend school or work.[1, 3, 4]

1.3. Company proposed position

The submitting company has requested that rimegepant is restricted for use in the preventive treatment of episodic migraine as an option for patients with episodic migraine who have at least 4 migraine attacks per month, but fewer than 15 headache days per month and who have had prior failure on three or more migraine preventive treatments.

1.4. Treatment pathway and relevant comparators

The management of migraine includes lifestyle changes and avoiding triggers, acute treatment and preventive treatment. Depending on the impact of migraine attacks on patients' quality of life, preventive treatment may be initiated to reduce the number of headache days. Oral preventive treatment options for migraine include propranolol, topiramate, amitriptyline, candesartan (used off-label) and sodium valproate (used off-label).[3, 4]

Several parenteral CGRP antagonists have been licensed for the prophylaxis of migraine in adults with at least 4 migraine days per month. SMC has accepted galcanezumab (SMC2313), fremanezumab (SMC2226) and eptinezumab (SMC2547) for restricted use for patients with chronic or episodic migraine who have had prior failure on three or more preventive treatments, and has accepted erenumab for restricted use in patients with chronic migraine in whom at least three prior prophylactic treatments have failed (SMC2134). Botulinum toxin A (Botox®) is licensed for the prophylaxis of headaches in adults with chronic migraine and has been accepted for restricted use by SMC for use in adults with chronic migraine whose condition has failed to respond to at least three prior oral prophylactic treatments, where medication overuse has been appropriately

managed (SMC692/11). Since erenumab and botulinum toxin A are restricted to prophylaxis of chronic migraine only, and SMC has only recently published advice for eptinezumab, these medicines are not considered relevant comparators. The relevant comparators for this submission are therefore galcanezumab and fremanezumab.[5-9]

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of rimegepant for the preventive treatment of episodic migraine comes from one phase II/III study (Study 305), details of which are summarised in Table 2.1.

Table 2.1. Overview of relevant study.[1, 10]

Criteria	Study 305
Study design	Randomised, double-blind, phase II/III study comparing rimegepant with placebo for the preventive treatment of migraine, comprising a 4-week observation, a 12-week double-blind treatment and a 52-week open-label extension (OLE) phase.
Eligible patients	• Aged ≥18 years, with at least a one year history of migraine with or without aura according to the ICHD-III criteria. • Patients had four to 18 moderate to severe migraine attacks per month in the previous 3 months and ≥6 migraine days and ≤18 headache days during the 4-week screening period. Note: the study excluded patients who had no therapeutic response to more than two categories of preventive medicines for migraine.
Treatments	Rimegepant 75mg or placebo once every other day. Rimegepant was administered as an oral tablet formulation which was considered bioequivalent to the orodispersible formulation. Patients were allowed to continue one additional, preventive treatment (except CGRP antagonists) for migraine if it had been stable for ≥3 months. During the 12-week, treatment phase, patients with a migraine could use triptans, NSAIDs, paracetamol (up to 1,000mg/day for up to 2 consecutive days), baclofen, antiemetics and muscle relaxants. Patients were not allowed to use rimegepant as rescue. Triptans were not allowed as rescue during the OLE.
Randomisation	Randomised equally, stratified by use of preventive migraine medication (yes/no).
Primary outcome	Change from 4-week observation period in the mean number of migraine days per month in the last 4 weeks of double-blind treatment phase (weeks 9 to 12).
Secondary outcomes	There were six secondary outcomes (in the hierarchical order): • Proportion of patients who had a ≥50% reduction from observation period in mean number of moderate or severe migraine days per month in last 4 weeks of the double-blind treatment period (weeks 9 to 12). • Change from observational period in mean number of total migraine days per month over the entire double-blind treatment period (weeks 1 to 12). • Mean number of rescue medication days per month in last 4 weeks of the double-blind treatment period (weeks 9 to 12). • Change from observation period in the mean number of migraine days per month in first 4 weeks of double-blind treatment period (weeks 1 to 4). • Change from baseline in Migraine-Specific Quality of Life (MSQ) questionnaire restrictive role function domain score at week 12 in double-

	blind treatment period. • Change from baseline in Migraine Disability Assessment (MIDAS) total score at week 12 in double-blind treatment period.
Statistical analysis	Efficacy was assessed in the evaluable mITT population, which included all randomised patients who received at least one dose of study medicine and had ≥14 days of eDiary efficacy data from observation period and for at least one 4-week interval during the double-blind phase. A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

ICHD-III= International Classification of Headache Disorders third edition. NSAID=non-steroidal anti-inflammatory drug. OLE=open-label extension. mITT=modified intention-to-treat

In study 305, there was a significantly greater reduction in the mean number of migraine days per month from the observation period to the last 4 weeks of the double-blind treatment period in patients treated with rimegepant compared with placebo. The proportion of patients with ≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9 to 12 and the change in the mean number of total migraine days per month during weeks 1 to 12 also both favoured rimegepant over placebo and were significant within the hierarchical testing strategy. Since the difference between rimegepant and placebo in the mean number of rescue medication days per month was not statistically significant, further formal statistical testing was not performed and the subsequent results are considered descriptive only.[1, 10] Details are presented in Table 2.2.

Table 2.2. Results for the primary and selected secondary outcomes in the evaluable mITT population of study 305.[1, 2, 10]

	Rimegepant (n=348)	**Placebo (n=347)**
Mean number of migraine days per month during observation period	10.3	9.9
Primary Outcome		
LSM change from OP in migraine days per month during weeks 9 to 12, (days)	-4.3	-3.5
Difference versus placebo (95% CI), p-value	-0.8 (-1.5 to -0.2) p=0.010	
Secondary Outcomes (in hierarchical order)		
≥50% reduction from OP in mean number of moderate or severe migraine days per month during weeks 9 to 12, (%, [n/N])	49%	41%
Difference versus placebo (95% CI), p-value	7.6% (0.2% to 15%), p=0.044	
LSM change from OP in migraine days per month during weeks 1 to 12, (days)	-3.6	-2.7
Difference versus placebo (95% CI), p-value	-0.8 (-1.3 to -0.3), p=0.0017	
LSM rescue medication days per month during weeks 9 to 12, (days)	3.7	4.0
Difference versus placebo (95% CI), p-value	-0.2 (-0.8 to 0.3), p=0.39	

LSM change from OP in migraine days per month during weeks 1 to 4, (days)	-2.9	-1.7
Difference versus placebo (95% CI)	-1.2 (-1.7 to -0.6)	
LSM change from baseline in MSQ role function restrictive domain score at week 12[a]	18	14.6
Difference versus placebo (95% CI)	3.5 (0.2 to 6.7)	
LSM change from baseline in MIDAS total score at week 12[a]	-11.8	-11.7
Difference versus placebo (95% CI)	-0.1 (-4.7 to 4.5)	

[a]n=269 for rimegepant and n=266 for placebo. mITT=modified intention-to-treat; LSM=least squares mean; OP=observation period; CI=confidence interval; MSQ=Migraine-Specific Quality of Life Questionnaire; MIDAS=Migraine Disability Assessment.

Patients who completed the double-blind treatment phase of study 305 could enter the 52-week, open-label extension and receive rimegepant 75mg every other day during weeks 13 to 64. Of the 741 patients treated in the double-blind treatment period, 603 patients received rimegepant during the extension (301 who continued rimegepant and 302 who switched from placebo). Patients were allowed to use rimegepant to treat acute migraine attacks on non-scheduled dosing days, provided the maximum rimegepant dose of 75mg daily was maintained. Unlike the double-blind treatment period, patients were not allowed to take triptans as rescue medication during the extension. Patients took a mean of 14.6 (standard deviation 2.45) doses of rimegepant per month. During the 52-week extension, the reduction in the mean number of migraine days per month was maintained.[1, 2, 11]

2.2. Evidence to support the positioning proposed by the submitting company

No data were presented to support the proposed positioning in patients who have failed three or more preventive oral drug treatments since details on the number of previous preventive treatments were not collected during study 305. Furthermore, patients were excluded from the study if they had failed on more than two categories of preventive treatment.

2.3. Health-related quality of life outcomes

Health-related quality of life was assessed as secondary outcomes using the role function restrictive domain of the Migraine-Specific Quality of Life (MSQ) questionnaire and the Migraine Disability Assessment (MIDAS) total score. Both questionnaires were used at baseline and then at week 12 at the end of the double-blind treatment phase. Results, presented in Table 2.2, suggest a small improvement favouring rimegepant in the MSQ role function restrictive domain only. Meaningful reductions compared with baseline in MIDAS scores were reported over time in patients who remained in the open-label extension phase of study 305.[1, 10]

2.4. Supportive studies

Study 201 was an open-label, single-arm, phase II/III study designed to assess the long-term safety of rimegepant for the acute treatment of migraine but also included a group of patients treated with preventive rimegepant. This study enrolled 1,800 patients who had at least a one-year history of migraine and a self-reported history of two to 14 attacks per month. Patients were not

randomised but were allocated to one of three treatment groups according to their self-reported history of migraine attacks per month:[1]

- two to eight attacks per month; received rimegepant 75mg as required for 52 weeks (PRN 2-8; n=1,033)
- nine to 14 attacks per month; received rimegepant 75mg as required for 52 weeks (PRN 9-14; n=481)
- four to 14 attacks per month; received preventive rimegepant 75mg every other day and as required on other days for acute attacks over 12 weeks (preventive plus PRN group; n=286).

In all patients, the maximum dose of rimegepant was 75mg per day. Patients were allowed to continue on preventive migraine treatment that had been stable for ≥3 months before study entry (14%) and were not allowed to take triptans during the study period.

Efficacy outcomes were exploratory only and compared migraine days from the baseline 30-day observation period to the study treatment period: the use of triptans as rescue medication was allowed during the observation period but not the study treatment period. The mean number of migraine days per 4 weeks was reduced from the observational period by -2.2 days in the preventive plus PRN group (n=278). In the subgroup of patients who were also receiving concomitant preventive treatment, the mean number of migraine days per 4 weeks was reduced -0.9 days in the preventive plus PRN group (n=27).[1]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing rimegepant with fremanezumab and galcanezumab, the submitting company presented an indirect treatment comparison. This has been used to inform the economic base case analysis.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian network meta-analysis (NMA) of rimegepant versus erenumab, fremanezumab and galcanezumab for the preventive treatment of migraine.
Population	Patients with episodic or mixed episodic and chronic populations
Comparators	Erenumab, fremanezumab and galcanezumab.
Studies included	NMA included the following 10 studies: Rimegepant: study 305 Erenumab: STRIVE, EMPoWER and LIBERTY Fremanezumab: HALO EM, NCT03303092 and FOCUS Galcanezumab: EVOLVE-1, EVOLVE-2 and CONQUER
Outcomes	Proportion of patients with ≥50% reduction in total monthly migraine days Change from baseline in monthly migraine days (which was not used in the economic case).
Results	Rimegepant was less efficacious than fremanezumab and galcanezumab in the proportion of patients who had ≥50% reduction in total monthly migraine days. There was no evidence of a difference between rimegepant and fremanezumab or galcanezumab in the change from baseline in monthly migraine days. Although the mean differences numerically favoured fremanezumab and galcanezumab.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

During the 12-week double-blind treatment phase of study 305, a treatment-emergent adverse event (AE) was reported by 36% of patients in both the rimegepant (133/370) and placebo groups (133/371) and these were considered treatment-related in 11% and 8.6%, respectively. In the rimegepant and placebo groups respectively, patients with a reported serious AE were 0.8% and 1.1% and patients discontinuing treatment due to an AE was 1.9% and 1.1%.[1, 10]

The most frequently reported treatment-emergent AEs in the rimegepant versus the placebo group were: nasopharyngitis (3.5% versus 2.4%), nausea (2.7% versus 0.8%), urinary tract infection (2.4% versus 2.2%), upper respiratory tract infection (2.2% versus 2.7%) and sinusitis (1.1% versus 3.0%).[1, 10]

No safety data were presented to support the proposed positioning.

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In study 305, there was a significantly greater reduction in the mean number of migraine days per month from the observation period to the last 4 weeks of the double-blind treatment period in the rimegepant group compared with the placebo group.
- Results were supported by secondary outcomes, which were tested hierarchically. The proportion with ≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9 to 12 and the change in the mean number of total migraine days per month during weeks 1 to 12 both significantly favoured rimegepant over placebo.
- Rimegepant is the first oral CGRP antagonist and is the first of this therapeutic class to be licensed for the acute treatment of migraine as well as preventive treatment of episodic migraine. All other available CGRP antagonists (erenumab, galcanezumab, fremanezumab and eptinezumab) are administered parenterally and are only licensed for the prophylaxis of migraine. However, in contrast to rimegepant, they are licensed for prophylaxis of chronic migraine in addition to episodic migraine.[5-7, 9]

4.2. Key uncertainties

- The treatment effect of rimegepant was modest with a reduction of 0.8 migraine days per month compared with placebo and a 7.6% increase in the proportion of patients with ≥50% reduction in mean number of moderate or severe migraine days per month. There was no significant difference between rimegepant and placebo in the secondary outcome of mean number of rescue medication days per month and further formal statistical testing was not performed.
- The study 305 population was broader than the licensed indication for preventive treatment of episodic migraine and included patients with a confirmed history of chronic migraine (23%); 44% of patients had no confirmed history of chronic migraine and history was not reported in 34%. The regulator noted that results for the primary outcome in

patients with a history of chronic migraine were not robust and since this subgroup was small, evidence was considered insufficient for a positive benefit to risk balance in this population. [1, 2, 10]

- The submitting company noted that since data on the number of previous preventive migraine treatments were not collected during study 305, it was not possible to provide evidence to support the proposed positioning in patients who had failed three or more preventive oral treatments. However, the study excluded patients with a history of no therapeutic response to more than two categories of preventive treatments (defined as no reduction in headache frequency, duration, or severity after an adequate trial but did not include lack of sustained response or unable to tolerate). Therefore, it is unlikely that study patients would represent the proposed positioning.[10]
- Study patients could continue to take one other preventive treatment that had been stable for ≥3 months and randomisation was stratified accordingly. In the subgroup receiving concomitant preventive medication (n=153), there was only a small numerical difference between treatment groups in the primary outcome: a reduction of 0.1 migraine days per month. Therefore, although subgroup analyses cannot support definitive conclusions, the treatment effect of rimegepant in patients who are already receiving one other preventive medication is unclear.[1]
- During the double-blind treatment phase, patients could take usual standard medications to treat migraine attacks (such as triptans, NSAIDs, paracetamol, baclofen, antiemetics and muscle relaxants) but were not allowed to use rimegepant to treat an acute attack. However, in clinical practice and in line with the marketing authorisation, patients could receive rimegepant 75mg on alternate days as preventive treatment and also for acute attacks up to the maximum recommended dose of 75mg daily. If a scheduled preventive dose has been taken, rimegepant could not also be used to treat an acute attack on the same day and patients would need an alternative acute treatment. Evidence to support the use of rimegepant as acute treatment in patients with migraine already receiving preventive rimegepant is limited to uncontrolled data in some patients from study 201 and the open-label extension of study 305.[1, 2, 10]
- There is no direct evidence versus relevant comparators, fremanezumab and galcanezumab, and the submitting company presented indirect evidence versus these medicines. The company concluded that rimegepant was an efficacious preventive treatment compared to placebo and not substantially different in proportion of patients achieving ≥50% reduction in total monthly migraine days or change from baseline in monthly migraine days when compared with fremanezumab and galcanezumab. However, the NMA results suggest that rimegepant was less effective than fremanezumab and galcanezumab in achieving a ≥50% reduction in total monthly migraine days. A number of limitations affect the validity of the NMA results including the target population being broader than the licensed indication and proposed positioning for rimegepant. There was heterogeneity between study populations, definitions of outcomes and assessment time points. Study results were recalculated to allow comparison across similar outcomes, but relied on some post hoc data and exploratory outcomes thus limiting the quality of the

data. There was heterogeneity in results in the common placebo comparator group across studies. Safety and health-related quality of life outcomes were not assessed. Due to these limitations, the results of the NMA are considered highly uncertain.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that rimegepant fills an unmet need in this therapeutic area, namely offering an oral alternative for patients. They also consider rimegepant as a potential therapeutic advancement as it is the first medicine that can be used as a preventative and also for acute treatment. It could be useful for patients who do not respond to current treatment options.

4.4. Service implications

Rimegepant is orally administered with minimal service implications to patients and the service.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The Migraine Trust, which is a registered charity.

- The Migraine Trust has received 4.7% pharmaceutical company funding in the past two years, with none from the submitting company.

- Migraine is a complex brain disorder that significantly impacts the day-to-day lives of people who live with the condition. Patients say it impacts their ability to work or progress in their career and education, plan activities and live up to their potential, and has a significant detrimental impact on mental health and wellbeing. Patients are typically affected in their most productive years, making non-treatment very expensive.

- Current oral preventive treatments (such as tricyclic anti-depressants, beta blockers and anti-epileptic medications) were not designed for migraine. Whilst useful for some, they have contraindications, side effects or lack of efficacy. Injectable migraine preventive treatments such as CGRP mAbs and botulinum toxin A, have helped many people and were preferable to repurposed medicines based on the efficacy and side effects reported but are limited in access and in practice are prioritised for chronic migraine patients at specialist clinics. Despite the currently available treatment options, there is still a large unmet need in this population.
- There are potential benefits to rimegepant in terms of being easily administered orally, with fewer side effects and is not associated with medication overuse headache, which can be a significant issue for many people affected by migraine. The patient group feel that an oral CGRP preventive treatment such as rimegepant, which specifically targets migraine, would be appropriate and beneficial for people with migraine.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1: Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	20 years
Population	The submitting company requested SMC considers rimegepant for the preventive treatment of migraine when positioned as an option for adults with episodic migraine who have at least four migraine attacks per month but fewer than 15 headache days per month, and have failed three or more conventional preventive therapies.
Comparators	Fremanezumab or galcanezumab.
Model description	Decision tree plus Markov model with a cycle length of 28 days. Assessment made at 12 weeks to categorise responders, using a response rate of the proportion achieving at least a 50% reduction in the mean number of all (mild, moderate and severe) monthly migraine days (MMD) vs baseline over 12 weeks. Patients allocated into subsequent Markov stage health states of responder or discontinuer, with background general mortality applied. The distribution of MMD was modelled using statistical distributions generating the frequency of MMD in each 28 day cycle period. The distribution of MMD in the model was conditional on treatment arm (cycle 1 and 2) and response status (cycle 3+), with baseline MMD applied in cycle 0. Responders maintained the 12-week responder MMD distribution. The same MMD distribution was applied to all treatments, meaning that effectiveness between rimegepant and the comparators was modelled solely as difference in the response rates. Non-responders maintain non-responder MMD distribution, reverting to baseline MMD linearly over 12 months. Subsequent discontinuers immediately revert to baseline MMD.
Clinical data	Response rate and MMD distribution data from study 305.[10] Discontinuation rate derived from the study 305 open-label extension. NMA used to derive the odds ratio for at least a 50% reduction from baseline in MMD at 12-weeks for fremanezumab and galcanezumab.
Extrapolation	A constant discontinuation rate was applied in each cycle of the Markov model to all comparators.
Quality of life	Utilities obtained from study 305, mapping from Migraine-Specific Quality of Life Questionnaire (MSQv2.1) to EQ-5D-3L,[12] adjusted for age and sex.[13] Utility regression model generated utility values for each MMD value for BSC and rimegepant arms. Utility advantage present for those on-treatment. Rimegepant utility values applied to all comparators.
Costs and resource use	Medicine acquisition costs. Administration costs for galcanezumab and fremanezumab were included. The list price of rimegepant has been reduced from £20 to £12.90 per 75mg tablet.
PAS	A PAS discount is in place for fremanezumab and galcanezumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

This resubmission has been assessed under the fast track resubmission process. The base case results are presented in Table 6.2. The majority of incremental costs were from the treatment acquisition costs. The majority of incremental QALYs accrued in the responder Markov health state, due to the different response rates for the treatments.

The results presented do not take account of the PAS for fremanezumab and galcanezumab but these were considered in the results used for decision-making. SMC is unable to present the

results provided by the company which used an estimate of the PAS price for comparator medicines due to commercial confidentiality and competition law issues.

Table 6.2: Base case results

			List prices		
	Total QALYs	**Incr. QALYS**	**Total Costs**	**Incr. Costs**	**ICER (£/QALY)**
Fremanezumab	9.077	-	£25,201	-	
Rimegepant	9.033	-0.044	£17,449	-£7,752	£174,673 (SW)
Galcanezumab	9.086	-	£25,987	-	
Rimegepant	9.033	-0.053	£17,449	-£8,538	162,267 (SW)

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; QALYs, quality-adjusted life years; SW, Southwest (a south west quadrant ICER, meaning the intervention has both lower incremental cost and incremental QALYs)

6.3. Sensitivity analyses

A number of sensitivity analyses were provided and the key scenarios are summarised in Table 6.3. The scenarios with the largest impact on the ICER were the odds ratios determining response rates for the comparators. ICERs were generally consistent with the base case, with south-west quadrant ICERs exceeding £117,000 per QALY. When assuming the odds ratio for response for comparators was equivalent to rimegepant, rimegepant dominated the comparators. However, this result is highly uncertain given the confidence intervals for the odds ratios.

Table 6.3: Scenario analyses

				List prices	
				Galcanezumab	**Fremanezumab**
	Description	**Base case**	**Scenario**	**ICER**	**ICER**
1	Base case	--	--	162,267 (SW)	174,673 (SW)
2	Time horizon	20 years	5 years	167,215(SW)	177,633 (SW)
			40 years	162,253(SW)	174,679 (SW)
3	Reversion to baseline MMD for 12-week non-responders	12 months	Immediate (0 months)	159,075 (SW)	171,241 (SW)
4	NMA comparator response OR	Fixed effect (Fremanezumab, galcanezumab)	Random effect (Fremanezumab, galcanezumab)	165,006 (SW)	160,582 (SW)
5	NMA comparator response OR	Fixed effect (Fremanezumab, galcanezumab)	OR set to 1 for comparators	Rimegepant dominant	Rimegepant dominant
6	Galcanezumab OR	Base case value	Lower bound 95% CI	345,811 (SW)	174,673 (SW)
			Upper bound 95% CI	118,408 (SW)	174,673 (SW)

				List prices	
				Galcanezumab	Fremanezumab
	Description	Base case	Scenario	ICER	ICER
7	Fremanezumab OR	Base case value	Lower bound 95% CI	162,267 (SW)	580,863 (SW)
			Upper bound 95% CI	162,267 (SW)	117,395 (SW)
8	Rimegepant response rate	Base case value 0.491	Lower bound 95% CI (0.439)	150,581 (SW)	161,425 (SW)
			Upper bound 95% CI (0.544)	177,121 (SW)	191,356 (SW)

Abbreviations: ICER, incremental cost-effectiveness ratio; MMD, monthly migraine day(s); OR, odds ratio. Scenario 5 of dominant refers to rimegepant being cheaper and delivering equivalent health benefits compared to galcanezumab and fremanezumab.

6.4. Key strengths

- Model structure and assumptions based on previous SMC health technology appraisals in preventive migraine (galcanezumab [SMC2313], fremanezumab [SMC 2226] and erenumab [SMC 2134]).
- Response rates and MMD data for rimegepant taken from study 305, a randomised, double-blind, phase III study.[10]
- Utility values derived from study 305 using a mapping algorithm previously used in SMC health technology appraisals in the preventive migraine setting.[12]

6.5. Key uncertainties

- Uncertainties in the NMA increased uncertainty in the ICERs. The odds-ratios for comparators were identified as parameters that had the most impact on the ICER (scenarios 6 and 7). Although variation was present, the ICERs remained in the southwest quadrant exceeding £117,000. This was also the case when considering the odds ratios derived from the random effects model (scenario 4). These scenarios provide indicative evidence that the cost-effectiveness conclusions from the ICERs would remain unchanged when varying NMA parameters in the economic model. However, if these are not sufficient to explore the NMA limitations, a degree of ICER uncertainty may remain.
- The model used a 12-week assessment for rimegepant to determine response and assign an MMD responder distribution for the model time horizon. There may be uncertainty in accepting the longer-term efficacy of preventive rimegepant in the model. However, ICERs were insensitive to a shorter time horizon (Scenario 2). Although this can give some confidence to the stability of the ICER, further longer-term efficacy data would ease this limitation.
- The rimegepant response rates derived in study 305 did not reflect the positioning of rimegepant for episodic migraine only, as the trial population included patients with both episodic and chronic migraine (77% and 23% respectively). Post-hoc analysis on response rates was conducted for the two groups.[10] The response data were similar across the groups, providing indicative evidence of a limited effect on the ICER. Even with the

supportive nature of these results, given their post-hoc nature, ICER uncertainty may remain.

- The rimegepant response rates derived in study 305 may not reflect the positioning of rimegepant for patients who have a history of three or more failed preventive treatments. Details of previous preventive treatments for migraine were not collected during the 305 study. The rimegepant response probability was noted as a parameter within the top-10 affecting the ICER, although ICERs showed limited variation (Scenario 8). Although this may be sufficient to capture the uncertainty in the ICER, a degree of uncertainty may remain if the 95% confidence intervals do not capture the variation in response rates that may result when considering a history of three or more failed preventive treatments.
- The comparators of fremanezumab and galcanezumab were assumed to have the same MMD distributions as rimegepant, including the week 12 responder MMD distribution. As the NMA did not demonstrate similar efficacy for comparators from the odds ratios applied in the model, there is potentially some uncertainty in this approach. Sensitivity analyses using alternate MMD distributions for comparators were not available.

7. Conclusion

After considering all the available evidence, the Committee accepted rimegepant for restricted use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published national clinical guideline 155 "Pharmacological management of migraine" in February 2018, revised in September 2022.[3]

The National Institute for Health and Care Excellence (NICE) published NICE clinical guideline 150 "Headaches in over 12s: diagnosis and management" in September 2012 which was last updated in December 2021.[4]

9. Additional Information

9.1. Product availability date

10 June 2022

9.2. Summary of product characteristics

See the SPC for further information including dosing and safety. Rimegepant 75mg oral lyophilisate (Vydura®)

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Rimegepant	**75mg once every other day**	**2,348**

Costs from BNF online on 12 July 2023.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1,795 patients eligible for preventive treatment with rimegepant in year 1, rising to 1,829 patients in year 5, to which confidential uptake rates were applied.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 06 July 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.