rimegepant oral lyophilisate (Vydura®)

Pfizer Limited

07 April 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 full submission

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

Indication Under Review: for the acute treatment of migraine with or without aura in adults.

SMC restriction: for patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol.

In three double-blind, randomised, phase III studies, significantly more patients who received acute treatment with rimegepant compared with placebo for a single migraine attack were free from pain and most bothersome symptom of migraine after 2 hours.

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 from the trigeminal nerve to the caudal trigeminal nucleus.[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, including intense pain, photophobia, phonophobia, nausea and vomiting 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 acute treatment of migraine for patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol.

1.4. Treatment pathway and relevant comparators

The management of migraine includes lifestyle changes and avoiding triggers, acute treatment and preventive treatment. Acute treatment aims to stop the attack or significantly reduce the headache severity and associated symptoms. Options for acute treatment include unspecific analgesics (aspirin, ibuprofen or paracetamol), antiemetics and specific treatment with triptans. Sumatriptan is the triptan of choice but patients who do not respond to one triptan are offered an alternative. Not all patients respond to or tolerate triptans. Scottish guidance notes that patients have a variable response to triptans and it is worth sequencing through the triptans to find the most effective treatment.[3] There are seven triptans currently available in the UK. In patients not responding to triptan monotherapy, combination therapy with naproxen can also be considered. The use of triptans may also be limited by cardiovascular safety concerns in some patients, contraindicating their use.[1, 3, 4] The company considered that rimegepant would not be used for patients in whom triptans are suitable; best supportive care (BSC) was the relevant comparator.

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. All other available CGRP antagonists (erenumab, galcanezumab and fremanezumab) are administered by subcutaneous

injection and are only licensed for the prophylaxis of migraine in patients who have ≥4 migraine days per month.[5-7]

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 acute treatment of migraine comes from three similar phase III studies (301, 302 and 303), details of which are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[1, 8-10]

Criteria	Studies 301, 302 and 303
Study design	Randomised, double-blind, phase III studies comparing rimegepant with placebo for the acute treatment of a single migraine attack.
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 two to eight moderate to severe migraine attacks per month and less than 15 headache days per month in the previous 3 months.
Treatments	Rimegepant 75mg or placebo to treat one single migraine attack of moderate to severe pain intensity. Rimegepant was administered as an oral tablet formulation in studies 301 and 302 and as the orodispersible tablet formulation in study 303; these were considered bioequivalent. Rescue medication with analgesics or antiemetics was allowed after 2 hours and triptans after 48 hours if not contraindicated. Patients were allowed to continue on preventive migraine therapy that had been stable for ≥3 months.
Randomisation	Randomised equally, stratified by use of preventive migraine medication (yes/no).
Primary outcome	Each study had two co-primary outcomes: • Freedom from pain at 2 hours post-dose assessed using a 4-point Likert scale (0=none, 1=mild, 2=moderate and 3=severe). • Freedom from most bothersome symptoms associated with migraine (reported prior to dosing) at 2 hours post dose. The symptoms that could be nominated included phonophobia, photophobia or nausea and were assessed as 0=absent or 1=present These were assessed in the mITT population, which included randomised patients who took study medication, had a migraine of moderate to severe pain intensity before treatment and had at least one post-baseline assessment.
Secondary outcomes	Each study had multiple secondary outcomes, which varied in hierarchical order of testing. Pain relief at 2 hours (defined as proportion of patients with a pain level of none or mild) was a secondary outcome in all studies and was the key efficacy outcome used in the economics.
Statistical analysis	A hierarchical statistical testing strategy was applied in each 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; mITT=modified intention to treat

In the three studies of acute treatment, significantly more patients achieved the co-primary outcomes, at 2 hours post dose, of freedom from pain and most bothersome symptom, with rimegepant compared with placebo. Details are presented in Table 2.2. Each study included multiple secondary outcomes, which were tested hierarchically in differing orders. Results for the secondary outcomes at 2 hours of pain relief, freedom from photophobia and freedom from phonophobia, significantly favoured rimegepant over placebo. However, the difference between rimegepant and placebo in freedom from nausea at 2 hours was not statistically significant in any study and further formal statistical testing was stopped. Results of subsequent secondary outcomes numerically favoured rimegepant.[1, 8-10]

Table 2.2. Results for the co-primary and selected secondary outcomes in studies 301, 302 and 303[1, 2, 8-11]

	Study 301		Study 302		Study 303	
	Rimegepant (n=543)	**Placebo (n=541)**	**Rimegepant (n=537)**	**Placebo (n=535)**	**Rimegepant (n=669)**	**Placebo (n=682)**
Co-primary outcomes						
Pain free at 2 hours	19%	14%	20%	12%	21%	11%
Risk difference (95% CI), p-value	4.9% (0.5 to 9.3), p=0.03		7.6% (3.3 to 12), p<0.001		10% (6.5 to 14), p<0.001	
MBS free at 2 hours	37%	28%	38%	25%	35%	27%
Risk difference (95% CI), p-value	8.9% (3.4 to 14), p=0.002		12% (6.9 to 18), p<0.001		8.3% (3.4 to 13), p<0.001	
Selected secondary outcomes						
Pain relief at 2 hours	56%	46%	58%	43%	59%	43%
Risk difference (95% CI), p-value	10% (4.4 to 16), p<0.001		15% (9.4 to 21), p<0.001		16% (11 to 21), p<0.001	
Sustained pain relief at 2 to 48 hours	34%	24%	36%	23%	42%	25%
Risk difference (95% CI), p-value	-		14% (8.3 to 19)		17% (12 to 22), p<0.05	
Sustained pain freedom, 2 to 48 hours post dose	12%	7.2%	9.9%	6.0%	13%	5.4%
Risk difference (95% CI), p-value	4.4% (0.9 to 7.8)		3.9% (0.7 to 7.1)		8.0% (4.9 to 11), p<0.001	

CI=confidence interval; MBS=most bothersome symptom

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

To support the proposed positioning for the acute treatment of patients who have had inadequate symptom relief after at least two triptans or in whom triptans are contraindicated or not tolerated, the submitting company presented results of post-hoc subgroup analysis of pooled data from the three phase III studies. In this analysis, triptan treatment failure was defined as self-reported history of discontinuing a triptan (but not necessarily all formulations) due to inadequate efficacy or poor tolerability (n=325; which represents 9.3% of the pooled populations).[12] Results for the co-primary outcomes were similar to the modified intention to treat (mITT) populations. Details are presented in Table 2.3.

Table 2.3. Results for the co-primary outcomes in the post hoc subgroup of patients who had failed at least two triptans in the pooled 301, 302 and 303 study populations[12, 13]

	Rimegepant (n=148)	Placebo (n=177)	Risk difference
Pain free at 2 hours	20%	10%	9.8%
MBS free at 2 hours	43%	21%	22%

MBS=most bothersome symptom.

2.3. Health-related quality of life outcomes

In the three studies, health-related quality of life was assessed as an exploratory outcome using the Migraine Quality of Life questionnaire in the mITT population at 24 hours post dose. After 24 hours, the total scores were similar in the rimegepant and placebo groups across the three studies. The scores were slightly higher in the rimegepant compared with placebo groups but without baseline assessments, any treatment-related effect is unknown.[8-11, 14, 15]

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 75mg tablet for the acute treatment of migraine in 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 attack frequency:

- two to eight attacks per month; received rimegepant as required for 52 weeks (PRN 2-8; n=1,033)
- nine to 14 attacks per month; received rimegepant 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.[1]

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 during the study treatment period. The mean number of migraine days per month was reduced from the observational period by -0.9 days in the PRN 9-14 group and by -2.2 days in the preventive plus PRN group. In the PRN 2-8 group, the mean migraine days increased by 0.1 days.[1]

3. Summary of Safety Evidence

Pooled safety data for the three phase III studies (301, 302 and 303) on acute treatment of migraine include adverse events (AEs) occurring after the study treatment dose to day 7. In the pooled analysis of the three studies 11% (192/1,771) of rimegepant treated patients and 8.6%

(154/1,782) of placebo-treated patients reported an AE and these were considered treatment-related in 6.4% and 4.8% respectively. A severe treatment-related AE was reported by four patients (0.2%) in the rimegepant groups and one patient (0.1%) in the placebo groups. There were no discontinuations due to adverse events.[1]

The most frequently reported treatment-emergent AEs in the rimegepant and placebo groups respectively were: nausea (1.5% versus 0.8%), urinary tract infection (0.8% versus 0.3%) and dizziness (0.6% versus 0.7%). Two patients in the rimegepant group (0.1%) reported diarrhoea as a severe AE. Treatment-related AEs reported in the rimegepant group versus the placebo group were: nausea (1.2% versus 0.8%), somnolence (0.4% versus 0.3%), vomiting (0.1% in both groups), dry mouth (0.1% versus 0.2%), decreased glomerular filtration rate (0.1% versus 0) and maculo-papular rash (0.1% versus 0). In the rimegepant group, one patient reported back pain as a serious AE and in the placebo group, one reported chest pain and one urinary tract infection as serious.[1]

During study 201, on-treatment AEs were reported in 60% (1,088/1,800) of patients. The most frequently reported were upper respiratory tract infections, nasopharyngitis, sinusitis, influenza, bronchitis, urinary tract infections, nausea, dizziness, back pain and arthralgia.[1]

No safety data were presented to support the proposed positioning in patients who had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated.

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below:

4.1. Key strengths

- Significantly more patients in the rimegepant groups compared with placebo were free of pain and most bothersome symptom of migraine 2 hours after treatment in the three key single attack studies (co-primary outcomes). The primary outcomes evaluated in the key studies are clinically relevant and in line with regulator guidance.[1] Supportive, uncontrolled, exploratory data on treating repeated attacks were presented in study 201.
- Many secondary outcomes were statistically significant in favour of rimegepant including pain relief at 2 hours, freedom from photophobia at 2 hours and freedom from phonophobia at 2 hours in the three studies. There was no significant difference between rimegepant and placebo for freedom from nausea at 2 hours, possibly due to the pharmacology of rimegepant, and subsequent secondary outcomes were not formally tested. However, results numerically favoured rimegepant over placebo including results for more sustained treatment effects, freedom from pain and pain relief at 2 to 24 hours and at 2 to 48 hours.[1, 8-10]
- Outcomes were also improved with rimegepant compared with placebo in the subgroup of patients from the pooled phase III studies who had failed at least two previous triptans.
- 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. All other

available CGRP antagonists (erenumab, galcanezumab and fremanezumab) are administered by subcutaneous injection and are only licensed for the prophylaxis of migraine in patients who have ≥4 migraine days per month.[5-7]

4.2. Key uncertainties

- The treatment effect of rimegepant over placebo was modest. In the three single attack studies, after 2 hours, the absolute difference in the proportions of patients who were pain free was 4.9% to 10% and most bothersome symptom free, 8.3 to 12%.
- Supportive uncontrolled data on the treatment of more than one attack from study 201 suggest modest efficacy. In study 201, rimegepant did not reduce the mean number of migraine days in patients with a history of two to eight attacks each month, similar to the population of the three phase III studies, and modestly reduced the mean number of migraine days in patients with a history of nine to 14 attacks each month. Pain freedom or pain relief were not assessed in study 201 and results are limited by their uncontrolled and exploratory nature and comparison with observational period which allowed triptan use.[1]
- The key studies have assessed the efficacy of rimegepant for the acute treatment of a single migraine attack over a 48-hour period. However, there is limited evidence for the use of rimegepant to treat more than one attack and to support consistency in treatment effect. Study patients had a history of two to eight moderate to severe migraine attacks per month (median of 4.0) and <15 headache days per month over the previous 3 months suggestive of episodic migraine. It is unclear if the study results would be generalisable to patients with more frequent migraine attacks in practice.[1]
- To support the proposed positioning, the company presented results for the subgroup of patients in a pooled analysis of the three studies who had failed at least two previous triptans due to efficacy or tolerability. This analysis was performed post-hoc and in a small proportion of study patients (9.3% [325/3,507]). Since this analysis was not planned, results should be treated with caution.[13]
- Within the proposed positioning, the submitting company considered that BSC was the most relevant comparator for patients who had inadequate symptom relief after at least two triptans. However, clinical experts consulted by SMC noted that patients who have failed at least two triptans may not be considered to have exhausted all acute treatment and may receive a trial of additional triptans or combination therapy. Therefore in current practice, BSC may not be the most relevant comparator after two triptans. There are no data comparing rimegepant with further triptan or combination therapy in these patients.
- The company's proposed positioning includes use in patients with contraindications to triptans. The three studies allowed patients with contraindications to triptans to enrol provided that they met the other inclusion criteria. However patients with uncontrolled, unstable or recently diagnosed cardiovascular disease were excluded. As a result, the number of study patients who had a contraindication to triptans was small; 1.0% (17/1,749) and 0.7% (12/1,758) of the pooled rimegepant and placebo groups respectively. It is unclear if the results would be generalisable to patients with contraindications to triptans in clinical practice. Due to the assumed absence of vasoconstrictive properties with

rimegepant and the apparent favourable cardiovascular risk profile, no cardiovascular contraindications were noted for rimegepant.[1, 2]

- In the key studies, rimegepant was not used for both acute and preventive treatment. However in clinical practice and in line with the marketing authorisation, patients could receive rimegepant 75mg on alternate days as preventive treatment for migraine and also take it 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 (the key study to support preventive treatment).[1, 2]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that rimegepant fills an unmet need in this therapeutic area, namely offering an alternative for patients and is a therapeutic advancement for patients who do not respond to, tolerate or are unsuitable for triptans.

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.

- People living with migraine say in addition to the pain and debilitating symptoms, it impacts their ability to work or progress in their career and education, plan activities and live up to their potential. It also has a significant detrimental impact on mental health and wellbeing and families and relationships.

- NSAIDs and over-the-counter (OTC) analgesics are non-specific for migraine and are often inadequately effective. Triptans are the currently available acute migraine treatment. However, triptans are contraindicated in cardiovascular disease, some get intolerable side effects or lack of any or adequate benefit. This significant group do not yet have an appropriate treatment.

- Rimegepant is not associated with medication overuse headache, which can be a significant issue for many people affected by migraine and had good outcomes in clinical trials. As an oral

treatment it is likely to be beneficial and acceptable to a range of people with migraine and can potentially reduce the need for multiple medications. This could facilitate easier access to the treatment.

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 year time horizon.
Population	The submitting company requested SMC considers rimegepant for the acute treatment of migraine when positioned as an option for patients who have had inadequate symptom relief after trials of at least two triptans or in whom triptans are contraindicated or not tolerated; and have inadequate pain relief with NSAIDs and paracetamol.
Comparators	Rimegepant was compared against BSC. BSC was defined as no additional migraine specific treatment.
Model description	The submitted model featured a decision tree to capture the first 48 hours following treatment initiation. Response was assessed using pain relief at 2 hours, categorising patients as responders (those who had achieved pain relief) or non-responders (those who had not achieved pain relief). Subsequently, a Markov model with cycle length 48 hours and 20 year time horizon was used. In the Markov portion of the model there were 2 states. The first of these states captured responder patients. The second state captured non-responders and rimegepant patients who had discontinued treatment. In the Markov portion, in each state and cycle, the model estimated the proportion of patients with and without a migraine.
Clinical data	Response data for pain relief at 2 hours were from a post hoc pooled analysis of the 301, 302, and 303 acute migraine studies in patients who failed at least two triptans.[12, 13] Clinical data from patients who failed at least two triptans in the long-term safety study 201 were used to obtain the monthly migraine days (MMD) frequency distribution and long-term rimegepant discontinuation rate. Clinical data from study 201 were also used to estimate changes in MMD through treatment for rimegepant responders.[16]
Extrapolation	The model assumed that rimegepant response status was constant across the 20 year time horizon, but subject to discontinuation and mortality rates. A constant discontinuation rate for rimegepant was applied in each cycle. Mortality was based on Scottish general population mortality rates. Patients in the BSC arm were subject to the same mortality rate as neither migraines nor treatment were expected to have any impact on longevity. Rimegepant was also assumed to provide some preventative benefit for patients with 8 or more MMD. This reduction was estimated from regression analysis applied to data from the 201 study.
Quality of life	Baseline utilities, applied to the proportion of patients not experiencing a migraine, were derived from study 201 Migraine-Specific Quality of Life Questionnaire (MSQv2) responses mapped to EQ-5D utilities.[17] The baseline utility values were estimated from a regression model, which included MMD as a coefficient. This meant that as MMD increased the baseline utility value for that patient decreased. Utility for those experiencing a migraine in that cycle were captured by Quality Adjusted Life Hours (QALHs), out of a possible maximum of 48 to account for the 48 hour model cycle. The concept of the QALH is similar to the quality adjusted life year (QALY), but scaled downward. QALHs were estimated using patient level hourly pain severity data from the pooled analysis

	of studies 301, 302 and 303, combined with migraine event severity level utilities from an external source.[18] Regression analyses adjusted for patient covariates to generate QALHs per migraine event. The QALH value was highest for patients responding to rimegepant. The value was lowest for non-responders, and this was equal across treatment arms. BSC responders were assumed to receive a time-limited QALH premium over non-responders through a placebo effect. BSC responders were assigned BSC responder QALHs per migraine event for 12 months, before transitioning to BSC non-responder QALHs per migraine event. Rimegepant responders who subsequently discontinued treatment experienced 12 months of BSC responder QALHs per migraine event, before transitioning to BSC non-responder QALHs per migraine event.
Costs and resource use	Medicine costs included the acquisition cost of rimegepant. Resource use for general practitioner visits, emergency department visits and hospitalisations were obtained from wider literature.[19]
PAS	There is no PAS discount.

6.2. Results

The base case results are presented in Table 6.2. The incremental costs were primarily from the acquisition cost of rimegepant. The incremental QALYs for rimegepant were the result of increased utility when experiencing a migraine attack for rimegepant responders, compared to those in the BSC arm experiencing a migraine attack.

Table 6.2: Base case results

Technologies	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Rimegepant	11,464	8.38	8,872	0.48	18,501
BSC	2,592	7.9			

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio;; QALYs, quality-adjusted life years

6.3. Sensitivity analyses

A number of sensitivity analyses were provided and the key scenarios are summarised in Table 6.3.

Table 6.3: Scenario analyses

#	Description	Base case	Parameter value in scenario	Inc. costs (£)	Inc. QALYs	ICER £/QALY
1	Time horizon	20 years	2 years	2,313	0.10	22,515
		20 years	5 years	4,705	0.24	19,591
		20 years	10 years	7,065	0.38	18,803
2	Responder definition	Pain relief at 2-hours	Pain relief at 8-hours	8,305	0.77	10,729
3	Reduction of migraine frequency for rimegepant patients with ≥8 MMD	Include	Exclude	9,782	0.44	22,199
4	Rimegepant discontinuation rate	Discontinuation estimated from adverse events, lack of efficacy, or participant withdrawal categories	Discontinuation estimated from all causes in 201 study	5,378	0.30	18,110

#	Description	Base case	Parameter value in scenario	Inc. costs (£)	Inc. QALYs	ICER £/QALY
		in 201 study				
5	QALH during migraine following rimegepant discontinuation	Assumed to revert to BSC non-responder value after one year at BSC responder value	Immediately revert to BSC non-responders value at discontinuation	8,872	0.45	19,600
6	BSC waning effect (time period before BSC responders transition to BSC non-responder QALH value)	12 months	6 months	8,848	0.48	18,531
		12 months	18 months	8,895	0.48	18,459
7	BSC waning effect	12 months	20 years	9,522	0.26	£36,008
	QALH during migraine following rimegepant discontinuation	Assumed to revert to BSC non-responder value after one year at BSC responder value	Immediately revert to BSC all-comer value at discontinuation			

QALYs rounded to 2 decimal places. Abbreviations: BSC, best supportive care; Inc, incremental; ICER, incremental cost-effectiveness ratio; MMD, monthly migraine days; PRN, as needed; QALH, Quality adjusted life hours; QALYs, quality-adjusted life years.

6.4. Key strengths

- Patient level data were available, allowing for analyses of QALH per migraine and analysis in the population of interest (at least two triptan failures).
- The model structure was consistent with those of the published cost-utility analysis in the acute migraine setting.

6.5. Key uncertainties

- SMC clinical experts provided general support for the submitting company's comparator. However, it was noted that the availability of rimegepant could potentially alter the dynamic of triptan treatment as rimegepant could displace further triptan therapy after patients have failed at least 2 triptan in practice. It may therefore not be used at the point of existing acute treatment exhaustion. This may have a limited impact on the ICER if further triptan therapy has limited benefit. However, uncertainty remained, as there are no comparative efficacy data versus other active treatments.
- The model assumed that frequent use of rimegepant would lead to a reduction in the MMD. This assumption was supported by some wider clinical evidence, but the estimated value was associated with uncertainty. A scenario excluding the preventative effect of rimegepant led to a small increase the ICER (see Scenario 3, Table 6.3).
- The modelled transitions between responder QALH and non-responder QALH during a migraine event was a source of uncertainty. BSC responders experience 12 months of BSC responder QALHs per migraine event, before transitioning to the BSC non-responder QALHs

per migraine event. This diminishing placebo effect in the comparator arm has previously been accepted in other SMC submissions for migraine treatments, although is potentially a simplification which favours rimegepant.[20,21] Rimegepant discontinuers were also assumed to experience 12 months of BSC responder QALHs per migraine event before transitioning to the BSC non-responder QALHs per migraine event. A combined scenario, removing the placebo effect adjustment and assuming rimegepant responders transition to the average QALH of the BSC group immediately led to an increase in the ICER (Scenario 7).

- The model did not have the capacity to include patients who try rimegepant several times before achieving an adequate response, which limited the generalisability of results. SMC clinical experts stated that 2-3 trials for acute attacks would be tried in practice. The company explored alternative response rates using outcomes at 8-hours as the definition of a responder, which decreased the ICER (Scenario 2). This was indicative that allowing for several administrations of rimegepant to assess response status may have led to an improved economic case.
- The pooled analysis of studies 301, 302, and 303 contained very few patients in whom triptans were contraindicated. Therefore the response rate in that population is uncertain. However, limited ICER variation was observed when varying response rates, suggesting this was not a significant issue in the economic case.

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 SIGN 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 dose (£)
Rimegepant	**75mg once daily if required to treat acute migraine**	**20**

Costs from BNF online on 5 January 2023.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 1,054 patients eligible for treatment with rimegepant in year 1 and 1,073 patients in year 5. The estimated update rate was 5% in year 1 and 40% in year 5. Accounting for discontinuation, this resulted in 50 patients estimated to receive treatment in year 1 rising to 408 patients in year 5.

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 with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*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 20 March 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.