International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
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ARTICLE TITLE	RIMEGEPANT AS A NOVEL THERAPEUTIC OPTION FOR MIGRAINE: A SYSTEMATIC REVIEW OF SAFETY AND TOLERABILITY
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5290
RECEIVED	10 January 2026
ACCEPTED	25 March 2026
PUBLISHED	27 March 2026
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RIMEGEPANT AS A NOVEL THERAPEUTIC OPTION FOR MIGRAINE: A SYSTEMATIC REVIEW OF SAFETY AND TOLERABILITY

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ABSTRACT

Objective. The aim of this paper is to analyze and evaluate currently available data and studies on the safety and tolerability of rimegepant in the treatment of migraine.
Methodology. This literature review was based on articles from 2019–2026 available on PubMed and Google Scholar, including randomized controlled trials, open-label studies, and meta-analyses.
Findings. Adverse reactions to rimegepant observed in clinical trials are largely mild or moderate. Serious adverse reactions and those leading to treatment discontinuation are rare and often considered unrelated to the drug. The most frequently reported adverse events in the databases were related to "general disorders and administration site conditions". Rimegepant is safe for patients with high cardiovascular risk and no hepatotoxicity associated with this drug is observed. Compared to other available therapies, rimegepant also ranks highly in terms of both efficacy and safety.
Conclusion. Rimegepant is a safe and well-tolerated oral medication for both acute and preventative migraine treatment. It is also a good alternative to other poorly tolerated or contraindicated migraine drugs.

KEYWORDS

Migraine, Rimegepant, Treatment, Safety, Adverse Events

CITATION

Weronika Zarzycka, Jakub Skrzypek, Natalia Fidut, Karol Szyprowski, Kamila Zioło, Maciej Kisielewski, Julia Wawerska, Weronika Wrzosek, Mateusz Zugaj, Bartosz Okliński. (2026) Rimegepant as a Novel Therapeutic Option for Migraine: A Systematic Review of Safety and Tolerability. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5290

1. Introduction

Definition and epidemiology

Migraine is a chronic neurological disorder that significantly affects daily functioning. It is a common disease, with a global prevalence estimated at 14.1%. Migraine is significantly more common in women than in men and it also frequently affects young adults. In terms of the YLD (years lived with disability), in 2023 migraine caused 40.9 million YLDs, ranking eighth among all diseases with a rate of 487.5 YLDs per 100,000. It is worth mentioning that among the diseases associated with headache, migraine alone accounted for 90% of YLDs (GBD 2023 Headache Collaborators, 2025).

This primary headache disease is characterized by unilateral, pulsating headache with moderate to severe pain level, lasting from 4 to 72 hours. Accompanying symptoms are nausea or vomiting, photophobia, and phonophobia as well as visual or speech abnormalities, difficulty concentrating, and increased pain during physical activity (Jakubowska & Sowa-Kućma, 2025).

Traditional methods of treatment

People suffering from this condition, in addition to negative effects on their daily well-being, work efficiency and overall quality of life, are exposed to mental health consequences, including a higher risk of developing depression compared to healthy people. Therefore it is important to treat migraine effectively and safely, taking into account its pathophysiology. Tracing the history of migraine treatment, ergot alkaloids - ergotamine and dihydroergotamine- were the first antimigraine medications, but due to numerous side effects related to their interaction with various receptors, a need arose for more selective medications - triptans. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) were widely used to treat acute attacks (Jakubowska & Sowa-Kućma, 2025). Both groups of drugs have their limitations, for example triptans are contraindicated in people with cardiovascular disease, and both triptans and NSAIDs carry the risk of medication overuse headache (Edvinsson, 2024). When it comes to the preventive treatment of migraine, non-specific drugs have traditionally been used, such as antiepileptic drugs, antidepressants, beta blockers, or onabotulinumtoxinA in chronic migraine (Jakubowska & Sowa-Kućma, 2025).

The role of Calcitionin Gene-Related Peptide (CGRP), drugs affecting it and rimegepant

Understanding the role of CGRP in the pathophysiology of migraine has proven crucial. The CGRP molecule, which has two isoforms, is found in both the central and peripheral nervous systems, as well as the enteric nervous system. It contributes to neurogenic inflammation and intracranial vasodilation. Currently, drugs that affect CGRP activity are available (Jakubowska & Sowa-Kućma, 2025). These include small-molecule CGRP receptor antagonists (gepants), approved for acute (rimegepant, ubrogepant, zavegepant) and preventive (rimegepant, atogepant) treatment as well as approved for migraine prevention monoclonal antibodies (eptinezumab, fremanezumab, galcanezumab, erenumab) (Edvinsson, 2024). Rimegepant, belonging to the 2nd generation of gepants, is the only one approved for the treatment of both- acute migraine attacks and prevention. In both cases, the recommended dose is 75 mg, but the dosing methods are different. In acute migraine treatment, rimegepant is taken at this dose as needed, up to once daily, while in preventive treatment, it is taken every other day (Edvinsson, 2024). Regarding pharmacokinetics, rimegepant at a dose of 75 mg reaches maximum concentration after 1.5 hours and the half-life is 11 hours (Edvinsson, 2024). Due to the involvement of cytochrome P450 3A4 in the metabolism of rimegepant, caution is required when co-administering rimegepant with strong inhibitors and inducers of this cytochrome (Jakubowska & Sowa-Kućma, 2025). Many studies evaluating rimegepant have shown its effectiveness and good tolerability in both acute migraine treatment and preventive treatment. However, there is insufficient evidence to support the safety of this therapy in pregnant women (Edvinsson, 2024).

2. Methodology

This review utilizes current literature available on PubMed and Google Scholar. It is based on randomized controlled trials, open-label studies, including long-term studies, and meta-analyses addressing rimegepant, its tolerability, and safety.

3. General safety profile

Safety in Randomized Controlled Trials

Rimegepant has been evaluated for safety in numerous randomized controlled trials and open-label studies. The most recent studies indicate good efficacy and a favorable safety profile, comparable to placebo (Croop et al., 2024; Lipton et al., 2024; Pozo-Rosich et al., 2025). In randomized controlled trials comparing rimegepant and placebo in acute treatment of migraine the most frequently reported adverse event was nausea. Overall, the incidence of adverse events was similar in both study groups (Lipton et al., 2019, 2024). In Japan nasopharyngitis was the most common, however, the overall frequency of adverse events did not exceed 10% and most of them were mild or moderate in intensity. It is worth mentioning that it was first study outside of the United States aimed at assessing the effectiveness and safety of rimegepant (Ikeda et al., 2025). Serious adverse events were very rare, most often assessed as unrelated to the study drug (Ikeda et al., 2025; Lipton et al., 2019, 2024).

Safety in open-label studies

In open-label studies, both for the treatment of acute migraine attacks and for prevention, the vast majority of adverse events were mild to moderate in severity. The most common were upper respiratory tract infection (4.2%), nasopharyngitis (3.1%), urinary tract infection (2.8%), sinusitis (2.4%), and back pain (2.1%) (Croop et al., 2024). In another open-label uncontrolled trial assessing the safety of taking 75 mg of rimegepant once daily for migraine prevention, nasopharyngitis came first (9,2%) (Antinew et al., 2025).

4. Long-term safety

Safety of long-term use in acute and preventive treatment

As mentioned in the analyzed randomized controlled trials, most adverse events of rimegepant were mild or moderate and their incidence was comparable to placebo. However, long-term, open-label, multi-center studies were conducted to assess the safety of rimegepant in conditions similar to clinical practice. These studies provide significant information regarding regular administration of the study medication.

One of the largest such open-label studies, involving 1,800 participants and lasting up to 52 weeks, assessed the safety of rimegepant in the treatment of acute migraine (Croop et al., 2024). This study included adults with a history of migraine (with or without aura) lasting ≥1 year and with its onset before the age of 50, with 2–14 moderate or severe migraine attacks per month in the 3 months preceding screening (Croop et al., 2024). Participants were divided into three groups based on the number of acute migraine attacks per month.

Two groups received 75 mg of rimegepant as needed for 52 weeks, while the third group received both 75 mg of rimegepant as needed and the same dose every other day for 12 weeks. The aim of the third group observation was to assess safety with more frequent use of the drug. The most common adverse events occurring in ≥ 2% of participants were: upper respiratory tract infection (8.8%), nasopharyngitis (6.8%), and sinusitis (5.1%). Most of adverse events were mild to moderate in severity. 20% were considered related to the study drug. Importantly, serious adverse events were very rare and occurred in 2.6% of participants, and only 1 of them was considered to be possibly related to the study drug. Regarding liver-related adverse events - no hepatotoxicity was identified and there wasn't a connection between the increase in liver transaminase activity and the frequency of dosing. The results of laboratory tests were also assessed, in which the most common abnormality was increased cholesterol level (Croop et al., 2024).

Another 52-weeks open-label extension study was focused on evaluating the safety of rimegepant in the preventive treatment of migraine. (Kudrow et al., 2026) It was a continuation of a previous 12-week double-blind, placebo-controlled study that assessed the efficacy and safety of rimegepant taken every other day as preventive treatment. However, in this case, in addition to 75 mg of rimegepant every other day, participants were also allowed to take this drug as needed. As in the previous long-term study, adverse events were mild or moderate in most cases. The most common were upper respiratory tract infection, nasopharyngitis, and influenza. Adverse events related to rimegepant accounted for approximately 15% and included: constipation, upper respiratory tract infection, nausea, migraine, elevation of ALT or AST and weight gain. 3 severe adverse events were connected to study drug (hepatic enzyme increased, sunburn, migraine), but none of serious side effects were related to this medicine. It is worth mentioning that adverse events related to the liver were rare and most of them concerned liver function tests abnormalities. Two of hepatic-related adverse events led to discontinuation of treatment. The study authors didn’t find any cardiovascular risk, drug abuse potential or suicidal behavior that was closely related to the study drug (Kudrow et al., 2026).

Safety in patients with depression and anxiety disorders

In published analyses the issue of rimegepant’s safety in people with anxiety disorders, depression and those treated with antidepressants was raised. It seems to be important because anxiety and depression, along with migraines, influence each other in two directions. Anxiety and depression are more common in people with migraines and further reduce their quality of life, which is already reduced due to migraines. Another thing is combining antidepressants with medications used for acute treatment of migraine, such as triptans and diltans. Both some of the antidepressants and the above-mentioned migraine medications affect serotonin receptors, which creates a risk of serotonin syndrome. Rimegepant, on the other hand, does not affect serotonin levels or its receptors.(Kudrow et al., 2025) According to this post-hoc analysis 35,6 % participants had a history of anxiety and/or depression, 11,2% had a history of both of these conditions and 19,1% were using SSRIs and/or another antidepressants on or after treatment with rimegepant. The researchers reported no deaths or documented cases of serotonin syndrome. There were 5 suicidality adverse events, all of them concerned suicidal ideations. 4 of them were considered as unrelated to rimegepant and 1 - unlikely to be related to rimegepant. It should be noted that all 5 participants had a prior history of psychiatric disorders. Overall, this analysis shows that rimegepant is safe in patients with anxiety and depression, as well as in those taking antidepressants (Kudrow et al., 2025).

5. Hepatotoxicity

The assessment of potential hepatotoxicity occupied a special place in the research. This was dictated by the established hepatotoxicity of first-generation CGRP antagonists (Woodhead et al., 2022). Rimegepant has been approved by the FDA without reservations regarding hepatotoxicity (Woodhead et al., 2022). In a randomized, double-blind study with a single dose of 75 mg rimegepant, no hepatotoxicity was observed (Lipton et al., 2024). Alanine and aspartate transaminase levels greater than the upper limit of normal were similar in the rimegepant (2%) and placebo (3,6%) groups. One person from each group had transaminase levels greater than 3x upper limit of normal and the bilirubin concentration of none of the participants exceeded 2x the upper limit of the normal range (Lipton et al., 2024). In long-term open-label studies involving up to 52 weeks of patient observation, no cases of clinically apparent drug-induced liver injury were reported. Adverse events related to the liver were observed in 2.6% of participants. Most of them were mild or moderate in severity. Two cases classified as severe were considered unlikely to be related to the study drug (Croop et al., 2024).

Rimegepant should not be used in severe hepatic impairment or end-stage chronic kidney disease with creatinine clearance <15 mL/min. Despite these limitations, this drug is a good alternative for people with mild to moderate hepatic impairment and mild to severe renal impairment, and in these cases, no dose adjustment is necessary (Edvinsson, 2024).

6. Rimegepant and cardiovascular risk factors

Rimegepant belongs to the class of calcitonin gene-related peptide antagonists (CGRP). Its action is based on selective blockade of the CGRP receptor, which inhibits vasodilation and neurogenic inflammation. This allows rimegepant to relieve migraine pain without directly affecting vasoconstriction (Edvinsson, 2024).

Unlike rimegepant, widely used, migraine-specific triptans act on 5-HT1B/1D receptors, which directly influences vasoconstriction. Despite their good pain-relieving efficacy, even greater than gepants (including rimegepant), they are contraindicated in people with cardiovascular disease. This limits their use in a large group of migraine sufferers (de Vries et al., 2021). However, it should be noted that CGRP is a potent vasodilator, so blocking it could potentially worsen ischemic events. The authors of the publication emphasize that this mechanism of action of rimegepant should be the reason for research on the safety of rimegepant in people with cardiovascular diseases and in those with increased cardiovascular risk (de Vries et al., 2021).

In post hoc subgroup analyses focused on the safety of rimegepant in relation to cardiovascular risk. In the primary open-label study participants were divided into 3 groups. People from the first and the second group took 75 mg of rimegepant as needed up to once daily to treat migraine attacks for 52 weeks. Third group received rimegepant 75 mg every other day, regardless of migraine attacks, and as needed, up to once a day on other days for 12 weeks (True et al., 2024).

The study included people with and without cardiovascular risk factors (0,1,≥2) and with low to high Framingham 10-year risk of developing a CV condition (<10%, ≥10%). Some of them had a history of cardiovascular disease (True et al., 2024).

The frequency of adverse events was similar across all study groups, mostly mild or moderate in intensity. The frequency of severe and serious adverse events, as well as those leading to discontinuation, was low and similar across all groups. 4 adverse events related to the cardiovascular system were reported (angina pectoris, hemiparesis, hemiplegia, and ischemic colitis), but only ischemic colitis was considered possibly related to rimegepant (True et al., 2024).

The author's conclusion from the described analysis is good safety of rimegepant in people with cardiovascular risk factors, including those with moderate or high risk. However, the analysis emphasized that further research is needed to determine the relationship between comorbidities that increase cardiovascular risk and adverse events leading to treatment discontinuation (True et al., 2024).

7. Rimegepant safety real-world data

Real-world clinical evidence of rimegepant safety

Assessing drug safety in real-world clinical practice is an essential complement to clinical trials. RCTs and their open-label extensions are limited to a small, heterogeneous population. This is due to specific inclusion criteria and a large number of exclusion criteria.

An example of a real-world study is the prospective, multicenter GAINER study. This study assessed, among others, the safety and tolerability of rimegepant taken according to participant preference (at any time after pain onset and regardless of pain intensity) at a dose of 75 mg for the acute treatment of migraine. Importantly, in addition to participants with episodic migraine, the study also included patients with chronic migraine (25 % of the study group), which, as the author emphasizes, was a differentiating factor from previous trials of acute migraine treatment with rimegepant. This population was also characterized by a high frequency of acute migraine attacks and a high number of failures of previous preventive therapies. Adverse events were mild and most common of them were: fatigue, gastrointestinal symptoms, somnolence and transient cognitive difficulties (Iannone et al., 2025).

Another study involving a Chinese population is this real-world study, which focused on the effectiveness and tolerability of 75 mg rimegepant ODT taken as needed in the treatment of acute migraine. In the group of 99 participants there were 2 subgroups including i) people with documented lack of response to any acute or preventive medication one month before enrollment in the study, ii) people taking rimegepant for the treatment of migraine attacks and eptinezumab for preventive purposes. The drug proved effective in all groups, with side effects reported by 6% of participants, all of them were mild and largely related to gastrointestinal abnormalities (Z. Yang et al., 2024).

Post-marketing pharmacovigilance and adverse event databases

An important complement to clinical trials, which have certain limitations, are databases of reported adverse effects of drugs introduced to the market. One of such databases are: the VigiAccess database launched by the World Health Organization and Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. Thanks to such tools, it is possible to expand knowledge about previously undetected adverse events, which allows for even more effective and personalized treatment (Liang et al., 2024). This study analyzes adverse events of gepants from the VigiAccess database up to 31 March 2024, and the FAERS database covering the period from the first quarter of 2020 to the fourth quarter of 2023. An important issue is the impact of gepants on various organs shown in these analyses. The majority of reports were from women, with the predominant age group being those between 45 and 64 years of age. Furthermore, the majority of reports came from America. Interestingly, the highest number of reported adverse events from both databases concerned rimegepant compared to the also analyzed: atogepant and ubrogepant. The most common of them for rimegepant were related to "general disorders and administration site conditions". Regarding gastrointestinal abnormalities, nausea was the most severe with rimegepant. It is also worth mentioning that side effects in oral cavity were frequent and intense in regard to mentioned drug. Other relatively more frequent side effects of rimegepant compared to the rest of the analyzed gepants were: rash and pruritus, alopecia, Reynaud's phenomenon. No hepatotoxicity connected to discussed group of drugs (including rimegepant) was reported, which is consistent with other studies (randomized and open-label) cited in this paper. Despite the undoubted benefits of the analysis, the authors emphasize that this study has limitations and can only constitute a basis for further detailed research (Liang et al., 2024).

8. Comparison to other therapies

Rimegepant compared to triptans, lasmiditan and other gepants

Migraine-specific medications, triptans, are a widely used class of medications for acute migraine attacks. They are undoubtedly not free from adverse effects and contraindications. It is important to note that frequent use of triptans can cause headaches associated with overdose. This class of medications is also contraindicated in individuals with cardiovascular risk. The network meta-analysis compares lasmiditan (5-HT1F receptor agonist) and gepants (CGRP receptor antagonists) with triptans in terms of their benefits (C.-P. Yang et al., 2021). Regarding safety, gepants considered in the study, also including rimegepant, were associated with a lower risk of adverse events than lasmiditan and some triptans. Additionally, lasmiditan was associated with the highest risk of any adverse events among all treatments, and common of them were related to the central nervous system (C.-P. Yang et al., 2021). Other analyses confirm that lasmiditan has a worse safety profile than gepants and, at higher doses, a high risk of developing side effects such as somnolence, dizziness and nausea compared to placebo (Johnston et al., 2022). On the other hand, rimegepant 75 mg and ubrogepant 50 mg and 100 mg were both effective and well tolerated. However, it is worth mentioning that ubrogepant at a dose of 100 mg was associated with a higher risk of somnolence compared with placebo (Puledda et al., 2023). A meta-analysis that included a relatively recently FDA-approved drug, zavegepant, confirmed its good efficacy. However, it appears that rimegepant at a dose of 75 mg is more effective in relieving headaches within 2 hours. Nevertheless, the author emphasizes the need for further clinical trials to comprehensively assess the efficacy and safety of this drug and compare it with other therapies. In terms of safety, zavegepant has been associated with side effects such as dysgenusia, nausea, nasal discomfort, throat irritation. The advantage of zavegepant is its nasal spray form, which can be a significant improvement for people who have difficulty taking medications orally. It is important that in the analysis of randomized controlled trials rimegepant at a dose of 75 mg did not show significant differences in side effects compared to placebo, making it a good alternative in the treatment of acute migraine (Deng et al., 2024).

Another problem with triptans is discontinuation of their use or addition of other drugs due to inadequate effectiveness or limited tolerability. Moreover, as mentioned above, frequent use of triptans is associated with a risk of medication-overuse headache, which has not been demonstrated for gepants. On the contrary, frequent use of gepants helps reduce this risk. A retrospective analysis using information on reports from US claims data assessed the persistence of recently initiated rimegepant or oral triptan therapy. As the researchers emphasize, this persistence of treatment is an important aspect showing the attitude of patients to using therapy for a longer period of time, which indirectly informs about the effectiveness, tolerance and satisfaction with a specific treatment. The primary finding of this study was significantly greater persistence for rimegepant compared to oral triptans, which allows to conclude that rimegepant is an effective and well-tolerated drug despite frequent dosing (Tepper et al., 2025).

Rimegepant and monoclonal antibodies in preventive therapy

Well-chosen preventive treatment for migraine can reduce the frequency and severity of headaches and improve patients' quality of life (Messina et al., 2023). In addition to the long-existing on the market migraine non-specific preventive drugs, such as antiseizure drugs and beta blockers, migraine-specific drugs targeting CGRP have also been introduced (Tassorelli et al., 2024). These types of therapies include: i. subcutaneously administered monoclonal antibodies blocking the CGRP peptide (fremanezumab, galcanezumab, eptinezumab) or its receptor (erenumab), ii. orally administered CGRP receptor antagonists (rimegepant, atogepant) (Messina et al., 2023). When comparing antibodies and gepants in terms of adverse events, antibodies, particularly galcanezumab and high-dose fremanezumab, were associated with a higher risk of injection-site-related adverse events - erythema, induration, and pruritus. However, erenumab and atogepant were associated with a risk of constipation. Fatigue was associated with atogepant, particularly with increasing doses. According to this analysis of 19 studies, there were no reports of fatigue or constipation with rimegepant. Most antibodies and all gepants were associated with a lower risk of serious adverse events compared with placebo. Only patients treated with galcanezumab had this risk higher (Messina et al., 2023)

In a double-blind, 3-month clinical trial, galcanezumab was not superior to rimegepant in achieving ≥50% reduction in monthly migraine headache days (primary endpoint). Both treatments were effective, and the safety and tolerability of both drugs were satisfactory (Schwedt et al., 2024).

It is worth emphasizing, the advantage of gepants is that they are eliminated from the body faster than monoclonal antibodies, which may be beneficial for women planning a pregnancy or people who have experienced an adverse event requiring discontinuation of therapy (Edvinsson, 2024).

9. Discussion

Migraine is a widespread disease that significantly reduces quality of life. The need for effective, safe, and well-tolerated treatment, along with a better understanding of the pathophysiology of migraine, has led to the development of drugs targeting CGRP. Rimegepant, as one of the CGRP receptor-targeted gepants, is effective in both acute and preventive treatment. In randomized, controlled trials and open-label studies for the treatment of acute attacks and prevention, rimegepant demonstrated satisfactory safety, with most adverse events being mild or moderate in severity. The incidence of adverse events is similar between the rimegepant and placebo-treated groups. With long-term use, this drug is well tolerated, and as before, most adverse events are mild or moderate, serious events are very rare. Rimegpant also demonstrates safety in real-world clinical settings, including patients with more severe migraine, those who have failed previous therapies, and those with chronic migraine. Adverse event reports in databases were more frequent for rimegepant compared to other gepants. Rimegepant is not connected with hepatotoxicity and is safe for patients with increased cardiovascular risk, making it a good alternative to triptans. It is also a safe option for people with depression, anxiety disorders, and those treated with antidepressants. Comparing its concurrent efficacy and safety with other available migraine medications, such as triptans, lasmiditan, and other therapies targeting CGRP, rimegepant appears to be a very good treatment option.

10.Conclusions

Rimegepant appears to be an excellent drug in terms of safety for both acute and preventive migraine treatment. It is well tolerated in both as-needed and every-other-day dosing regimens. The lack of hepatotoxicity, good tolerability in patients at cardiovascular risk, infrequent and largely non-serious side effects, and convenient ODT formulation provide ample scope for rimegepant's use in clinical practice.

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All authors have read and agreed with the published version of the manuscript.
Funding Statement: This study received no special funding.
Conflicts of Interest: The authors declare no conflict of interest.

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