

## PHARMACY / MEDICAL POLICY – 5.01.584

## CGRP Inhibitors for Migraine Prophylaxis

BCBSA Ref. Policy: 5.01.29

Effective Date: Mar. 1, 2025

Last Revised: Feb. 11, 2025

Replaces: N/A

## RELATED PHARMACY / MEDICAL POLICIES:


5.01.503 Migraine and Cluster Headache Medications

5.01.512 Botulinum Toxins

5.01.605 Medical Necessity Criteria for Pharmacy Edits

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [APPENDIX](#) | [HISTORY](#)

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## Introduction

Migraine is a debilitating disease, with severe headaches. Some people have other symptoms like seeing auras, experiencing nausea or vomiting, and suffering an inability to tolerate bright light or loud noises. About one in eight Americans has migraines. It's the seventh most disabling disease worldwide. Women are twice as likely as men to suffer from migraine.

Some people have just a few headaches a month. These may be treated with pills like ibuprofen or prescription medications. These treatments stop the headaches after they've started. However, if people take too much of the headache-stopping medications, over time they may end up with more headaches. This is a poor long-term strategy. It's estimated that more than 40% of migraine individuals have unmet needs. These include experiencing disability during a migraine attack, not being happy with existing treatments, or overusing habit-forming medications. Newer types of migraine-preventing drugs have been developed to address these unmet needs. This policy describes when these types of drugs may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a

service may be covered.

## Policy Coverage Criteria

Drug	Medical Necessity
<ul style="list-style-type: none"><li>• <b>Aimovig (erenumab-aooe) SC,</b></li><li>• <b>Ajovy (fremanezumab-vfrm) SC,</b></li><li>• <b>Emgality (galcanezumab-gnlm) SC,</b></li><li>• <b>Vyepti (eptinezumab-jjmr) IV</b></li></ul>	<p><b>Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and Vyepti (eptinezumab-jjmr) may be considered medically necessary for the preventive treatment of migraine when all the following are met:</b></p> <ul style="list-style-type: none"><li>• The individual is aged 18 years or older</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has an average of 4 or more migraine days per month</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Tried two different categories of prophylactic migraine headache therapies listed in the <a href="#">Appendix</a> section</li></ul>
<p><b>Nurtec ODT (rimegepant) oral</b></p>	<p><b>Nurtec ODT (rimegepant) may be considered medically necessary for the preventive treatment of episodic migraine when all the following are met:</b></p> <ul style="list-style-type: none"><li>• The individual is aged 18 years or older</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has an average of 4 to 14 migraine days per month</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Tried two different categories of prophylactic migraine headache therapies listed in the <a href="#">Appendix</a> section</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• The dose is limited to 75 mg taken orally every other day</li></ul> <p><b>Note:</b> Please see Policy <a href="#">5.01.503 Migraine and Cluster Headache Medications</a> when Nurtec ODT (rimegepant) is being requested for the acute treatment of migraines.</p>
<p><b>Qulipta (atogepant) oral</b></p>	<p><b>Qulipta (atogepant) may be considered medically necessary for the preventive treatment of migraine when all the following are met:</b></p> <ul style="list-style-type: none"><li>• The individual is aged 18 years or older</li></ul> <p><b>AND</b></p> <ul style="list-style-type: none"><li>• Has an average of 4 or more migraine days per month</li></ul>



Drug	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Tried two different categories of prophylactic migraine headache therapies listed in the <a href="#">Appendix</a> section</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The dose is limited to 60 mg taken orally once daily</li> </ul>
<p><b>Emgality (galcanezumab-gnlm) SC</b></p>	<p><b>Emgality (galcanezumab-gnlm) may be considered medically necessary when all the following are met:</b></p> <ul style="list-style-type: none"> <li>• The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has an episodic cluster headache as documented by at least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of <math>\geq 3</math> months</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Occurring with a frequency between one every other day and 8 per day</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Tried two triptan medications for abortive use unless triptan medications are contraindicated</li> </ul>

Drug	Investigational
<p><b>As listed</b></p>	<p><b>The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</b></p> <p><b>Use of the above-named agents when used in combination with each other is considered investigational.</b></p> <p><b>All other uses of the above-named agents for conditions not outlined in this policy or policy 5.01.503 are considered investigational such as the following:</b></p> <ul style="list-style-type: none"> <li>• Hemiplegic migraines</li> <li>• Vestibular migraines</li> </ul>



Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<p><b>Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.</b></p> <p><b>All other reviews for all drugs listed in the policy may be approved up to 6 months.</b></p>
<b>Re-authorization criteria</b>	<p><b>Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months if the individual has shown a positive clinical benefit by:</b></p> <ul style="list-style-type: none"> <li>• A sustained reduction in headache frequency OR severity compared to baseline prior to initiation of treatment with the CGRP inhibitor</li> </ul>

Documentation Requirements
<p><b>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</b></p> <ul style="list-style-type: none"> <li>• Office visit notes that contain the diagnosis, relevant history, physical evaluation, headache frequency, headache severity, and medication history</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
C9399	Unclassified drugs or biologicals (used to report Aimovig)
J3031	Injection, fremanezumab-vfrm, (Ajovy) 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J3032	Injection, eptinezumab-jjmr, (Vyepiti) 1 mg
J3590	Unclassified biologics (use to report Aimovig and Emgality)

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).



## Related Information

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### Benefit Application

#### Pharmacy Benefit

Nurtec ODT (rimegepant) and Qulipta (atogepant) are managed through the pharmacy benefit.

#### Medical Benefit

Vyepti (eptinezumab-jjmr) is managed through the medical benefit.

#### Pharmacy/Medical Benefit

Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), and Emgality (galcanezumab-gnlm) are managed through both the pharmacy benefit and medical benefit.

## Evidence Review

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### Description

#### Medical Condition

Migraine is a debilitating neurologic disorder, characterized by severe headache that can be accompanied by aura and additional symptoms such as nausea, vomiting, photosensitivity, phonophobia, visual disturbance, and tingling in the hands and feet. Migraine affects 12-16% of the US population and is the seventh most disabling disease worldwide. It disproportionately affects females, with females 2-2.5 times more likely to suffer from migraine.

The frequency of migraine attacks an individual experiences guides migraine treatment approach. Low frequency of attacks (1-3 migraines per month) can be treated with abortive



therapy, such as triptans, NSAIDs, and other analgesics. However, sufferers of episodic migraine, with 4-14 migraine days per month, and chronic migraine, with >15 headache days per month (8 of which are migraine), should receive preventative migraine therapy. Individual response to migraine therapy is highly variable, with over 23 genes purported to being linked to the neuronal and vascular pathophysiology of migraine, and effective migraine treatment options to date are limited.

As few therapies are effective in preventing migraine, drug tolerance and subsequent overuse of abortive therapies is common and carry the risk of causing rebound headaches. Thus, these are not a viable long-term treatment option. Over 40% of individuals with migraines have unmet needs, including disability, treatment dissatisfaction, and opioid/barbiturate overuse or dependence. Thus, new treatments, both for prophylaxis and acute therapy, are eagerly awaited to help alleviate the burden of migraine-related disability.

Migraines have a significant economic and social impact in the US. During a migraine attack, sufferers of migraines are often bedridden and have severe impairment to their ability to function.

Migraineurs frequently isolate themselves in a quiet, dark area and can lose several days of productivity while experiencing substantial pain. This, in turn, can lead to further comorbid conditions—most commonly depression—which contribute to the economic burden as well. The economic impact on both employers due to loss of productivity and the healthcare systems due to utilization, are estimated to be over 13 billion dollars.

## **Treatment Alternatives**

Migraine treatment consists of two pillars: abortive treatment for acute migraine attacks and prophylactic treatment. While there are many numerous medications indicated for use in chronic and episodic migraine prophylaxis, there are currently no reliable treatments for the prevention of migraine, as all are drugs designed for targets other than migraine. Medications approved for the prevention of chronic and episodic migraine include beta-blockers, antiepileptic drugs, and antidepressants. The most commonly used medications are propranolol, topiramate and amitriptyline. Due to low efficacy in migraine prevention and the side effect profile, adherence is poor, with about 26% of individuals at 6 months and 17% of individuals at 12 months continuing these drugs.

Triptans, via inhibition of 5-hydroxytryptamine receptors in the intracranial vasculature, are effective for treating acute migraine, and can be used to prevent progression if administered in the early stage of migraine. However, tolerance to these medications occurs quickly and overuse



contributes to headache exacerbation. NSAIDs and ergotamines can also be used as abortive therapies, though as with triptans, rebound headaches from overuse can occur with these as well.

Botox (onabotulinumtoxinA) is FDA approved to prevent headaches in adults with chronic migraine (headache lasting  $\geq 4$  hours on  $\geq 15$  days/month). Botox was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies in chronic migraine adults not using concurrent prophylaxis. Individuals were randomized to receive placebo or 155 Units to 195 Units Botox injections every 12 weeks for the 2-cycle, double-blind phase. Individuals were allowed to use acute headache treatments during the study. Botox treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo; however, this treatment requires an office procedure that is unpleasant and must be repeated four times a year.

### **Aimovig (erenumab-aooe)**

Aimovig (erenumab) is a fully human monoclonal antibody that targets the calcitonin gene-related peptide (CGRP) receptor through competitive, reversible inhibition. Erenumab binds the CGRP receptor with high specificity and potency, blocking the action of CGRP and prevent vasodilation.

### **Ajovy (fremanezumab-vfrm)**

Fremanezumab is a humanized monoclonal antibody that targets the CGRP receptor through competitive, reversible inhibition. Like Erenumab, fremanezumab binds the CGRP receptor with high specificity and potency, blocking the action of CGRP and prevent vasodilation.

### **Emgality (galcanezumab-gnlm)**

Like fremanezumab, galcanezumab is a humanized monoclonal antibody that binds to the CGRP receptor. Erenumab, fremanezumab and galcanezumab all bind the CGRP receptor with high specificity and potency, blocking the action of CGRP and prevent vasodilation.



## **Nurtec ODT (rimegepant)**

Rimegepant is a small molecule taken orally that binds to the CGRP receptor.

## **Qulipta (atogepant)**

Atogepant is a small molecule taken orally that binds to the CGRP receptor.

## **Vyepti (eptinezumab-jjmr)**

Eptinezumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for CGRP ligand. Eptinezumab is produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

## **Rationale**

### **Efficacy/Effectiveness**

#### **Aimovig (erenumab-aooe)**

Aimovig (erenumab-aooe) is a fully human monoclonal antibody that targets the calcitonin-gene-related peptide receptor to prevent both episodic and chronic migraine. Evidence for efficacy of erenumab in the prevention of episodic migraine was evaluated in STRIVE, a Phase III, randomized controlled trial (RCT), which included 955 individuals with history of episodic migraine; STRIVE observed a reduction of 3.2 and 3.7 migraine days per month for individuals treated with erenumab 70 mg and erenumab 140 mg, respectively, compared to a 1.8 migraine day per month reduction in the placebo group.

Evidence for efficacy of erenumab in the treatment of chronic migraine was evaluated in a Phase II RCT, which included 656 individuals with history of chronic migraine and observed a mean reduction in mean monthly migraine days (MMMD) of 6.6 days in individuals treated with erenumab 70mg, 6.6 days in individuals treated with erenumab 140mg, and 4.2 days in placebo group.

Though no studies yet show the long-term efficacy and durability of treatment with CGRP monoclonal antibodies beyond one year, efficacy has been demonstrated in individuals treated with erenumab 70 mg and erenumab 140 mg every 4 weeks for 6 months. Additionally, an





ongoing open-label extension has evaluated the efficacy of erenumab 70 mg every 4 weeks at one year.

In STRIVE, 50% of individuals receiving erenumab 140 mg and 43.3% of individuals receiving erenumab 70 mg were able to achieve >50% reduction in MMMD. In the OLE, individuals were able to reduce MMMD from 8.8 days at baseline, to 6.3 days at the end of the 12-week double-blind period, to 3.7 days at the one-year interim analysis. Due to this level of efficacy at one year, erenumab is likely to significantly improve the quality of life for individuals within the episodic migraine population.

### **Ajovy (fremanezumab-vfrm)**

Ajovy (fremanezumab-vfrm) is a humanized IgG2a monoclonal antibody that selectively binds both  $\alpha$  and  $\beta$  isoforms of the CGRP. Evidence for efficacy of fremanezumab in the prevention of chronic migraine was evaluated in HALO CM, a phase III, RCT, which included 1130 individuals with chronic migraine. HALO CM observed a reduction of 4.9 and 5.0 headache days per month for individuals treated with fremanezumab 675 mg quarterly and fremanezumab 675 mg followed by a monthly fremanezumab dose of 225 mg, respectively, compared to a reduction of 3.2 headache days per month in the placebo group. Thirty-eight percent of individuals in the fremanezumab quarterly group and 41% of individuals in the fremanezumab monthly group attained at least 50% reduction in the average number of headache days per month, compared to 18% of individuals in the placebo group.

Evidence for efficacy of fremanezumab in the treatment of high-frequency episodic migraine was evaluated in a phase II RCT, which included 297 individuals with at most 14 headache days but at least 8 migraine days per month. The observed mean reduction in mean monthly migraine days (MMMD) from baseline to weeks 9 – 12 was 6.27 days in individuals treated with fremanezumab 225mg monthly and 6.09 days in individuals treated with fremanezumab 675 mg monthly, compared to 3.46 days in placebo group.

Further evidence for efficacy of fremanezumab in the treatment of episodic migraine is being evaluated the phase III HALO EM trial but the results have not been published in any peer-reviewed journal.

### **Emgality (galcanezumab-gnlm)**

Galcanezumab was studied in the EVOLVE-1 and EVOLVE-2 Phase 3, double-blind, randomized-controlled trials that compared galcanezumab at 120 mg and 240 mg to placebo for six months



in individuals diagnosed with episodic migraine. The main difference between the two trials was that EVOLVE-1 observed individuals in North America only, while EVOLVE-2 observed individuals internationally. In EVOLVE-1, individuals saw significant benefits in the galcanezumab 120 mg and 240 mg groups with a reduction of 4.7 and 4.6 monthly migraine headache days (MHDs), respectively, compared to placebo with a reduction of 2.8 monthly MHDs ( $p < 0.001$  for both comparisons). Similar improvements were seen in EVOLVE-2; the galcanezumab 120 mg and 240 mg groups saw a reduction of 4.3 and 4.2 monthly MHDs, respectively, compared to placebo with a reduction of 2.3 monthly MHDs ( $p < 0.001$  for both comparisons). For EVOLVE-1 and EVOLVE-2, galcanezumab further demonstrated improvements in terms of monthly MHDs with acute migraine medication use, Migraine-Specific Quality of Life Role-Functioning Restrictive (MSQ RF-R) scores, and percent reductions in monthly MHDs (>50%, >75%, and >100%).

REGAIN is an unpublished Phase 3, double-blind, randomized-controlled trial that compared galcanezumab at 120 mg and 240 mg to placebo for three months in individuals diagnosed with chronic migraine. Both galcanezumab groups saw significant improvement with reductions of 4.83 and 4.62 monthly MHDs, respectively, compared to placebo with a reduction of 2.47 monthly MHD ( $p < 0.001$  for both comparisons). 50% and 75% reductions in monthly MHDs had significant improvements in both galcanezumab groups. <2% of individuals saw a 100% reduction in monthly MHDs with no significant differences between groups. Changes in the number of monthly MHDs with acute migraine medication use and MSQ RF-R scores showed improvements in both galcanezumab groups.

REBUILD is an ongoing trial studying galcanezumab in ages 6-17 and CONQUER is another ongoing trial studying galcanezumab in individuals who have failed previous migraine preventive medications in the past 10 years due to inadequate efficacy or tolerability. A long-term open-label study is also being conducted in individuals with episodic or chronic migraines. Once available, these studies may expand galcanezumab's applicability and generalizability.

### **Vyepti (eptinezumab-jjmr)**

Eptinezumab is efficacious for the prevention of chronic and episodic migraine. In PROMISE-1 and PROMISE-2, eptinezumab 100 and 300 mg significantly reduced monthly migraine days (MMD) over months 1-3 compared to placebo. Eptinezumab 100 and 300 mg produced  $\geq 75\%$  reductions in MMD over month 1 and months 1-3, though eptinezumab 100 mg over months 1-3 in PROMISE-1 lacked statistical significance. Eptinezumab 100 and 300 mg produced significant  $\geq 50\%$  reductions in MMD over months 1-3. While eptinezumab produced numerically higher rates of 100% reductions in MMD compared to placebo, the statistical



significance of these comparisons was not reported. These doses of eptinezumab also significantly reduced the incidence of migraine on day 1 after infusion.

### **Nurtec ODT (rimegepant)**

Rimegepant efficacy for the preventive treatment of episodic migraine in adults was demonstrated in one randomized, double-blind, placebo-controlled trial of a different oral dosage form of rimegepant. The study enrolled adult individuals with at least a 1-year history of migraine (with or without aura). Individuals experienced an average of 10.9 headache days during the 28-day observational period, which included an average of 10.2 migraine days, prior to randomization into the trial. Individuals were randomized to receive every other day dosing of rimegepant 75 mg (N=373) or placebo (N=374) for 12 weeks. Individuals were allowed to use acute headache treatments (i.e., triptans, NSAIDs, acetaminophen, antiemetics, muscle relaxants, and aspirin) as needed. Approximately 10% of individuals were taking one preventive medication for migraine at baseline. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either the acute or preventive treatment of migraine. The primary efficacy endpoint was the change from baseline in the mean number of monthly migraine days (MMDs) during Weeks 9 through 12 of the double-blind treatment phase. The percentage of individuals who achieved at least a 50% reduction from baseline in moderate to severe MMDs during Weeks 9 through 12 of the double-blind treatment phase compared to placebo was also evaluated. Rimegepant 75 mg dosed every other day demonstrated statistically significant improvements for these efficacy endpoints compared to placebo.

### **Qulipta (atogepant)**

Atogepant has been studied in two moderate-quality trials for prevention of migraine in adults with 4-14 monthly migraine days (MMD). The ADVANCE trial is a 12-week, multicenter, double-blind, placebo-controlled, Phase 3 trial which randomized 902 individuals to atogepant 10 mg po QD, 30 mg po QD, 60 mg po QD, or placebo. Enrolled individuals included adults 18-80 years of age with a history of migraine  $\pm$  aura for  $\geq 1$  year with an onset  $< 50$  years of age and 4-14 migraine or probable migraine days per month. Of note, individuals with cardiovascular disease (CVD) were included in the trial. Individuals without response to  $> 4$  medications for migraine including two different mechanisms of action (MOA) or those with chronic or cluster migraine were excluded. The primary outcome was change from baseline in MMD. All doses of atogepant significantly decreased MMD compared to placebo (-3.69, -3.86, -4.20, -2.47 days for atogepant 10 mg, 30 mg, 60 mg, and placebo, respectively;  $p < 0.0001$  for all comparisons). The difference in



MMD between atogepant and placebo was -1.21, -1.38, and -1.72 days, respectively. The proportion of individuals who achieved  $\geq 50\%$  reduction in the 3-month average of MMD was 56%, 59%, and 61% with atogepant 10 mg, 30 mg, and 60 mg, respectively, compared to 29% with placebo ( $p < 0.0001$  for all comparisons). Other secondary outcomes were described as significant for all doses of atogepant compared to placebo; however, data was not available. These secondary outcomes include change from baseline in mean monthly headache (HA) days, acute medication use days, and an assessment of quality of life (QoL). An assessment of the impact of migraine on activity diary (AIM-D) was also significantly improved with atogepant 30 mg and 60 mg only compared to placebo.

Goadsby published a 12-week, multicenter, double-blind, placebo-controlled, Phase 2b/3 trial which randomized 834 individuals to placebo, atogepant 10 mg po QD, atogepant 30 mg po QD, atogepant 60 mg po QD, atogepant 30 mg po BID, or atogepant 60 mg po BID. Enrolled individuals included adults 18-75 years of age with a history of migraine  $\pm$  aura for  $> 1$  year, onset before age 50, and 4-14 MMD for 3 months. Those with inadequate response to  $\geq 3$  migraine medications including two different MOAs or those with overuse of migraine medications were excluded. Of note, individuals with cardiovascular disease (CVD) were included in the trial. The primary endpoint of change from baseline in MMD was significantly improved with all doses of atogepant compared to placebo (-3.6 to -4.2 days with atogepant vs -2.9 days with placebo;  $p < 0.05$  for all comparisons). The difference in MMD between atogepant and placebo ranged from -0.7 to -1.3 days and did not demonstrate a clear dose response relationship. Similarly, all doses of atogepant significantly decreased monthly headache days compared to placebo (-3.9 to -4.3 vs -2.9 days atogepant vs placebo). The proportion of individuals who achieved  $\geq 50\%$  reduction in MMD was significantly greater with only atogepant 30 mg BID and 60 mg BID than placebo (58%, 62% vs 40%;  $p = 0.0034$  and  $0.0097$ , respectively). Also, mean change in acute medicine use was significantly decreased with atogepant 30 mg BID and 60 mg BID only (-3.8 and -3.6 vs -2.4, respectively;  $p = 0.0034$  and  $0.0097$ ).

The safety and efficacy of atogepant for the preventive treatment of chronic migraine in adult individuals were evaluated in a randomized, multicenter, double-blind, placebo-controlled study. The inclusion criteria required to have 1-year history of chronic migraine based on ICHD-3 diagnostic criteria. The individuals were randomized to receive Qulipta™ 60 mg once daily ( $n = 262$ ) or placebo ( $n = 259$ ) for 12 weeks. The primary efficacy endpoint was the comparison of change in Monthly Migraine Days (MMD) between treatment and placebo groups from baseline to week 12. The study showed a statistically significant reduction in the MMD in the treatment group compared to the placebo group. The mean change from baseline in the treatment was -6/9, whereas the mean change from baseline in the placebo group was -5.1, with  $p$ -value of  $< 0.001$ .



Some of the secondary endpoints were the comparison of change in Monthly Headache Days, and Monthly Acute Medication Use days from baseline in mean MMD between treatment and placebo groups from baseline to week 12. The study showed a statistically significant reduction in the monthly headache days, and monthly acute medication use day compared to the placebo group with p- value < 0.001.

## **Safety/Tolerability**

### **Aimovig (erenumab-aooe)**

The safety of erenumab has been evaluated in 2537 individuals with migraine who received at least one dose of erenumab, representing 2310 individual-years of exposure. Of these, 2057 individuals were exposed to 70 mg or 140 mg once monthly for at least 6 months, 1198 individuals were exposed for at least 12 months, and 287 individuals were exposed for at least 18 months. In placebo-controlled clinical studies (Studies 1, 2, and 3) of 2184 individuals, 787 individuals received at least one dose of erenumab 70 mg once monthly, 507 individuals received at least one dose of erenumab 140 mg once monthly, and 890 individuals received placebo during 3 months or 6 months of double-blind treatment. Approximately 84% were female, 91% were white, and the mean age was 42 years at study entry. The most common adverse reactions (incidence  $\geq$  3% and more often than placebo) in the migraine studies were injection site reactions and constipation.

### **Ajovy (fremanezumab-vfrm)**

The safety of fremanezumab was evaluated in 2512 individuals with migraine who received at least 1 dose of fremanezumab, representing 1279 individual-years of exposure. Of these, 1730 individuals were exposed to fremanezumab 225 mg monthly or fremanezumab 675 mg quarterly for at least 6 months, 775 individuals for at least 12 months, and 138 individuals for at least 15 months. In placebo-controlled clinical trials (Studies 1 and 2), 662 individuals received fremanezumab 225 mg monthly for 12 weeks (with or without a loading dose of 675 mg), and 663 individuals received fremanezumab 675 mg quarterly for 12 weeks. In the controlled trials, 87% of individuals were female, 80% were White, and the mean age was 41 years. The most common adverse reactions in the clinical trials for the preventive treatment of migraine (incidence at least 5% and greater than placebo) were injection site reactions. The adverse reactions that most commonly led to discontinuations were injection site reactions (1%).



## **Emgality (galcanezumab-gnlm)**

### ***Migraine***

The safety of galcanezumab has been evaluated in 2586 individuals with migraine who received at least one dose of galcanezumab, representing 1487 individual-years of exposure. Of these, 1920 individuals were exposed to galcanezumab once monthly for at least 6 months, and 526 individuals were exposed for 12 months. In placebo-controlled clinical studies (Studies 1, 2, and 3), 705 individuals received at least one dose of galcanezumab 120 mg once monthly, and 1451 individuals received placebo, during 3 months or 6 months of double-blind treatment. Of the galcanezumab-treated individuals, approximately 85% were female, 77% were white, and the mean age was 41 years at study entry. The most common adverse reaction was injection site reactions. In Studies 1, 2, and 3, 1.8% of individuals discontinued double-blind treatment because of adverse events.

### ***Episodic Cluster Headache***

Galcanezumab was studied for up to 2 months in a placebo-controlled trial in individuals with episodic cluster headache (Study 4). A total of 106 individuals were studied (49 on galcanezumab and 57 on placebo). Of the galcanezumab-treated individuals, approximately 84% were male, 88% were white, and the mean age was 47 years at study entry. Two galcanezumab-treated individuals discontinued double-blind treatment because of adverse events. Overall, the safety profile observed in individuals with episodic cluster headache treated with galcanezumab 300 mg monthly is consistent with the safety profile in migraine individuals.

## **Vyepti (eptinezumab-jjmr)**

The safety of eptinezumab was evaluated in 2076 individuals with migraine who received at least one dose of eptinezumab, representing 1615 individual-years of exposure; of these, 1524 individuals were exposed to 100 mg or 300 mg. Across all doses, 1872 individuals were exposed for at least 6 months and 991 individuals were exposed for 12 months. In the placebo-controlled clinical studies (Study 1 and Study 2) of 1372 individuals, 579 individuals received at least one dose of eptinezumab 100 mg, 574 individuals received at least one dose of eptinezumab 300 mg, and 588 individuals received placebo. Approximately 86% were female, 89% were white, and the mean age was 40.4 years at study entry. The most common (incidence at least 2% and at least 2% greater than placebo) adverse reactions in the clinical trials for the preventive treatment of migraine were nasopharyngitis and hypersensitivity.



### **Nurtec ODT (rimegepant)**

The safety of rimegepant for the preventive treatment of episodic migraine in adults has been established in a randomized, double-blind, placebo-controlled trial with an open-label extension. In the 12-week, double-blind treatment period, 370 individuals with migraine received one 75 mg dose of rimegepant every other day. Long-term safety was assessed in an open-label extension study that included 603 individuals who were treated for up to one year. Overall, 527 individuals were exposed to rimegepant 75 mg for at least 6 months, and 311 were exposed for at least one year. The most common adverse reactions (occurring in at least 2% of rimegepant-treated individuals and at a frequency of at least 1% higher than placebo) were nausea (2.7% in individuals who received rimegepant compared with 0.8% of individuals who received placebo) and abdominal pain/dyspepsia (2.4% in individuals who received rimegepant compared with 0.8% of individuals who received placebo).

### **Qulipta (atogepant)**

The safety of atogepant was assessed in 2657 individuals with migraine who received at least one dose of atogepant. Among them, 1225 were treated with Qulipta for at least 6 months, and 826 individuals were exposed for 12 months. In the placebo-controlled clinical studies (study 1, 2, and 3) that lasted 12 weeks, a total of 314 individuals received at least one dose of Qulipta 10 mg once daily, 411 individuals received at least one dose of Qulipta 30mg once daily, 678 individuals received at least one dose of Qulipta 60 mg once daily, and 663 individuals received placebo. The most common adverse reactions reported with Qulipta were nausea, constipation, fatigue, and somnolence. During the clinical trials, some participants experienced transaminase elevation exceeding three times the upper limit of normal. Furthermore, the incidence of at least 7% body weight reduction was observed in approximately 3.8% of individuals receiving Qulipta 10 mg compared to 2.5% in the placebo group.

## **2019 Update**

Annual review, literature search from 1/1/2018 to 3/31/2019 identified no new information that would impact this policy.



## 2020 Update

Annual review conducted literature search from 4/1/2019 to 2/28/2020 and reviewed prescribing information for Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm) and Emgality (galcanezumab-gnlm). Added criteria for Emgality for the treatment of episodic cluster headache. Added a new medication Vyepti (eptinezumab-jjmr) to policy which is an IV dosage form for the preventive treatment of migraines.

## 2021 Update

Reviewed prescribing information for Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and Vyepti (eptinezumab-jjmr). No new evidence was identified that would require changes to drugs listed in this policy.

## 2022 Update

Reviewed prescribing information for all drugs in policy and conducted a literature search on prophylactic migraine treatment. Updated the prophylactic therapy drugs in the appendix table by removing clonidine, cyproheptadine, and other anticonvulsants and added the drugs candesartan, gabapentin, and valproic acid. Also, updated the investigational table to list that these medications when used in combination with each other or for conditions not outlined in this policy or policy 5.01.503 are considered investigational.

## 2023 Update

Reviewed prescribing information for all drugs in policy. Updated Qulipta (atogepant) criteria to include expanded FDA indication of preventive treatment of chronic migraine. Updated existing criteria for CGRPs for preventive use. For preventive use, updated requirement to trial and failure of 2 prophylactic medications and no requirement to try a triptan first.

## 2024 Update

Reviewed prescribing information for all drugs in policy. No new information identified that would change existing policy statements.





## 2025 Update

Reviewed prescribing information for all drugs in policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that use of drugs in this policy for the prevention or treatment of hemiplegic migraines and vestibular migraines is considered investigational.

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## Appendix

### Prophylactic Therapy

Antidepressants, Beta blockers, Calcium channel blockers, Botulinum toxin (Botox), Candesartan, Divalproex sodium, Gabapentin, Naproxen (when used daily), Topiramate, Valproic acid.

### History

Date	Comments
06/01/18	New policy, approved May 17, 2018. Add to Prescription Drug section. Aimovig (erenumab) may be considered medically necessary in patients with an average of more than 4 migraine days per month who have failed at least three preventive migraine therapies and are receiving a maximum monthly supply of abortive migraine treatments.
10/01/18	Interim Review, approved September 20, 2018. Added criteria for Ajovy (fremanezumab).



Date	Comments
01/01/19	Interim Review, approved December 13, 2018. Added criteria for Emgality (galcanezumab).
05/01/19	Annual Review, approved April 18, 2019. No changes to criteria.
08/01/19	Interim Review, approved July 25, 2019. Updated criteria from three to one triptan medications.
04/01/20	Annual Review, approved March 10, 2020. Added criteria for Vyepiti (eptinezumab-jjmr) which is an IV dosage form for the preventive treatment of migraines. Added HCPCS code J3590. Added criteria for Emgality (galcanezumab) for the treatment of episodic cluster headache.
08/01/20	Interim Review, approved July 2, 2020. Updated criteria to consider medically necessary in patients 18 years of age or older.
10/01/20	Coding update. Added HCPCS code J3032 and removed J3590.
05/01/21	Annual Review, approved April 22, 2021. Removed CGRP antagonists from Appendix.
07/01/21	Interim Review, approved June 8, 2021. Updated Aimovig (erenumab), Ajovy (fremanezumab), Emgality (galcanezumab), and Vyepiti (eptinezumab-jjmr) criteria from an average of five to four migraine days per month. Updated policy initial authorization duration of approval from three to six months.
01/01/22	Interim Review, approved December 14, 2021. Added Nurtec ODT (rimegepant) to policy for the preventive treatment of episodic migraine in adults. Added Qulipta (atogepant) to policy for the preventive treatment of episodic migraine in adults. Updated criteria for Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), and Vyepiti (eptinezumab-jjmr) to document the covered indication is for the preventive treatment of migraine in adults. Removed ergotamine preparations from Appendix for prophylactic therapy. Added HCPCS code J3031 and J3590.
07/01/22	Annual Review, approved June 27, 2022. Updated the prophylactic therapy drugs in the appendix table by removing clonidine, cyproheptadine, and other anticonvulsants and added the drugs candesartan, gabapentin, and valproic acid. Updated the investigational table to list that these medications when used in combination with each other or for conditions not outlined in this policy or policy 5.01.503 are considered investigational.
01/01/23	Interim Review, approved December 23, 2022. Added a note to Nurtec ODT (rimegepant) to please see Policy 5.01.503 Migraine and Cluster Headache Medications when Nurtec ODT (rimegepant) is being requested for the acute treatment of migraines. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. Updated Qulipta (atogepant) criteria to include expanded FDA indication of preventive treatment of chronic migraine.



Date	Comments
10/01/23	Interim Review, approved September 12, 2023. Updated existing criteria for CGRPs for preventive use. For preventive use, updated requirement that trial and failure of 2 prophylactic medications.
01/01/24	Interim Review, approved December 12, 2023. Removed requirement for trial with a triptan for preventive treatment of migraines criteria for Aimovig, Ajovy, Emgality, Nurtec, Qulipta, and Vyepti.
09/01/24	Annual Review, approved August 26, 2024. No changes to policy statements.
03/01/25	Annual Review, approved February 11, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that use of drugs in this policy for the prevention or treatment of hemiplegic migraines and vestibular migraines is considered investigational. Added HCPC C9399 for Aimovig.

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