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 patients 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
--- | ---
Aimovig™ (erenumab) | Aimovig™ (erenumab), Ajovy™ (fremanezumab), or Emgality™ (galcanezumab) may be considered medically necessary in patients who have:
- An average of 5 or more migraine days per month
- Tried three different categories of prophylactic migraine headache therapies listed in the Appendix section
- Tried three different triptan medications for abortive use unless triptan medications are contraindicated

Ajovy™ (fremanezumab)
Emgality™ (galcanezumab)

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### Length of Approval

| Approval       | Criteria                                                                 |
--- | --- |
Initial Approval | Initial approval will be for three months. |
Reauthorization  | Continued therapy will be approved for periods of up to one year as long as the patient has shown and continues to show a sustained reduction in headache frequency OR severity compared to baseline prior to initiation of treatment with the CGRP inhibitor. |

### Required Documentation

Chart notes describing patient’s diagnosis and progress including headache frequency; medication history, if not documented by our prescription claims record.

### Coding

N/A

### Related Information
Benefit Application

All CGRP inhibitors are managed through the pharmacy benefits.

Evidence Review

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 disproportionally affects females, with females 2-2.5 times more likely to suffer from migraine.

The frequency of migraine attacks a patient 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 patient 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 patients 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.

Migraine has a significant economic and social impact in the U.S. During a migraine attack, sufferers of migraine 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 patients at 6 months and 17% of patients at 12 months continuing these drugs.

Triptans, via inhibition of 5-hydroxytriptamine 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. Triptan quantity limits are typically set to accommodate treatment of three migraine days per month. NSAIDs and ergotamines can also be used as abortive therapies, though as with triptans, rebound headaches from overuse can occur with these as well.

Based on the data published from the PREEMPT trials I and II in 2011, onabotulinumtoxinA (Botox) was approved for use in chronic migraine despite numerous studies conducted previously failed to show a statistically significant difference between Botox™ and placebo in reduction of migraine days. Since, incobotulinumtoxinA (Xeomin™) and abobotulinumtoxinA (Dysport™) have been approved for the treatment of CM, however, failure to respond and development of antibodies to the botulinum toxin, in addition to the specialized administration these injections require, prevent these drugs from being a viable migraine prevention treatment for many patients.
**Aimovig™ (erenumab)**

Aimovig™ (erenumab) is a fully human monoclonal antibody that targets the 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)**

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)**

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.

**Rationale**

**Efficacy/Effectiveness**

Aimovig™ (erenumab) 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 patients with history of episodic migraine; STRIVE observed a reduction of 3.2 and 3.7 migraine days per month for patients 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 randomized controlled trial (RCT), which included 656 patients with history of chronic migraine and observed a mean reduction in mean monthly migraine days (MMMD) of 6.6 days in patients treated with erenumab 70mg, 6.6 days in patients 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 patients 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 patients receiving erenumab 140 mg and 43.3% of patients receiving erenumab 70 mg were able to achieve >50% reduction in MMMD. In the OLE, patients 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 patients within the episodic migraine population.

Ajovy™ (fremanezumab) is a humanized IgG2a monoclonal antibody that selectively binds both α and β isoforms of the calcitonin gene-related peptide (CGRP). Evidence for efficacy of fremanezumab in the prevention of chronic migraine was evaluated in HALO CM, a phase III, randomized controlled trial (RCT), which included 1130 patients with chronic migraine. HALO CM observed a reduction of 4.9 and 5.0 headaches days per month for patients 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 patients in the fremanezumab quarterly group and 41% of patients in the fremanezumab monthly group attained at least 50% reduction in the average number of headache days per month, compared to 18% of patients in the placebo group.

Evidence for efficacy of fremanezumab in the treatment of high-frequency episodic migraine was evaluated in a phase II randomized controlled trial (RCT), which included 297 patients 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 patients treated with fremanezumab 225mg monthly and 6.09 days in patients 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.

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 patients diagnosed with episodic migraine. The main difference between the two trials was that EVOLVE-1 observed patients in North America only, while EVOLVE-2
observed patients internationally. In EVOLVE-1, patients 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 patients 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 patients 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 patients 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 patients with episodic or chronic migraines. Once available, these studies may expand galcanezumab’s applicability and generalizability.

**Safety/Tolerability**

The overall safety profile of erenumab was similar to that of placebo in clinical trials. The 28 week open-label continuation study with STRIVE patients is still underway, results from which will be required to assess long term safety of erenumab. In the interim analysis of the OLE from phase II trial, 13.1% of patients developed drug-binding antibodies, and 2.4% developed drug-neutralizing antibodies; this lead to a transient response in a total of 37 patients.

A larger portion of patients treated with fremanezumab had a treatment-related adverse event than those in the placebo group. However, the most common adverse events were injection-site reactions (pain, induration, and erythema), which should not have any significant impact on the
safety of the product. There is no published study evaluating long-term efficacy and safety of fremanezumab. The ongoing phase III FOCUS trial will evaluate the efficacy and safety as a migraine prophylaxis up to 24 weeks (with the last 12 weeks as open label). Another ongoing phase III trial in patients with cluster headaches may shed light on adverse events with longer use up to 36 weeks.

The overall safety profile of galcanezumab was slightly worse than that of placebo in clinical trials. In EVOLVE-1, the rate of patients reporting >1 treatment-emergent adverse event (TEAE) was reported for 65.5% and 67.7% of patients in the 120 mg and 240 mg groups, compared to 60.4% in the placebo group. EVOLVE-2 saw 65% and 71.5% of patients in the 120 mg and 240 mg groups, respectively, report > TEAE, compared to 62.3% of patients in the placebo group. Serious adverse events (SAEs) were rare and uncommon in glancanezumab. In some cases, investigators determined that SAEs were not associated with the drug. Injection-site related adverse events were the most frequent adverse event (AE) in all the trials, ranging from 6-20%, but none were significantly different from the placebo group. Neutralizing anti-drug antibodies (ADAs) were reported in 18/415 patients in the EVOLVE-1 trial and 29 patients in EVOLVE-2 (EVOLVE-2’s rate included both placebo and galcanezumab). Galcanezumab was well-tolerated with about 1-4% of patients discontinuing due to adverse events, but investigators did not specify what these adverse events were.

References


33. Policy was reviewed by a board certified practicing neurologist with specialty in headache management. Approved by the independent P&T Committee May 30, 2018.

Appendix

Prophylactic Therapy

Antidepressants, Beta blockers, Calcium channel blockers, Naproxen, Ergotamine preparations, Divalproex sodium, Topiramate, Botulinum toxin (Botox®), Calcitonin gene-related peptide (CGRP) antagonists, Others (cyproheptadine, clonidine, other anticonvulsants)

History

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<tr>
<th>Date</th>
<th>Comments</th>
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<td>06/01/18</td>
<td>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.</td>
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<tr>
<td>01/01/19</td>
<td>Interim Review, approved December 13, 2018. Added criteria for Emgality (galcanezumab).</td>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
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