Calcitonin Gene-Related Peptide (CGRP) Antagonists

Policy #  00646
Original Effective Date:  11/21/2018
Current Effective Date:  02/20/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

• Benefits are available in the member’s contract/certificate, and
• Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider Aimovig™ (erenumab-aooe), Ajovy™ (fremanezumab-vfrm), and Emgality™ (galcanezumab-gnlm) to be eligible for coverage when the patient selection criteria are met.

Patient Selection Criteria
Coverage eligibility for Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), and Emgality (galcanezumab-gnlm) will be considered when the following criteria are met:

• The requested drug will be used for the prevention of migraine headaches; AND
• Patient is 18 years of age or older; AND
• Patient has greater than or equal to 4 migraine headache days per month (prior to initiating a migraine-preventive medication); AND
  (Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary if not met).
• Patient has tried and failed (e.g. intolerance or inadequate response) at least TWO standard prophylactic pharmacologic therapies for an adequate duration, each from a different pharmacologic class unless there is clinical evidence or patient history that suggests the use of the required prophylactic pharmacologic therapies from different classes will be ineffective or cause an adverse reaction to the patient. [Note: prophylactic pharmacologic classes include anticonvulsants (e.g. topiramate, divalproex), beta blockers (e.g. propranolol, metoprolol, nadolol), tricyclic antidepressants (e.g. amitriptyline, nortriptyline), calcium channel blockers (e.g. verapamil), and botulinum toxins (e.g. Botox®)] AND
  (Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary if not met).
• Patient has tried and failed (e.g. intolerance or inadequate response) at least one generic triptan therapy (e.g. sumatriptan) or the patient has a contraindication to the use of triptans; AND
  (Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary if not met).
• The requested drug will not be used in combination with another CGRP antagonist (e.g. Aimovig, Ajovy, Emgality).
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When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), and Emgality (galcanezumab-gnlm) when the patient has fewer than 4 migraine headache days per month, has not tried at least 2 prophylactic medications from different pharmacologic classes, or has not tried a triptan to be not medically necessary.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), and Emgality (galcanezumab-gnlm) for conditions other than migraine headache prevention, for patients younger than 18 years of age, or when used in combination with each other to be investigational.*

Background/Overview
The calcitonin gene-receptor (CGRP) antagonists are a new class of drugs indicated for the prevention of migraine headaches. They work by binding either to the CGRP receptor (Aimovig) or to the ligand (Ajovy and Emgality) to block the effects of CGRP, a protein with potent vasodilating actions that is thought to be associated with many of the phenomenon occurring with migraine attack (e.g. aura, pain, photophobia, and nausea). These drugs have not been compared to each other in clinical trials, but appear to have similar efficacy in preventing migraine headaches based on placebo-controlled trials with each individual drug. They do, however, vary in dosing recommendations. The recommended dosage of Aimovig is 70 mg injected subcutaneously once monthly, but may be increased to 140 mg once monthly if needed. The recommended dosage of Ajovy is 225 mg injected subcutaneously once monthly or 675 mg every 3 months. The quarterly dose is administered as three consecutive subcutaneous injections of 225 mg each. The recommended dosage of Emgality is 240 mg injected subcutaneously as a loading dose followed by 120 mg once monthly thereafter. The safety profile of each of these drugs is favorable with relatively few adverse events and no contraindications or warnings/precautions noted in the labeling.

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate to severe throbbing headache which is aggravated by routine physical activity and associated with nausea, vomiting, and/or photophobia and phonophobia. Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 13% of adults in the United States with three times more women affected than men. There are two major subtypes of migraine: migraine with aura and without aura. In up to 30% of patients, aura precedes migraine headache and is typically characterized by any combination of visual, hemisensory, or language abnormalities, with the most common being visual. Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on >15 days per month for more than 3 months, which has the features of migraine headache on >8 days per month. Episodic migraine is characterized by headaches that occur <15 days per month. Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of patients per year. Potential strategies for preventing migraine transformation include preventing and
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treating headaches, lifestyle modifications, or effective management of comorbidities. Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden.

The American Academy of Neurology (AAN) published an evidence-based guideline update for the prevention of episodic migraine in 2012. These guidelines recommend divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol as effective for migraine prevention and suggest that they should be offered to patients with migraine to reduce migraine attack frequency and severity. The guidelines have not been updated to address Aimovig. Guidelines also support the use of angiotensin receptor blockers, angiotensin converting enzyme inhibitors, tricyclic antidepressants, and other antidepressants as preventative therapies. Botox is indicated only for the prophylaxis of chronic migraine in adults and is administered intramuscularly once every 12 weeks.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Aimovig was approved in May 2018 and Ajovy and Emgality were approved in September 2018 for the preventive treatment of migraine in adults.

Rationale/Source

Aimovig

Aimovig’s efficacy was assessed in three randomized, double-blind, placebo-controlled studies: two studies in patients with episodic migraine (4 to 14 migraine days per month) and one study in patients with chronic migraine (>15 headache days per month).

Study 1 was a randomized, multi-center, 6-month, placebo-controlled, double-blind study evaluating Aimovig for the preventive treatment of episodic migraine. A total of 955 patients were randomized to receive Aimovig 70 mg, Aimovig 140 mg, or placebo by subcutaneous injection once monthly for 6 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and NSAIDs during the study. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over months 4 to 6. Aimovig treatment demonstrated a statistically significant reduction in mean monthly migraine days at both doses. The 70 mg group had a mean monthly migraine day reduction of -3.2 days, the 140 mg group had a mean monthly migraine day reduction of -3.7 days, and the placebo group had a mean monthly migraine day reduction of -1.8 days.

Study 2 was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Aimovig for the preventive treatment of episodic migraine. A total of 577 patients with a history of episodic migraine were randomized to receive either Aimovig 70 mg or placebo by subcutaneous injection once monthly for 3 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e. triptans, ergotamine derivatives) and NSAIDs during the study. The primary efficacy endpoint was the change from baseline in monthly migraine days at month 3. Aimovig treatment demonstrated a statistically significant improvement in the primary endpoint compared to placebo. Patients

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in the Aimovig group had a mean monthly migraine day change from baseline of -2.9 days compared to the placebo group which had a change from baseline of -1.8 days.

Study 3 was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating Aimovig as a preventive treatment of chronic migraine. A total of 667 patients with a history of chronic migraine with or without aura were randomized to receive Aimovig 70 mg, Aimovig 140 mg, or placebo by subcutaneous injection once monthly for 3 months. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e. triptans, ergotamine derivatives) and NSAIDs during the study. The primary efficacy endpoint was the change from baseline in monthly migraine days at month 3. Aimovig treatment demonstrated statistically significant improvement in the primary endpoint at both Aimovig doses compared to placebo. Patients in both the 70 mg group and the 140 mg group had a mean monthly migraine day change from baseline of -6.6 days compared to -4.2 days in the placebo group.

Ajovy
The efficacy of Ajovy was evaluated as a preventive treatment of episodic or chronic migraine in two multicenter, randomized, 3-month double-blind, placebo-controlled studies (Study 1 and Study 2).

Study 1 included adults with a history of episodic migraine (patients with <15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either Ajovy 675 mg every 3 months, Ajovy 225 mg monthly, or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant preventive medication. The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events. A total of 875 patients (742 females, 133 males), ranging in age from 18-70 years were randomized. A total of 791 patients completed the 3-month double-blind phase. The mean migraine frequency at baseline was approximately 9 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint in Study 1 was the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period. Both monthly and quarterly dosing regimens of Ajovy demonstrated statistically significant improvements in this efficacy endpoint compared to placebo. Patients in the 225 mg monthly group (n=287) experienced an average reduction in monthly migraine days of 3.7, patients in the 675 mg quarterly group (n=288) experienced an average reduction in monthly migraine days of 3.4, and patients in the placebo group experienced an average reduction in monthly migraine days of 2.2.

Study 2 included adults with a history of chronic migraine (patients with ≥15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either Ajovy 675 mg starting dose followed by 225 mg monthly, 675 mg every 3 months, or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant preventive medication. The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events. A total of 1130 patients (991
females, 139 males), ranging in age from 18 to 70 years, were randomized. A total of 1034 patients completed the 3-month double-blind phase.

The primary efficacy endpoint in Study 2 was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 3-month treatment period. Both monthly and quarterly dosing regimens of Ajovy treatment demonstrated statistically significant improvement for key efficacy outcomes compared to placebo. Patients in the 225 mg monthly group (n=375) experienced an average reduction of 4.6 monthly headache days, patients in the 675 mg quarterly group (n=375) experienced an average reduction of 4.3 monthly headache days, and patients in the placebo group (n=371) experienced an average reduction of 2.5 monthly headache days.

**Emgality**

The efficacy of Emgality was evaluated as a preventive treatment of episodic or chronic migraine in three multicenter, randomized, double-blind, placebo-controlled studies: two 6-month studies in patients with episodic migraine (Studies 1 and 2) and one 3-month study in patients with chronic migraine (Study 3).

In study 1 and study 2, adults (age 18-65 years) with a history of episodic migraine (4 to 14 migraine days per month) were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Emgality 120 mg, 240 mg, or placebo. A total of 703 patients completed study 1 and 785 patients completed study 2. All patients in the 120 mg group received an initial 240 mg loading dose. Patients were allowed to use acute headache treatments, including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs, and acetaminophen during the study. Both studies excluded patients on any other migraine preventive treatment, patients with medication overuse headache, patients with ECG abnormalities compatible with an acute cardiovascular event and patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening.

The primary efficacy endpoint for Studies 1 and 2 was the mean change from baseline in the number of monthly migraine headache days over the 6-month treatment period. Emgality 120 mg demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 6-month period with a reduction in monthly migraine headache days of 4.7 and 4.3 in study 1 and study 2, respectively. This corresponded to an increased reduction from placebo of 1.9 and 2.0 headache days. Emgality treatment with the 240 mg once-monthly dose showed no additional benefit over the Emgality 120 mg once-monthly dose.

Study 3 included adults with a history of chronic migraine (≥15 headache days per month with ≥8 migraine days per month). All patients (n=1037) were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of Emgality 120 mg, Emgality 240 mg, or placebo over a 3-month treatment period. All patients in the 120 mg Emgality group received an initial 240 mg loading dose. Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs, and acetaminophen. A subset of patients (15%) was allowed to use one concomitant migraine preventive medication. Patients with medication overuse headache were allowed to enroll.
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The primary endpoint was the mean change from baseline in the number of monthly migraine headache days over the 3-month treatment period. Emgality 120 mg demonstrated statistically significant improvement with a reduction of 4.8 days compared to a reduction of 2.7 days in placebo (difference of 2.1 days). Emgality treatment with the 240 mg once-monthly dose showed no additional benefit over the Emgality 120 mg once-monthly dose.

References

Policy History
Original Effective Date: 11/21/2018
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11/08/2018 Medical Policy Committee review
02/07/2019 Medical Policy Committee review
02/20/2019 Medical Policy Implementation Committee approval. Added two new drugs, Ajovy and Emgality along with relevant background information.
Next Scheduled Review Date: 02/2020

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
   A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
   B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
      1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
      2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
      3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
   A. In accordance with nationally accepted standards of medical practice;
   B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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