Calcitonin Gene-Related Peptide (CGRP) Antagonists

Policy # 00646
Original Effective Date: 11/21/2018
Current Effective Date: 09/09/2024

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.

Note: Reyvow™‡ (lasmiditan), Cambia®‡ (diclofenac), and select brand triptan medications are addressed separately in medical policy 00337. Ergotamine/dihydroergotamine products are addressed separately in medical policy 00582.

Small Molecule CGRP Antagonists ("gepants")

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.*

Patients with "Step Therapy" (generic before brand) ONLY:

Based on review of available data, the Company may consider Zavzpret™‡ (zavegepant) for the acute treatment of migraine headaches to be **eligible for coverage**** when the patient selection criteria are met**.**

Patient Selection Criteria

Coverage eligibility will be considered for Zavzpret (zavegepant) when one of the following criteria is met:

- Patient has tried and failed a GENERIC triptan medication (e.g., sumatriptan [tablets, nasal spray, or injection], naratriptan tablets, eletriptan tablets, rizatriptan [tablets or orally disintegrating tablets], almotriptan tablets, frovatriptan tablets, or zolmitriptan [tablets or orally disintegrating tablets]); OR
- There is clinical evidence or patient history that suggests the generically available oral or injectable products will be ineffective or cause an adverse reaction to the patient.

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Zavzpret (zavegepant) when patient selection criteria are not met or for usage not included in the above patient selection criteria to be **not medically necessary**.**

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.*

Acute Treatment of Migraine for Patients with "Prior Authorization" ONLY OR BOTH "Prior Authorization" and "Step Therapy":

Based on review of available data, the Company may consider Ubrelvy®‡ (ubrogepant), Zavzpret (zavegepant), or Nurtec™‡ ODT (rimegepant) for the acute treatment of migraine headaches to be **eligible for coverage**** when the patient selection criteria are met**.**

Patient Selection Criteria

Coverage eligibility for Ubrelvy (ubrogepant), Nurtec ODT (rimegepant), or Zavzpret (zavegepant) will be considered when the following criteria are met:

- The requested drug will be used for the acute treatment of migraine headaches; AND
- Patient is 18 years of age or older; AND
- Patient has tried and failed (e.g. intolerance or inadequate response) at least ONE GENERIC active ingredient triptan therapy (oral, nasal, injectable) unless there is clinical evidence or patient history that suggests the use of these generic products will be ineffective or cause an adverse reaction to the patient. Generic triptan products for the acute treatment of migraine include sumatriptan (available in nasal, oral, and injectable), zolmitriptan, almotriptan, frovatriptan, naratriptan, and rizatriptan; 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.)*

- If the requested drug is Zavzpret, patient has tried and failed ONE of the following preferred brands: Ubrelvy, Nurtec ODT, or Reyvow unless there is clinical evidence or patient history that suggests the use of these preferred brand products will be ineffective or cause an adverse reaction to the patient.
  *(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.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Ubrelvy (ubrogepant), Nurtec ODT (rimegepant), or Zavzpret (zavegepant) when the patient has not tried and failed at least ONE GENERIC active ingredient triptan therapies to be **not medically necessary.****

Based on review of available data, the Company considers the use of Zavzpret (zavegepant) when the patient has not tried and failed at least ONE preferred brand 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 Ubrelvy (ubrogepant), Zavzpret (zavegepant), or Nurtec ODT (rimegepant) for indications that have not been approved by the FDA or for patients younger than 18 years of age to be **investigational.***

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.*

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Prevention of Migraine for Patients with "Prior Authorization" ONLY OR BOTH "Prior Authorization" and "Step Therapy":
Based on review of available data, the Company may consider Nurtec ODT (rimegepant), or Qulipta™‡ (atogepant) for the preventive treatment of migraine to be **eligible for coverage**** when the patient selection criteria are met**.**

Patient Selection Criteria
Coverage eligibility for Nurtec ODT (rimegepant) or Qulipta (atogepant) will be considered when the following criteria are met:

- The requested drug will be used for the preventive treatment of migraine; 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 suggest the use of the required prophylactic pharmacologic therapies from different classes will be ineffective or cause an adverse reaction to the patient. 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®‡).
  *(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.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Nurtec ODT (rimegepant) or Qulipta (atogepant) when the patient has less than 4 migraine headache days per month or has not tried and failed at least TWO standard prophylactic pharmacologic therapies to be **not medically necessary.****

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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 Nurtec ODT (rimegepant) or Qulipta (atogepant) for indications that have not been approved by the FDA or for patients younger than 18 years of age to be **investigational.***

Monoclonal Antibody CGRP Antagonists

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.*

Migraine Headache Prevention

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

Patient Selection Criteria

Coverage eligibility for Aimovig (erenumab-aooe), Ajovy (fremanezumab-vfrm), Emgality (galcanezumab-gnlm), or Vyepti (eptinezumab-jjmr) 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. 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).*
- If the requested drug is Vyepti, the dose will not exceed 300 mg every 3 months.

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), Emgality (galcanezumab-gnlm), or Vyepti (eptinezumab-jjmr) for the prevention of migraines when the patient has fewer than 4 migraine headache days per month or has not tried at least TWO prophylactic medications from different pharmacologic classes 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), Emgality (galcanezumab-gnlm), or Vyepti (eptinezumab-jjmr) for indications that have not been approved by the FDA or for patients younger than 18 years of age to be **investigational.***

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.*

Episodic Cluster Headache

Based on review of available data, the Company may consider Emgality (galcanezumab-gnlm) for the treatment of episodic cluster headache to be **eligible for coverage.****

Patient Selection Criteria:

Coverage eligibility for the use of Emgality (galcanezumab-gnlm) will be considered when the following criteria are met:

- Patient has a diagnosis of episodic cluster headache; AND
- Patient is 18 years of age or older; AND
- Patient experiences at least 1 attack every other day for the duration of the cluster period; AND
- Cluster periods last less than or equal to 1 year with remission periods of at least 3 months.

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 Emgality (galcanezumab-gnlm) for indications that have not been approved by the FDA or for patients younger than 18 years of age to be **investigational.***

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Background/Overview

The calcitonin gene-receptor (CGRP) antagonists are a new class of drugs for the prevention and treatment of migraine headaches and can be divided into two sub-classes: gepants and monoclonal antibodies. The gepants include the oral small-molecule agents: Ubrelvy (ubrogepant), Nurtec ODT (rimegepant), Qulipta (atogepant), and Zavzpret (zavegepant). The monoclonal antibodies include the injectable agents: Aimovig, Ajovy, Emgality, and Vyepti. All of these products work by binding either to the CGRP receptor or to the ligand 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). Aimovig, Ajovy, Emgality, and Vyepti are indicated for the prevention of migraine headaches while Ubrelvy, Nurtec ODT, and Zavzpret are indicated for the acute treatment of migraine headaches. Nurtec ODT and Qulipta are also indicated for the preventive treatment of migraine. Emgality is also approved to treat episodic cluster headaches and is the only CGRP inhibitor with this indication. Ajovy was not found to be effective for cluster headaches and Aimovig has not been studied for cluster headache. Of note, clinical trials for Aimovig specifically excluded patients with hemiplegic migraine.

For migraine headache prevention, the recommended dosage of Aimovig is 70 mg injected subcutaneously once monthly that 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 for migraine prevention is 240 mg injected subcutaneously as a loading dose followed by 120 mg once monthly thereafter. For episodic cluster headache treatment, Emgality should be dosed as 300 mg (3 consecutive injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period. The recommended dose of Vyepti is 100 mg administered by intravenous infusion every 3 months. However, some patients may benefit from a dosage of 300 mg every 3 months. For acute treatment of migraine, the recommended dose of Ubrelvy is 50 or 100 mg taken orally with or without food. If needed, a second dose may be taken $\geq$ 2 hours after the initial dose. The recommended dose of Zavzpret is 10 mg given as a single spray in one nostril with a maximum dose of one spray per 24 hours. The recommended dose of Nurtec ODT for acute treatment of migraine is 75 mg taken orally with a maximum dose of 75 mg in a 24 hour period. For prevention of episodic migraine, Nurtec ODT should be dosed as 75 mg every other day. The recommended dose of Qulipta is 10 mg, 30

mg, or 60 mg taken orally once daily. The safety profile of each of these drugs is favorable with relatively few adverse events.

Migraine
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 phonophopbia. 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 $\geq$ 15 days per month for more than 3 months, which has the features of migraine headache on $\geq$ 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 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 the CGRP antagonists. 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.

The American Headache Society published an updated evidence-based guideline in 2018 that reaffirms previous migraine guidelines. This guideline addresses the CGRP antagonists Aimovig, Ajovy, and Emgality. It notes that a CGRP inhibitor should only be initiated in patients who are

diagnosed with migraine, have ≥ 4 migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. These guidelines have not yet been updated to include Ubrelvy and Nurtec ODT for acute treatment of migraine or Nurtec ODT and Qulipta for prevention of episodic migraine.

Episodic Cluster Headache
Cluster headaches are short-lasting, severe headaches that typically recur frequently for a period of time before subsiding for a period of remission. The average length of a cluster period is 6-12 weeks with remissions lasting 12 months or longer. Cluster headache can be classified as episodic or chronic disease depending on the frequency and recurrence of headaches. To be considered episodic, headaches must occur in bouts (cluster periods) and the patient must experience at least 2 cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of 3 months or more. Chronic cluster headaches do not have a remission period or have a remission lasting less than 3 months for at least 1 year. During a cluster headache bout, prophylactic therapy should be initiated in addition to oxygen or triptans used for acute treatment. The drug of choice is high-dose oral verapamil (up to 960 mg per day), but this may take up to 2 weeks of dose titration to take effect. During this time, oral glucocorticoids or oral ergotamine may be useful to prevent cluster headache attacks. Clinical guidelines have not yet been updated to describe the role of Emgality in the treatment of this disorder.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Aimovig was approved in May 2018, Ajovy and Emgality were approved in September 2018, and Vyepti was approved in February 2020 for the preventive treatment of migraine in adults. In June 2019, Emgality gained an additional indication for the treatment of episodic cluster headache in adults.

Ubrelvy was approved in December 2019 and Nurtec ODT was approved in February 2020 for the acute treatment of migraine with or without aura in adults. In December 2021, Nurtec ODT received an additional indication for the preventive treatment of episodic migraine in adults.

Qulipta was approved in September 2021 for the preventive treatment of episodic migraine in adults. This indication was updated in April 2023 to include preventive treatment of migraine (including chronic migraine) in adults.

Zavzpret was approved in March 2023 for the acute treatment of migraine with or without aura in adults.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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). All studies specifically excluded patients with hemiplegic migraine.

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 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). The efficacy of Emgality for the treatment of episodic cluster headache was evaluated in a randomized, 8-week, double-blind, placebo-controlled study (Study 4).

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.

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.

Study 4 included adults who met the International Classification of Headache Disorders 3rd edition diagnostic criteria for episodic cluster headache and had a maximum of 8 attacks per day, a minimum of one attack every other day, and at least 4 attacks during the prospective 7-day baseline period. All patients (n=106) were randomized in a 1:1 ratio to receive once-monthly subcutaneous injections of Emgality 300 mg or placebo. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen, and NSAIDs during the study. The primary efficacy endpoint was the mean change from baseline in weekly cluster headache attack frequency across weeks 1-3. Patients in the Emgality group experienced a statistically significant reduction in attack frequency compared to placebo with a mean reduction of 8.7 attacks in the Emgality group vs a reduction of 5.2 attacks in the placebo group (p=0.036).

Vyepti
The efficacy of Vyepti was evaluated as a preventive treatment of episodic and chronic migraine in two randomized, multicenter, placebo-controlled studies, both with 6-month double-blind periods: one study in patients with episodic migraine (Study 1) and one study in patients with chronic migraine (Study 2). Vyepti was administered by intravenous infusion every 3 months in both studies; however, the primary endpoint was measured at 12 weeks.

Study 1 included adults with a history of episodic migraine (4-14 headache days per month, of which at least 4 were migraine days). A total of 665 patients were randomized to receive placebo (n=222), 100 mg Vyepti (n=221), or 300 mg Vyepti (n=222) every 3 months for 12 months. Patients were allowed to use concurrent acute migraine or headache medications, including migraine-specific medications during the trial. The study excluded patients with a history of cardiovascular disease, neurological disease, or cerebrovascular disease. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over months 1-3. Vyepti treatment demonstrated statistically significant improvements compared to placebo with a change from baseline of -3.9 monthly migraine days in the Vyepti 100 mg group, -4.3 monthly migraine days in the Vyepti 300 mg group and -3.2 monthly migraine days in the placebo group.

Study 2 included adults with a history of chronic migraine (15-26 headache days per month, of which at least 8 were migraine days). A total of 1072 patients were randomized and received placebo (n=366), 100 mg Vyepti (n=356), or 300 mg Vyepti (n=350) every 3 months for 6 months. Patients were allowed to use and to continue an established stable regimen of acute migraine or headache preventive medication (except Botox). Patients with a dual diagnosis of chronic migraine and

medication overuse headache attributable to acute medication overuse were included in the study population. Patients using opioids or butalbital-containing products greater than 4 days per month were not allowed. Patients with a history of cardiovascular disease, neurological disease, or cerebrovascular disease were also excluded. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over months 1-3. Vyepti treatment demonstrated statistically significant improvements compared to placebo with a change from baseline of -7.7 days in the Vyepti 100 mg group, -8.2 days in the Vyepti 300 mg group, and -5.6 days in the placebo group.

Ubrelvy
The efficacy of Ubrelvy for the acute treatment of migraine was demonstrated in two randomized, double-blind, placebo-controlled trials. Study 1 randomized patients to placebo (n=559) or Ubrelvy 50 mg (n=556) or 100 mg (n=557) and Study 2 randomized patients to placebo (n=563) or Ubrelvy 50 mg (n=562). In all studies, patients were instructed to treat a migraine with moderate to severe headache pain intensity. A second dose of study medication (Ubrelvy or placebo), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Up to 23% of patients were taking preventive medications for migraine at baseline. None of these patients were on concomitant preventive medication that act on the CGRP pathway.

The primary efficacy analyses were conducted in patients who treated a migraine with moderate to severe pain. The efficacy of Ubrelvy was established by an effect on pain freedom at 2 hours post-dose and most bothersome symptom freedom at 2 hours post-dose, compared to placebo. Pain freedom was defined as a reduction of moderate or severe headache pain to no pain, and most bothersome symptom freedom was defined as the absence of the self-identified most bothersome symptom. Among patients who selected a most bothersome symptom, the most commonly selected was photophobia (56%), followed by phonophobia (24%), and nausea (19%).

In both studies, the percentage of patients achieving headache pain freedom and most bothersome symptom freedom 2 hours post-dose was significantly greater among patients receiving Ubrelvy compared to those receiving placebo. In study 1, 19.2% of patients in the Ubrelvy 50 mg group and 21.2% of patients in the Ubrelvy 100 mg group were pain free at 2 hours compared to 11.8% of patients in the placebo group. Both of these were statistically significant compared to placebo. In

study 2, 21.8% of patients in the Ubrelvy 50 mg group were pain free at 2 hours compared to 14.3% of patients in the placebo group (p=0.007).

Nurtec ODT
The efficacy of Nurtec ODT for the acute treatment of migraine with and without aura in adults was demonstrated in a randomized, double-blind, placebo-controlled trial. The study randomized patients to 75 mg of Nurtec ODT (n=732) or placebo (n=734). Patients were instructed to treat a migraine of moderate to severe headache pain intensity. Rescue medication (i.e., NSAIDS, acetaminophen, and/or an antiemetic) was allowed 2 hours after the initial treatment. Other forms of rescue medication such as triptans were not allowed within 48 hours of initial treatment. Approximately 14% of patients were taking preventive medications for migraine at baseline, but none of the patients were on concomitant preventive medications that act on the CGRP pathway.

The primary efficacy endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post dose. The percentage of patients achieving these endpoints was statistically significantly higher in the Nurtec ODT group than in the placebo group. In the Nurtec ODT group, 21.2% were pain free at 2 hours compared to 10.9% in the placebo group and 35.1% were MBS free compared to 26.8% in the placebo group.

The efficacy of Nurtec ODT 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. This study included adult patients with at least a 1-year history of migraine (with or without aura). Patients 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. Patients were randomized to receive every other day dosing of rimegepant 75 mg (n=373) or placebo (n=374) for 12 weeks. Patients were allowed to use acute headache treatments as needed. Approximately 10% of patients were taking one preventive medication for migraine at baseline. The use of a concomitant medication that acts on the CGRP pathway was not permitted. The primary efficacy endpoint was the change from baseline in the mean number of monthly migraine days during Weeks 9 through 12 of the double-blind treatment of phase. Rimegepant 75 mg dosed every other day demonstrated statistically significant improvements in this endpoint with a change from baseline in monthly migraine days of -4.3 in the rimegepant group and -3.5 in the placebo group (p=0.01).

Qulipta
The efficacy of Qulipta for the preventive treatment of episodic migraine in adults was demonstrated in two randomized, multicenter, double-blind, placebo-controlled studies. The studies enrolled patients with at least a 1-year history of migraine with or without aura, according to the International Classification of Headache Disorders (ICHD-3) diagnostic criteria. In Study 1, 910 patients were randomized 1:1:1:1 to receive Qulipta 10 mg (n=222), Qulipta 30 mg (n=230), Qulipta 60 mg (n=235), or placebo (n=223), once daily for 12 weeks. In Study 2, 652 patients were randomized 1:2:2:2 to receive Qulipta 10 mg (n=94), Qulipta 30 mg (n=185), Qulipta 60 mg (n=187), or placebo (n=186), once daily for 12 weeks. In both studies, patients were allowed to use acute headache treatments as needed. The use of a concomitant medication that acts on the CGRP pathway was not permitted for either acute or preventive treatment of migraine. The studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

In Study 1, the primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period. All three doses were found to have a statistically significant decrease in monthly migraine days compared to placebo with a reduction of 3.7 days in the 10 mg group ($p<0.001$), a reduction of 3.9 days in the 30 mg group ($p<0.001$), a reduction of 4.2 days in the 60 mg group ($p<0.001$), and a reduction of 2.5 days in the placebo group.

In Study 2, the primary efficacy endpoint was the change from baseline in mean monthly migraine days across the 12-week treatment period. There was found to be a significantly greater reduction in monthly migraine days in all three dose groups with a reduction of 4 days seen in the 10 mg group ($p=0.024$), a reduction of 3.8 days in the 30 mg group ($p=0.039$), a reduction of 3.6 days in the 60 mg group ($p=0.039$) and a reduction of 2.8 days in the placebo group.

Zavzpret
The efficacy of Zavzpret for the acute treatment of migraine with or without aura in adults was demonstrated in two randomized, double-blind, placebo-controlled trials (Study 1 and Study 2). In both studies, patients were instructed to treat a migraine of moderate to severe headache pain intensity. Rescue medication (i.e., NSAIDs, acetaminophen, and/or an antiemetic) was allowed 2 hours after the initial treatment. Other forms of rescue medication such as triptans were not allowed within 48 hours of initial treatment. In Study 1 and Study 2, 13.4% and 13.6% of patients were taking preventive medications for migraine at baseline, respectively. None of the patients were on concomitant preventive medications that act on the CGRP pathway.

In Study 1, patients were randomized to receive a single dose of Zavzpret 10 mg (n=623) or placebo (n=646). Efficacy was demonstrated with Zavzpret 10 mg by effect on the coprimary endpoints of pain freedom and most bothersome symptom (MBS) freedom at 2 hours after a single dose, compared to placebo. Pain freedom was defined as a reduction of moderate or severe headache pain to no headache pain, and MBS freedom was defined as the absence of the self-identified MBS (i.e., photophobia, phonophobia, or nausea). The most common MBS reported before dosing was photophobia (55%), followed by nausea (28%), and phonophobia (16%). The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received Zavzpret compared to those who received placebo. In the Zavzpret group, 23.6% were pain free at 2 hours compared to 14.9% in the placebo group. Additionally, 39.6% in the Zavzpret group were MBS free at 2 hours compared to 31.1% in the placebo group.

In Study 2, patients were randomized to receive a single dose of Zavzpret 10 mg (n=391) or placebo (n=401). Statistically significant efficacy was demonstrated with Zavzpret 10 mg by an effect on the coprimary endpoints of pain freedom and MBS freedom at 2 hours after a single dose, compared to placebo. Pain freedom was observed in 22.5% of patients receiving Zavzpret and 15.5% of patients receiving placebo. MBS freedom was observed in 41.9% of patients receiving Zavzpret and 33.7% of patients receiving placebo.

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12. Qulipta [package insert]. AbbVie Inc. North Chicago, IL. Updated October 2021.
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Policy History

Original Effective Date: 11/21/2018
Current Effective Date: 09/09/2024

11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. New policy.
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.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. Added criteria for new cluster headache indication for Emgality with relevant background information.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Added new drugs Ubrelvy, Nurtec ODT, and Vyepti to policy with relevant background information.
12/11/2020	Coding update
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Removed requirement to try and fail triptan therapy prior to use of CGRP inhibitors for migraine prevention.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Re-organized policy to include section for gepants and monoclonal antibodies. Added new indication for prevention of episodic migraine for Nurtec ODT with relevant criteria and background information. Added new drug, Qulipta, with relevant criteria and background information.
09/27/2022	Coding update
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. No change to coverage.
08/03/2023	Medical Policy Committee review

Coding

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Calcitonin Gene-Related Peptide (CGRP) Antagonists

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3031, J3032, J3490, J3590
ICD-10 Diagnosis	All related diagnoses

*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 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.

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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.