



Drug and Biologic Coverage Policy

Effective Date 9/1/2021

Next Review Date... 9/1/2022

Coverage Policy Number 2020

Calcitonin Gene-Related Peptide (CGRP) Inhibitors – Preventative Migraine Treatment for Individual and Family Plans

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Related Coverage Resources

[Botulinum Therapy - \(1106\)](#)
[Migraine Treatment - \(P0058\)](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Eptinezumab-jjmr (Vyepti™), Erenumab-aooe (Aimovig™) and Fremanezumab-vfrm (Ajovy™) are considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- For the preventative treatment of migraine in an individual experiencing 4 or more migraine headache days per month (prior to initiating a migraine-preventative medication)

Galcanezumab-gnlm (Emgality™) is considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- For the treatment of ONE of the following:
 - Documented diagnosis of cluster headache (as defined by IHS criteria: occurring with a frequency between one headache every other day and eight headaches per day)
 - For the preventative treatment of migraine in an individual experiencing 4 or more migraine headache days per month (prior to initiating a migraine-preventative medication)

Coverage for Calcitonin Gene-Related Peptide (CGRP) Inhibitors varies across plans. Refer to the customer's benefit plan document for coverage details.

Where coverage requires the use of preferred products, the following criteria apply.

For Individual and Family Plans:

Product	Individual and Family Plans
Aimovig (erenumab-aooe)	<ul style="list-style-type: none"> Documented failure or inadequate response following a minimum 3 month trial, contraindication per FDA label, intolerance, or not a candidate for at least TWO different prescription migraine prevention therapies from different classes of migraine prophylaxis medication: <ul style="list-style-type: none"> Antiepileptic drugs (divalproex, sodium valproate, topiramate) Antidepressants (amitriptyline, venlafaxine) Beta blockers (metoprolol, propranolol, timolol) Documented failure or inadequate response following a minimum 6 month trial (2 injection cycles), contraindication per FDA label, intolerance, inability to use, or not a candidate for onabotulinumtoxinA (Botox)
Ajovy (fremanezumab-vfrm)	<ul style="list-style-type: none"> Documented failure or inadequate response following a minimum 3 month trial, contraindication per FDA label, intolerance, or not a candidate for at least TWO different prescription migraine prevention therapies from different classes of migraine prophylaxis medication: <ul style="list-style-type: none"> Antiepileptic drugs (divalproex, sodium valproate, topiramate) Antidepressants (amitriptyline, venlafaxine) Beta blockers (metoprolol, propranolol, timolol) Documented failure or inadequate response following a minimum 6 month trial (2 injection cycles), contraindication per FDA label, intolerance, inability to use, or not a candidate for onabotulinumtoxinA (Botox)
Emgality (galcanezumab-gnlm)	<p>For the preventative treatment of migraine AND the following:</p> <ul style="list-style-type: none"> Documented failure or inadequate response following a minimum 3 month trial, contraindication per FDA label, intolerance, or not a candidate for at least TWO different prescription migraine prevention therapies from different classes of migraine prophylaxis medication: <ul style="list-style-type: none"> Antiepileptic drugs (divalproex, sodium valproate, topiramate) Antidepressants (amitriptyline, venlafaxine) Beta blockers (metoprolol, propranolol, timolol) Documented failure or inadequate response following a minimum 6 month trial (2 injection cycles), contraindication per FDA label, intolerance, inability to use, or not a candidate for onabotulinumtoxinA (Botox) <p>For the treatment of cluster headache AND the following:</p> <ul style="list-style-type: none"> Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following: <ul style="list-style-type: none"> injectable sumatriptan zolmitriptan nasal spray (Zomig)* <p>*May require prior authorization</p>
Vyepti (eptinezumab-jjmr)	<ul style="list-style-type: none"> Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for at least ONE triptan therapy (for example, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) Documented failure or inadequate response following a minimum 3 month trial, contraindication per FDA label, intolerance, or not a candidate for at least TWO different prescription migraine prevention therapies from different classes of migraine prophylaxis medication: <ul style="list-style-type: none"> Antiepileptic drugs (divalproex, sodium valproate, topiramate)

Product	Individual and Family Plans
	<ul style="list-style-type: none"> ○ Antidepressants (amitriptyline, venlafaxine) ○ Beta blockers (metoprolol, propranolol, timolol) ○ Documented failure or inadequate response following a minimum 6 month trial (2 injection cycles), contraindication per FDA label, intolerance, inability to use, or not a candidate for onabotulinumtoxinA (Botox) • Documented failure or inadequate response following minimum 3 month trial, contraindication per FDA label, intolerance, or not a candidate for TWO of the following: <ul style="list-style-type: none"> ○ erenumab-aooe (Aimovig)* ○ fremanezumab-vfrm (Ajovy)* ○ galcanezumab-gnlm (Emgality)* <p>*May require prior authorization</p>

The concurrent use of eptinezumab-jjmr (Vyepti), erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy) or galcanezumab-gnlm (Emgality) with onabotulinumtoxinA (Botox) is considered medically necessary when ALL of the following criteria are met:

- Individual is 18 years of age or older
- For the preventative treatment of chronic migraine in an individual continuing to experience 4 or more migraine headache days per month after therapy with ONE of the following:
 - A minimum 6 month trial (2 injection cycles) of onabotulinumtoxinA (Botox)
 - A minimum 3 month trial of eptinezumab-jjmr (Vyepti), erenumab-aooe (Aimovig), fremanezumab-vfrm (Ajovy) or galcanezumab-gnlm (Emgality)
- All prerequisite therapy requirements, in the table above, have been met

Initial authorization, for the preventive treatment of migraine, is up to 6 months for ONE of the following doses:

- Aimovig dose of either 70 mg OR 140 mg once monthly
- Ajovy dose of either 225 mg monthly OR 675 mg every 3 months (quarterly)
- Emgality loading dose of 240 mg (month 1), followed by monthly doses of 120 mg
- Vyepti dose of either 100 mg or 300 mg every 3 months

Initial authorization, for cluster headache, is up to 3 months for the following dose:

- Emgality dose of 300 mg (three consecutive subcutaneous injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period

Calcitonin Gene-Related Peptide (CGRP) Inhibitors are considered medically necessary for continued use, for migraine headache, when the initial criteria are met and ONE of the following:

- Reduction in monthly migraine days or hours
- Reduction in days requiring acute migraine-specific treatment

Reauthorization for up to 12 months for migraine headache.

Reauthorization for up to 6 months cluster headache.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Calcitonin Gene-Related Peptide (CGRP) Inhibitors are considered experimental, investigational or unproven for ANY other use including the following:

- Concurrent use (for example, during the same time period) of two CGRP inhibitors indicated for the preventative treatment of migraine (for example, Aimovig, Ajovy, Emgality, Nurtec ODT and Vyepti)
- Preventive treatment of migraine in pediatric individuals

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications and Dosing

Product	FDA Approved Indication(s)	Recommended Dosing
Aimovig (erenumab-aooe)	The preventive treatment of migraine in adults.	The recommended dosage of Aimovig is 70 mg injected subcutaneously once monthly. Some patients may benefit from a dosage of 140 mg injected subcutaneously once monthly.
Ajovy (fremanezumab-vfrm)	The preventive treatment of migraine in adults.	Two subcutaneous dosing options of Ajovy are available to administer the recommended dosage: <ul style="list-style-type: none"> • 225 mg monthly • 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each.
Emgality (galcanezumab-gnlm)	<ul style="list-style-type: none"> • Preventive treatment of migraine in adults. • Treatment of episodic cluster headache in adults. 	<p>Recommended Dosing for Migraine The recommended dosage of Emgality is 240 mg (two consecutive subcutaneous injections of 120 mg each) once as a loading dose, followed by monthly doses of 120 mg injected subcutaneously.</p> <p>Recommended Dosing for Episodic Cluster Headache The recommended dosage of Emgality is 300 mg (three consecutive subcutaneous injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period.</p>
Vyepiti (eptinezumab-jjmr)	The preventive treatment of migraine in adults.	The recommended dosage is 100 mg administered by intravenous infusion every 3 months. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 3 months.

General Background

Disease Overview

Migraine is a common, chronic condition marked by paroxysmal, unilateral attacks of moderate-to-severe throbbing headache which is aggravated by routine physical activity (e.g., walking or climbing stairs) and associated with nausea, vomiting, and/or photophobia and phonophobia. Migraine headache episodes typically last 4 to 72 hours if untreated. Migraine affects approximately 15% of US adults. Migraine headaches usually begin in late childhood or early adolescence and are more common in preadolescent boys than girls. However, they become three times more common in adult women than men. Migraine has two major subtypes, migraine with aura and without aura. Migraine headache is preceded by aura in up to 30% of patients. Aura is typically characterized by any combination of visual, hemisensory, or language abnormalities, with the most common being visual. Visual aura symptoms include a flashing light or an enlarged blind spot rimmed with a shimmering edge or jagged lines in the peripheral vision. The associated headache usually occurs within 1 hour, but auras do not always progress to headache pain. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue, and neck stiffness and/or pain. Migraines have been defined as chronic or episodic. Chronic migraine is described by the International Headache Society as headache occurring on 15 days, or more, per month for at least 3 months and has the features of migraine headache on 8 or more days per month. Episodic migraine is characterized by headaches that occur less than 15 days/month. Patients with episodic migraine may transform to chronic migraine over time at a rate of about 2.5% of episodic-migraine patients/year. Potential strategies for preventing

migraine transformation include preventing and treating headaches, lifestyle modifications, or effective management of comorbidities (e.g., obesity, obstructive sleep apnea, depression, anxiety). Episodic migraine is more common than chronic migraine; however, chronic migraine is associated with a markedly greater personal and societal burden. (IHS, 2013; Lipton, 2015; MacGregor, 2017)

Cluster headache is the most common of the group of headache disorders known as the trigeminal autonomic cephalalgias, with a lifetime prevalence exceeding 1 in 1,000. Cluster headaches are associated with attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15 to 180 minutes. The headaches occur from once every other day to eight times a day. Cluster headache is considered among the most severe of the primary headache disorders because of extreme pain, associated autonomic symptoms, and high attack frequency. In addition, a large proportion of patients with cluster headache have chronic cluster headache, which features only brief or no remission periods, and may be particularly refractory to medical therapies. Patients with cluster headache are often suboptimally treated, even though treatment of cluster headache in accordance with guidelines is associated with better outcomes. (IHS, 2013; Robbins, 2016)

Professional Societies/Organizations

American Headache Society (AHS) and American Academy of Neurology (AAN)

An updated assessment of the preventive and acute treatment of migraine by the American Headache Society reaffirms previous migraine guidelines. Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (4 or more monthly headache days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. (AHS, 2019)

Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); and frovatriptan (for short-term preventive treatment of menstrual migraine). The following treatments are probably effective and should be considered for migraine prevention: antidepressants (amitriptyline, venlafaxine) and beta-blockers (atenolol, nadolol); and angiotensin receptor blockers (candesartan). (Silberstein, 2012)

Four injectable preventive therapies for migraine are mentioned in the AHS consensus statement: Botox and three monoclonal antibodies targeting calcitonin gene-related peptide (CGRP); erenumab, fremanezumab and galcanezumab-gnlm injection. The guidelines have not been updated to address Vyepti. The update notes that a CGRP inhibitor should only be initiated in patients who are diagnosed with migraine, have 4 or more migraine headache days per month, and have intolerance or inadequate response to 6-week trials of at least two traditional oral migraine preventive medications. Clinical judgment may result in an emerging treatment being added to one or more established treatments. If initiating treatment with a CGRP inhibitor in a patient already on a preventive treatment, it is appropriate to add the CGRP inhibitor to the existing regimen and make no other changes until the effectiveness of the CGRP inhibitor is determined since the risk of interactions between traditional oral migraine preventive medications and the CGRP inhibitors is minimal or nonexistent. Making a decision regarding continuation of therapy for a CGRP inhibitor requires a trial of the medication for at least 3 months, and treatment should be continued only if benefits can be documented during that time (for example, reduction in mean monthly headache days of at least 50% relative to the pretreatment baseline). Since migraine may improve or remit over time, it is important to reevaluate therapeutic response and, if possible, taper or discontinue treatment if patients no longer meet the criteria for offering preventive treatment. However, once control is established, the decision to discontinue or taper treatment should be a shared decision between patient and clinician. (AHS, 2019)

Another AAN guideline notes that onabotulinumtoxinA (Botox) is a treatment option to increase the number of headache-free days (Level A) and may be considered to reduce headache impact on health-related quality of life (Level B). AAN concludes that Botox is ineffective for episodic migraine (Level A) and tension-type headache (Level B). (Simpson, 2016)

Published evidence-based guidelines on the treatment of cluster headache recommend sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen for acute treatment. For prophylactic therapy, suboccipital steroid injection has been established as effective for the prophylactic therapy of episodic and chronic cluster headache (Level A). Lithium, verapamil, and melatonin are considered possibly effective for the prophylactic therapy of episodic and chronic cluster headache (Level C). Currently, there is insufficient evidence to make a recommendation for frovatriptan and prednisone (Level U). These guidelines have not been updated to include Emgality. (Robbins, 2016)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for Calcitonin Gene-Related Peptide (CGRP) Inhibitors.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for eptinezumab, erenumab, fremanezumab or galcanezumab.

Other Covered Uses

AHFS Drug Information 2020 Edition does not support any off-label uses of Aimovig, Ajovy or Emgality. AHFS Drug Information 2020 Edition does not have a monograph for Vyepti.

Experimental, Investigational, Unproven Uses

There is no data evaluating the safety and efficacy of the combined use of eptinezumab, erenumab, fremanezumab or galcanezumab and onabotulinumtoxinA for the prevention of episodic or chronic migraine. The phase 2 trial in chronic migraine with erenumab did not permit concurrent use of botulinum therapy during the trial or at least 4 months prior. (Tepper, 2017)

There is no published data evaluating the safety and efficacy of erenumab, fremanezumab or galcanezumab in pediatric individuals (under 18 years of age). Aimovig, Ajovy, Emgality and Vyepti are FDA approved for use in adults.

Coding/ Billing Information

Note: Erenumab-aooe, fremanezumab-vfrm and galcanezumab-gnlm are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

References

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