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Eptinezumab-jjmr

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Eptinezumab-jjmr (Vyepti®) **may be considered medically necessary** for the preventive treatment of individuals with episodic or chronic migraine who meet **ALL** of the following criteria:

- Individual is ≥ 18 years of age; AND
- Individual has ≥ 4 migraine headache days per month; AND
- Individual has failed a trial (e.g., not effective or not tolerated) from ≥ 3 classes of prophylactic pharmacologic therapies (e.g., antidepressants, anticonvulsants, and beta-blockers, if not contraindicated).

Eptinezumab-jjmr (Vyepti®) **is considered experimental, investigational, and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Eptinezumab-jjmr (Vyepti®) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) specific for calcitonin gene-related peptide (CGRP) ligand. It is indicated for the preventive treatment of migraines in adult patients.

Migraine Headache

Migraine is a headache disorder characterized by recurrent moderate to severe headaches with associated symptoms. Approximately 15% of the population have migraines, with a higher prevalence in women than in men. (2) The typical migraine headache is throbbing, unilateral, and aggravated by motion. Migraines are frequently associated with nausea, vomiting, photophobia, and phonophobia, although other neurological symptoms may occur. Migraine attacks can last from several hours to several days and are often preceded by transient neurological symptoms (e.g., visual disturbance) known as migraine aura.

Migraines are categorized as episodic or chronic depending on the frequency of attacks. Episodic migraine is defined as migraine or headache for less than 15 days per month and accounts for more than 90% of cases of migraine. Chronic migraine is defined as 15 or more headache days each month, of which at least 8 are migraine days.

Migraine was previously thought to be primarily vascular, but recent evidence suggests that sensitization of pain pathways in the central nervous system may be involved. (3) At least 3 messenger molecules are thought to be involved during migraine attacks: nitric oxide, 5-hydroxytryptamine, and calcitonin gene-related peptide (CGRP). CGRP is produced in both peripheral and central neurons and is a potent vasodilator. Some preclinical studies suggest that during a migraine, sensory neurons in the trigeminal ganglion release CGRP from their peripherally projecting nerve endings in the meninges.

Treatment

Symptomatic treatment is available for both migraine attacks and cluster headaches. Initial treatment for migraine is the use of oral pain relievers, but those with severe disease typically try multiple therapies, including both non-drug (e.g., exercise, diet, relaxation techniques) and drug therapies. Acute drug therapies, such as triptans, treat symptoms after they've started. For patients who experience more than 4 migraine days per month, preventive treatment may be recommended and include certain antidepressants, anti-seizure medications, beta-blockers, and, for those with chronic migraine, onabotulinum toxin A. Oral medications approved by the U.S. Food and Drug Administration (FDA) for migraine prophylaxis include topiramate, propranolol, timolol, and valproate. All of these medications have contraindications and side effects that limit their use. For many people, preventive therapies are not effective or have intolerable side effects.

This medical policy addresses the drug eptinezumab-jjmr, a humanized monoclonal antibody (mAb) that binds to the CGRP receptor or CGRP molecule and is designed for the prevention or treatment of migraine. Unlike oral drug therapy, mAbs are not metabolized by the liver and can remain in the body for weeks or months.

Regulatory Status

Eptinezumab-jjmr (Vyepti®) was approved by the U.S. FDA on February 22, 2020 as an intravenous infusion for the preventive treatment of migraines in adults. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for eptinezumab-jjmr (Vyepti®).

The efficacy of Vyepti was evaluated in three randomized, multicenter, placebo-controlled double-blind studies that enrolled patients with episodic and chronic migraine who were eligible for preventive treatment of migraine. (1) In Study 1, which included patients with episodic migraine, and Study 2, which included patients with chronic migraine, either 100 mg or 300 mg Vyepti was administered by intravenous infusion every 3 months. In Study 3, 100 mg VYEPTI was administered as a single intravenous infusion to patients with episodic or chronic

migraine who were eligible for preventive migraine treatment and who had a concurrent migraine.

Study 1: Episodic Migraine (1)

Study 1 (NCT02559895) included adults with a history of episodic migraine (4 to 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 (i.e., triptans, ergotamine derivatives), during the trial.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater, and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 39 years (range: 18 to 71 years), 84% were female, and 84% were White. The mean migraine frequency at baseline was approximately 8.6 migraine days per month and was similar across treatment groups.

Vyepti treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 1; secondary endpoints are also summarized in Table 1.

Table 1. Efficacy Endpoint Results in Study 1

	Vyepti 100 mg N=221	Vyepti 300 mg N=222	Placebo N=222
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-3.9	-4.3	-3.2
Difference from placebo	-0.7	-1.1	
<i>p</i> -value	0.018	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	49.8%	56.3%	37.4%
Difference from placebo	12.4%	18.9%	
<i>p</i> -value	0.009 ^a	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	22.2%	29.7%	16.2%
Difference from placebo	6.0%	13.5%	
<i>p</i> -value	NS ^b	<0.001	

^a Nominal statistical significance

^b NS: Not statistically significant

Patients treated with Vyepti at both doses had greater mean decreases from baseline in mean monthly migraine days over Months 1-3 compared to placebo-treated patients.

Study 2: Chronic Migraine (1)

Study 2 (NCT02974153) included adults with a history of chronic migraine (15 to 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 onabotulinumtoxinA). Patients with a dual diagnosis of chronic migraine and medication overuse headache attributable to acute medication overuse (triptans, ergotamine, or combination analgesics greater than 10 days per month) were included in the study population. Patients using opioids or butalbital-containing products greater than 4 days per month were not allowed.

The study excluded patients with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days over Months 1-3. Secondary endpoints included the percentages of patients with 50% or greater and 75% or greater reductions from baseline in monthly migraine days over Months 1-3.

Patients had a median age of 41 years (range: 18 to 65 years), 88% were female, and 91% were White. Forty-one percent of patients were taking concomitant preventive medication for migraine. The mean migraine frequency at baseline was approximately 16.1 migraine days per month and was similar across treatment groups.

Vyepti treatment demonstrated statistically significant improvements compared to placebo for the primary efficacy endpoint, as shown in Table 2; secondary endpoints are also summarized in Table 2.

Table 2. Efficacy Endpoint Results in Study 2

	Vyepti 100 mg N=356	Vyepti 300 mg N=350	Placebo N=366
Monthly Migraine Days (MMD) – Months 1-3			
Change from baseline	-7.7	-8.2	-5.6
Difference from placebo	-2.0	-2.6	
<i>p</i> -value	<0.001	<0.001	
≥50% MMD responders – Months 1-3			
% Responders	57.6%	61.4%	39.3%
Difference from placebo	18.2%	22.1%	

p-value	<0.001	<0.001	
≥75% MMD responders – Months 1-3			
% Responders	26.7%	33.1%	15.0%
Difference from placebo	11.7%	18.1%	
p-value	<0.001	<0.001	

Patients treated with Vyepti at both doses had greater mean decreases from baseline in mean monthly migraine days over Month 1-3 compared to placebo-treated patients.

Study 3: Episodic Migraine or Chronic Migraine Study 3 (NCT01719055) included adults who were candidates for preventive migraine therapy with Vyepti and presented with a concurrent moderate to severe migraine on the day of infusion. A total of 480 patients were randomized to receive 100 mg Vyepti (n=238) or placebo (n=242) as a single dose. Vyepti demonstrated statistically significant improvements in headache pain freedom at 2 hours (Vyepti 23.5% vs placebo 12%; $p<0.001$) and absence of most bothersome symptom (such as nausea, photophobia, or phonophobia) at 2 hours (Vyepti 55.5% vs placebo 35.8%; $p<0.001$) as compared to placebo. The dose of 300 mg Vyepti was not evaluated in Study 3.

Practice Guidelines and Position Statements

American Headache Society

The American Headache Society (AHS) published a position statement on integrating new migraine treatments into clinical practice in 2018; (4) an update to this statement was published in 2021. (5) The AHS provides comprehensive criteria for initiating treatment with monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP). Per the 2021 update, CGRP mAbs are recommended for the prevention of migraine in adults with either episodic or chronic migraine with an inability to tolerate (due to side effects) or inadequate response to an 8-week trial of ≥ 2 conventional pharmacologic treatments for migraine prevention with established efficacy (i.e., classified as having Level A ["Established as Effective"] or B [Probably Effective"] supportive evidence per the American Academy of Neurology [AAN]; see Table 3). Additional agents that are established as effective or probably effective per the 2021 AHS position statement include candesartan (established efficacy), lisinopril (probably effective), and memantine (probably effective). For patients with chronic migraine, CGRP mAbs are also recommended for patients with an inability to tolerate or inadequate response to a minimum of 2 quarterly injections (6 months) of onabotulinumtoxinA therapy. The 2021 position statement also provides criteria for continuation of CGRP mAbs after an initial trial (defined as 3 months for treatments administered monthly and 6 months [2 cycles of treatment] for treatments delivered quarterly). However, in their most recent position statement, AHS removed the qualifier for treatment as failure of previous therapies and recommend CGRP-targeting treatments as first-line therapy.

In 2024, AHS published a position statement specifically regarding therapies targeting CGRP for the prevention of migraine. (6) Within this position statement, AHS states that CGRP-targeting treatments, which include mAbs (erenumab, fremanezumab, galcanezumab, and eptinezumab) and gepants (rimegepant and atogepant), should be considered first-line agents for the

prevention of migraine along with previous first-line therapies without a requirement for prior failure of other classes of migraine preventive treatment. This updated consensus is based on the clinical trial evidence existing for CGRP-targeting treatments and its similar efficacy in indirect comparisons to topiramate. A head-to-head study of topiramate and erenumab found adherence to erenumab was significantly better than topiramate and found that erenumab was statistically superior in terms of efficacy. Additionally, AHS cites "real-world" experience as useful in confirming results of randomized controlled trials regarding efficacy, tolerability, and safety.

American Headache Society/American Academy of Neurology

In 2012, the AAN and the AHS published guidelines on therapies for migraine prevention. (7) Recommended pharmacologic treatments for episodic migraine prevention are described in Table 3. These guidelines were reaffirmed in 2022 and an update is in progress.

Table 3. Recommended Pharmacologic Treatments for Episodic Migraine Prevention

Class	Drugs	LOE	Recommendation
Antidepressants	Amitriptyline and venlafaxine	B	Probably Effective
Antiepileptics	Divalproex sodium, sodium valproate, and topiramate	A	Established as Effective
Beta-Blockers	Metoprolol, propranolol, and timolol	A	Established as Effective
	Atenolol and nadolol	B	Probably Effective
Triptans	Fovatriptan for MAMs	A	Established as Effective
	Naratriptan and zolmitriptan for MAMs	B	Probably Effective

LOE: level of evidence; MAM: menstrually associated migraines.

American College of Physicians

In a 2025 clinical guideline on the prevention of episodic migraine headache using pharmacologic treatments in outpatient settings, the American College of Physicians (ACP) offered the following recommendations: (8)

“Recommendation 1:

ACP suggests clinicians initiate monotherapy to prevent episodic migraine headache in non-pregnant adults in the outpatient setting by choosing one of the following pharmacologic treatments (conditional recommendation; low-certainty evidence):

- A beta-adrenergic blocker, either metoprolol or propranolol
- The antiseizure medication valproate
- The serotonin and norepinephrine reuptake inhibitor venlafaxine
- The tricyclic antidepressant amitriptyline.

Recommendation 2:

ACP suggests clinicians use monotherapy with a calcitonin gene-related peptide (CGRP) antagonist-gepant (atogepant or rimegepant) or a CGRP monoclonal antibody (eptinezumab, erenumab, fremanezumab, or galcanezumab) to prevent episodic migraine headache in nonpregnant adults in outpatient settings who do not tolerate or inadequately respond to a

trial or trials of a beta-adrenergic blocker (metoprolol or propranolol), the antiseizure medication valproate, the serotonin and norepinephrine reuptake inhibitor venlafaxine, or the tricyclic antidepressant amitriptyline (conditional recommendation; low-certainty evidence).

Recommendation 3:

ACP suggests clinicians use monotherapy with the antiseizure medication topiramate to prevent episodic migraine headache in nonpregnant adults in outpatient settings who do not tolerate or inadequately respond to a first trial or trials of a beta-adrenergic blocker (metoprolol or propranolol), the antiseizure medication valproate, the serotonin and norepinephrine reuptake inhibitor venlafaxine, or the tricyclic antidepressant amitriptyline and a further trial with a calcitonin gene-related peptide (CGRP) antagonist-gepant (atogepant or rimegepant) or a CGRP monoclonal antibody (eptinezumab, erenumab, fremanezumab, or galcanezumab) (conditional recommendation; low-certainty evidence)."

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3032

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA- Highlights of Prescribing Information: Vyepiti® (revised 10/2025). Available at <<https://www.accessdata.fda.gov>> (accessed February 4, 2026).

Other:

2. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. Apr 2018; 58(4):496-505. PMID 29527677
3. Mitsikostas DD, Reuter U. Calcitonin gene-related peptide monoclonal antibodies for migraine prevention: comparisons across randomized controlled studies. Curr Opin Neurol. Jun 2017; 30(3):272-280. PMID 28240610

4. American Headache Society. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. Headache. Jan 2019; 59(1):1-18. PMID 30536394
5. Ailani J, Burch RC, Robbins MS. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. Jul 2021; 61(7):1021-1039. PMID 34160823
6. Charles AC, Digre KB, Goadsby PJ, et al. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. Headache. Apr 2024; 64(4):333-341. PMID 38466028
7. Silberstein SD, Holland S, Freitag F, et al. yes. Apr 24 2012; 78(17):1337-1345. PMID 22529202
8. Qaseem A, Cooney TG, Etzeandia-Ikobaltzeta I, et al. Prevention of Episodic Migraine Headache Using Pharmacologic Treatments in Outpatient Settings: A Clinical Guidelines From the American College of Physicians. Ann Intern Med. Mar 2025; 178(3):426-433. PMID 39899861

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

Policy History/Revision	
Date	Description of Change
04/01/2026	Document updated. Coverage unchanged. Reference 1 updated; no new references added.
01/01/2026	Document updated. The following changes were made to Coverage: 1) Added "Individual has ≥ 4 migraine headache days per month"; 2) Modified criterion specific to trial/treatment failure; 3) Removed "Individuals may not use eptinezumab-jjmr (Vyapti®) in combination with other preventative CGRP therapies (e.g., Aimovig)"; and 4) Added "non-Food and Drug Administration approved" to experimental, investigational and/or unproven statement. Added/updated references 1 and 4-8.
01/01/2025	Document updated with literature review. The following change was made to Coverage: Added "non-calcitonin gene-related peptide (CGRP)" to "Migraine is refractory to at least two non-calcitonin gene-related peptide (CGRP) migraine prophylactic medications from different classes (e.g.,

	tricyclic antidepressants, anticonvulsants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, or calcium channel blockers); AND". Added references 1 and 2; others removed.
09/15/2023	Document updated with literature review. Coverage unchanged. Added reference 4; others updated.
07/01/2022	Reviewed. No changes.
11/15/2021	Document updated. The following change was made to Coverage: Removed onabotulinumtoxin A (Botox™) from statement on combination therapy.
04/15/2021	Document updated with literature review. The following change was made to Coverage: Modified statement on concurrent use to state: "Patients may not use eptinezumab-jjmr (Vyepti™) in combination with onabotulinumtoxin A (Botox™) for chronic migraine or with other preventative calcitonin gene-related peptide (CGRP) therapies (e.g., Aimovig)." No new references added.
11/15/2020	New medical document. Eptinezumab-jjmr (Vyepti™) may be considered medically necessary for the preventive treatment of individuals with migraine who meet all of the following criteria: individuals 18 years of age and older; and patient has been diagnosed with episodic migraine (defined as 4 to 14 headache days per month) or chronic migraine (defined as 15 or more headache days per month); and migraine is refractory to at least two migraine prophylactic medications from different classes (e.g., tricyclic antidepressants, anticonvulsants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, or calcium channel blockers); and patients may not use eptinezumab-jjmr (Vyepti™) in combination with onabotulinumtoxin A (Botox™) for chronic migraine or any other calcitonin gene-related peptide (CGRP) therapies. Eptinezumab-jjmr (Vyepti™) is considered experimental, investigational, and/or unproven for all other indications.