Policy Number	**RX501.124**
Policy Effective Date	**01/01/2025**
Policy End Date	**12/31/2025**

Eptinezumab-jjmr

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. 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 acceptable standards of medical practice. 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 HCSC 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 migraine who meet **all** of the following criteria:

- Individuals 18 years of age and older; **AND**
- Individual has been diagnosed with episodic migraine OR chronic migraine; **AND**
- 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**
- Individuals may not use eptinezumab-jjmr (Vyepti®) in combination with other preventative CGRP therapies (e.g., Aimovig).

Eptinezumab-jjmr (Vyepti®) **is considered experimental, investigational, and/or unproven** for all other 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.

Migraines
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. (1) The typical migraine 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. (2) At least 3 messenger molecules are thought to be involved during migraine attacks: nitric oxide, 5-hydroxytryptamine, and 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 migraine attacks. 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 eprinezumab-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 can remain in the body for weeks or months.

Regulatory Status

Eptinezumab-jjmr (Vyepti®) was approved by the U.S. Food and Drug Administration (FDA) on February 22, 2020 as an intravenous infusion for the preventive treatment of migraines in adults. (3)

Rationale

This policy was developed in 2020 and is based on the U.S. Food and Drug Administration (FDA) labeled indications as of August 27, 2024.

Eptinezumab-jjmr (Vyepti®) (3)

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: Episodic Migraine

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 2; secondary endpoints are also summarized in Table 2.

Table 2. 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	
p-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%	
p-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%	
p-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

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 3; secondary endpoints are also summarized in Table 3.

Table 3. 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	
p-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.

Summary of Evidence

Based in part on the clinical studies reviewed by the U.S. Food and Drug Administration (FDA), eptinezumab-jjmr (Vyepti®) may be considered medically necessary for the preventive treatment of individuals diagnosed with episodic migraine OR chronic migraine who are 18 years of age and older when 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 eptinezumab-jjmr (Vyepti™) is not used in combination with other preventative CGRP therapies (e.g., Aimovig). Eptinezumab-jjmr (Vyepti®) is considered experimental, investigational, and/or unproven for all other indications.

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®) ©2023 American Medical Association: Chicago, IL.

References

1. 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

2. 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
3. U.S. Food and Drug Administration. Drugs @ FDA. Highlights of Prescribing Information: Vyepti® (revised 10/2022). Available at <https://www.accessdata.fda.gov> (accessed August 27, 2024).

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
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 onabotuliniumtoxin 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 onabotuliniumtoxin 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 onabotuliniumtoxin 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.