Vyepti® (Eptinezumab-Jjmr)

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➲ Instructions for Use

Table of Contents **Page**

Application 1
Coverage Rationale 1
Applicable Codes 2
Background 4
Benefit Considerations 4
Clinical Evidence 4
U.S. Food and Drug Administration 5
Centers for Medicare and Medicaid Services 6
References 6
Policy History/Revision Information 6
Instructions for Use 7

Related Commercial Policy
- Provider Administered Drugs – Site of Care

Community Plan Policy
- Vyepti® (Eptinezumab-Jjmr)

Medicare Advantage Policy
- Medicare Part B Step Therapy Programs

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans

Coverage Rationale

➲ See Benefit Considerations

Migraine

Vyepti is proven for the preventive treatment of migraines when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of migraine consistent with The International Classification of Headache Disorders, 3rd edition;[4] **and**
  - **One** of the following:
    - **Both** of the following:
      - 4 to 7 migraine days per month; **and**
      - **One** of the following:
        - Less than 15 headache days per month; **or**
        - Provider attests this is the member's predominant headache diagnosis (i.e., primary driver of headaches is not a different, non-migrainous condition)

      or
    - Greater than or equal to 8 migraine days per month

    and
  - Medication will not be used in combination with another biologic CGRP antagonist or inhibitor used for the preventive treatment of migraines (e.g., Aimovig, Emgality, Nurtec ODT, Qulipta); **and**
  - Dosing is in accordance with the U.S. Food and Drug Administration (FDA)–approved labeling; **and**
  - Authorization will be issued for no more than 12 months
- For **continuation of therapy**, **all** of the following:

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- Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity; **and**
- Medication will not be used in combination with another biologic CGRP antagonist or inhibitor used for the preventive treatment of migraines (e.g., Aimovig, Emgality, Nurtec ODT, Qulipta); **and**
- Dosing is in accordance with the FDA-approved labeling; **and**
- Reauthorization will be issued for no more than 12 months

Vyepti is medically necessary for the preventive treatment of migraines when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of migraine consistent with The International Classification of Headache Disorders, 3rd edition;[4] **and**
  - **One** of the following:
    - **Both** of the following:
      - 4 to 7 migraine days per month; **and**
      - **One** of the following:
        - Less than 15 headache days per month; **or**
        - Provider attests this is the member's predominant headache diagnosis (i.e., primary driver of headaches is not a different, non-migrainous condition)

      or
    - Greater than or equal to 8 migraine days per month

    and
  - Trial and failure (after a trial of at least two months), contraindication, or intolerance to **two** of the following prophylactic therapies from the list below:
    - One of the following tricyclic antidepressants: amitriptyline (Elavil) or nortriptyline (Pamelor)
    - One of the following beta-blockers: atenolol, metoprolol, nadolol, propranolol, or timolol
    - Candesartan (Atacand)
    - Divalproex sodium (Depakote/Depakote ER)
    - OnabotulinumtoxinA (Botox) [trial of at least 2 quarterly injections (6 months)]
    - Topiramate (Topamax)
    - One of the following serotonin-norepinephrine reuptake inhibitors: duloxetine (Cymbalta) or venlafaxine (Effexor/Effexor XR)

    and
  - Trial and failure (after a trial of at least three months), contraindication, or intolerance to **two** of the following (for Medicare reviews, refer to the CMS section*) therapies used for the preventive treatment of migraines:
    - Aimovig (erenumab- aooe)
    - Emgality (galcanezumab-gnlm) (120 mg strength)
    - Nurtec ODT (rimegepant)
    - Qulipta (atogepant)

    and
  - Medication will not be used in combination with another biologic CGRP antagonist or inhibitor used for the preventive treatment of migraines (e.g., Aimovig, Emgality, Nurtec ODT, Qulipta); **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Authorization will be issued for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient has experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity; **and**
  - Medication will not be used in combination with another biologic CGRP antagonist or inhibitor used for the preventive treatment of migraines (e.g., Aimovig, Emgality, Nurtec ODT, Qulipta); **and**
  - Dosing is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be issued for no more than 12 months

Vyepti is unproven and not medically necessary for:

- Acute attack of migraine
- Episodic cluster headache

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and

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applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

HCPCS Code	Description
J3032	Injection, eptinezumab-jjmr, 1 mg

Diagnosis Code	Description
G43.001	Migraine without aura, not intractable, with status migrainosus
G43.009	Migraine without aura, not intractable, without status migrainosus
G43.011	Migraine without aura, intractable, with status migrainosus
G43.019	Migraine without aura, intractable, without status migrainosus
G43.101	Migraine with aura, not intractable, with status migrainosus
G43.109	Migraine with aura, not intractable, without status migrainosus
G43.111	Migraine with aura, intractable, with status migrainosus
G43.119	Migraine with aura, intractable, without status migrainosus
G43.401	Hemiplegic migraine, not intractable, with status migrainosus
G43.409	Hemiplegic migraine, not intractable, without status migrainosus
G43.411	Hemiplegic migraine, intractable, with status migrainosus
G43.419	Hemiplegic migraine, intractable, without status migrainosus
G43.501	Persistent migraine aura without cerebral infarction, not intractable, with status migrainosus
G43.509	Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
G43.519	Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
G43.601	Persistent migraine aura with cerebral infarction, not intractable, with status migrainosus
G43.609	Persistent migraine aura with cerebral infarction, not intractable, without status migrainosus
G43.611	Persistent migraine aura with cerebral infarction, intractable, with status migrainosus
G43.619	Persistent migraine aura with cerebral infarction, intractable, without status migrainosus
G43.701	Chronic migraine without aura, not intractable, with status migrainosus
G43.709	Chronic migraine without aura, not intractable, without status migrainosus
G43.711	Chronic migraine without aura, intractable, with status migrainosus
G43.719	Chronic migraine without aura, intractable, without status migrainosus
G43.801	Other migraine, not intractable, with status migrainosus
G43.809	Other migraine, not intractable, without status migrainosus
G43.811	Other migraine, intractable, with status migrainosus
G43.819	Other migraine, intractable, without status migrainosus
G43.821	Menstrual migraine, not intractable, with status migrainosus
G43.829	Menstrual migraine, not intractable, without status migrainosus
G43.831	Menstrual migraine, intractable, with status migrainosus
G43.839	Menstrual migraine, intractable, without status migrainosus
G43.901	Migraine, unspecified, not intractable, with status migrainosus
G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.911	Migraine, unspecified, intractable, with status migrainosus
G43.919	Migraine, unspecified, intractable, without status migrainosus
G43.A0	Cyclical vomiting, in migraine, not intractable
G43.A1	Cyclical vomiting, in migraine, intractable
G43.B0	Ophthalmoplegic migraine, not intractable
G43.B1	Ophthalmoplegic migraine, intractable

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Diagnosis Code	Description
G43.C0	Periodic headache syndromes in child or adult, not intractable
G43.C1	Periodic headache syndromes in child or adult, intractable
G43.D0	Abdominal migraine, not intractable
G43.D1	Abdominal migraine, intractable
G43.E01	Chronic migraine with aura, not intractable, with status migrainosus
G43.E09	Chronic migraine with aura, not intractable, without status migrainosus
G43.E11	Chronic migraine with aura, intractable, with status migrainosus
G43.E19	Chronic migraine with aura, intractable, without status migrainosus

Background

Vyepti is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

The PROMISE 1 (PRevention Of Migraine via Intravenous eptinezumab Safety and Efficacy 1) trial was a Phase 3 randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of eptinezumab for episodic migraine prevention. In the study, 888 patients were randomized to receive eptinezumab (300 mg, 100 mg or 30mg), or placebo administered by infusion once every 12 weeks. Inclusion criteria included patients that had experienced ≤ 14 headache days per month, of which at least four met the criteria for migraine. The primary endpoint was the mean change from baseline in monthly migraine days over the 12 week, double-blind treatment period. Eptinezumab achieved statistically significant reductions in monthly migraine days from baseline (8.6 days average) over weeks 1 through 12, was 4.3 monthly migraine days for the 300mg dose ($p = 0.0001$) and 3.9 days for 100mg ($p = 0.0179$) compared to an average 3.2 days for placebo. Patients experienced day 1 clinical benefit, with ≥ 50% reduction in the proportion of patients experiencing a migraine after the first administration. The observed safety profile in the study to date was similar to placebo. The authors concluded that eptinezumab (100 mg or 300 mg) significantly reduced migraine frequency, was well tolerated, and had an acceptable safety profile when used for the preventive treatment of migraine in adults with episodic migraine.

The PROMISE 2 trial was a Phase 3, randomized, double-blind, placebo-controlled global trial evaluating the safety and efficacy of eptinezumab for chronic migraine prevention. In the study, 1,072 patients were randomized to receive eptinezumab (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks. Inclusion criteria required patients have experienced at least 15 headache days per month, of which at least eight met criteria for migraine. Patients that participated in the trial had an average of 16.1 migraine days per month at baseline. The primary endpoint was the mean change from baseline in monthly migraine days over the 12 week, double-blind treatment period. Secondary study endpoints assessed through 12 weeks included reduction in migraine prevalence day 1 and days 1-28, reduction of at least 50%, 75%, and 100% from baseline in mean monthly migraine days, change from baseline in mean monthly acute migraine-specific medication days, and reductions from baseline in patient-reported impact scores on the Headache Impact Test (HIT-6). Compared to placebo, eptinezumab significantly reduced monthly migraine days by 8.2 days versus 5.6 days for placebo ($p < 0.0001$). Eptinezumab reduced migraine risk following the first administration, reducing the migraine risk by 52% compared to 27% for placebo ($p < 0.0001$). Through 12 weeks, eptinezumab demonstrated significant response rates: 61% of patients achieved at least 50% reduction in migraine days from baseline compared to 39% for placebo ($p < 0.0001$); 33% achieved 75% or greater reduction in migraine days from baseline compared to 15% with placebo ($p < 0.0001$); and 15% of patients on average for each month achieved a 100% reduction in migraine days, compared to 5% for placebo ($p < 0.0001$). Adverse event rates among eptinezumab-treated subjects were similar to placebo-treated subjects.

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Professional Societies

In 2025, the American College of Physicians (ACP) developed a clinical guideline for clinicians caring for adults with episodic migraine headache (defined as 1 to 14 headache days per month) in outpatient settings. All 3 ACP recommendations have conditional strength and low-certainty evidence:

- Recommendation 1: ACP suggests clinicians initiate monotherapy to prevent episodic migraine headache in nonpregnant adults in outpatient settings 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).

In 2024, the American Headache Society (AHS) published a position statement update regarding therapies targeting calcitonin gene-related peptide (CGRP) for the prevention of migraine. In this position statement, the AHS states that the CGRP-targeting migraine therapies are a first-line option for migraine prevention. Per AHS, the basis for this focused position statement is:

- There is solid human evidence that establishes CGRP as a fundamental mechanism of migraine and therefore establishes CGRP-targeting therapies as “migraine-specific” in contrast to all the other established therapies.
- The cumulative evidence for the efficacy, safety, and tolerability of CGRP-targeting therapies is significantly greater than that for any established migraine preventive therapy. The remarkable tolerability of the CGRP-targeting therapies is a particularly positive feature.
- Nearly all CGRP-targeting therapies are FDA-approved for the preventive treatment of both episodic and chronic migraine, which simplifies decision-making in patients who may spontaneously transition back and forth between episodic and chronic migraine.
- There are multiple categories of evidence supporting the use of CGRP-targeting therapies that do not exist for other migraine preventive therapies, including: responder rates, efficacy in patients with multiple prior treatment failures, efficacy in those with acute medication overuse, and those who do and do not have aura.
- There is one head-to-head study demonstrating the superiority of a CGRP-targeting therapy (erenumab) over an established migraine preventive therapy (topiramate). In addition, multiple studies indicating the efficacy of CGRP-targeting migraine preventive therapies in those who have previously failed multiple other established treatments provide indirect evidence of the superiority of CGRP-targeting therapies for some patients.
- Acknowledging CGRP-targeting therapies as first-line approaches will increase the likelihood that their efficacy and safety will be more thoroughly evaluated in understudied populations, particularly youth.
- Cost considerations regarding migraine therapies should include not only the direct cost of the treatments, but also the indirect costs of healthcare utilization and acute therapies, as well as socioeconomic costs for those who are disabled by the disease.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Vyepti is a calcitonin gene-related peptide antagonist indicated for 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.

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Centers for Medicare and Medicaid Services (CMS)

Coverage guidelines for certain Part B drugs may be found in the Medicare Advantage Medical Policy titled Medications/Drugs (Outpatient/Part B). National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. These NCDs/LCDs/LCAs are available at https://www.cms.gov/medicare-coverage-database/new-search/search.aspx.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that certain criteria are met, including that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

*Preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

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Policy History/Revision Information

Date	Summary of Changes

09/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added *Application* section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Coverage Rationale
	Individual Exchange Only
	• Revised coverage criteria:

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Date	Summary of Changes
	Proven ○ Removed criterion requiring: ▪ Trial and failure (after a trial of at least two months), contraindication or intolerance to two of the following prophylactic therapies from the list below: – One of the following tricyclic antidepressants: Amitriptyline (Elavil) or nortriptyline (Pamelor) – One of the following beta-blockers: atenolol, metoprolol, nadolol, propranolol, or timolol – Candesartan (Atacand) – Divalproex sodium (Depakote/Depakote ER) – OnabotulinumtoxinA (Botox) [trial of at least 2 quarterly injections (6 months)] – Topiramate (Topamax) – One of the following serotonin-norepinephrine reuptake inhibitors: duloxetine (Cymbalta) or venlafaxine (Effexor/Effexor XR) ▪ Trial and failure (after a trial of at least three months), contraindication, or intolerance to one of the following: – Aimovig (erenumab) – Emgality (galcanezumab) – Ajovy (fremanezumab) Medically Necessary ○ Replaced criterion requiring "trial and failure (after a trial of at least three months), contraindication, or intolerance to *one* of the following: Aimovig (erenumab), Emgality (galcanezumab), *Ajovy (fremanezumab)*" with "trial and failure (after a trial of at least three months), contraindication, or intolerance to *two* of the following *therapies used for the preventive treatment of migraines*: Aimovig (erenumab-*aooe*), Emgality (galcanezumab-*gnlm*) *(120 mg strength)*, *Nurtec ODT (rimegepant), Qulipta (atogepant)*" **Supporting Information** • Updated *Benefit Considerations*, *FDA, CMS,* and *References* sections to reflect the most current information • Archived previous policy versions 2025D0090M and IEXD0090.10

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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