BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Eptinezumab-jjmr (Vyepti™) **"Notification"**

File Name:	eptinezumab_vyepti
Origination:	5/2020
Last CAP Review:	10/2020
Next CAP Review:	10/2021
Last Review:	2/2021

Policy Effective May 18, 2021

Description of Procedure or Service

Eptinezumab-jjmr (Vyepti™) is a calcitonin gene-related peptide (CGRP) antagonist indicated for the preventative treatment of migraine in adult patients. Eptinezumab is a humanized monoclonal antibody that was approved by the U.S. Food and Drug Administration (FDA) in February 2020. It works by binding to CGRP ligand and blocking its binding to the receptor.

Migraine is a common disabling headache disorder characterized by recurrent moderate to severe headaches with associated symptoms. 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. At least three 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.

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 have begun. For patients who experience more than four migraine days per month, preventive treatment may be recommended and includes certain antidepressants, anti-seizure medications, beta-blockers, and, for those with chronic migraine, onabotulinum toxin A. Oral medications approved by the 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.

Related Medical Policies:
Botulinum Toxin Injection

Related Pharmacy Policies:

Eptinezumab-jjmr (Vyepti™) **"Notification"**

CGRP Therapy for Migraine

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for eptinezumab-jjmr (Vyepti™) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Eptinezumab-jjmr (Vyepti) is covered

Initial Therapy

Eptinezumab-jjmr (Vyepti) may be considered medically necessary for the preventative treatment of migraine in adults (≥ 18 years of age) when the following criteria are met:

1. The patient has been diagnosed with chronic migraine and over the last 3 months the patient has experienced both of the following:
    a. Greater than or equal to 15 headache days per month; and
    b. Greater than or equal to 8 migraine days per month; OR
2. The patient has been diagnosed with episodic migraine and over the last 3 months the patient has experienced the following:
    a. Less than or equal to 14 headache days per month of which at least 4 are migraine days; or
    b. Migraine attacks are attributed to a diminished quality of life despite the use of acute rescue medications; or
    c. The patient has contraindications to acute therapies; or
    d. The patient has tried and had an inadequate response to acute therapies; or
    e. The patient has serious side effects to acute therapies; or
    f. The patient is at risk of medication overuse headache without preventative therapy;

    AND

3. The patient has had an adequate trial* and was adherent to** at least two of the distinct categories of migraine prophylaxis treatment options (see Policy Guidelines) including:
    a. Beta blockers
    b. Antidepressants
    c. Anticonvulsants; OR
4. The patient has a clinical contraindication or intolerance to a beta blocker, antidepressant, and an anticonvulsant (see Policy Guidelines); AND
5. The patient has tried and had an inadequate response to both erenumab (Aimovig) AND galcanezumab (Emgality); OR
6. The patient has a clinical contraindication or intolerance to both erenumab (Aimovig) AND galcanezumab (Emgality) that is not expected to occur with eptinezumab; AND
7. The patient will not be starting therapy with a botulinum toxin agent and has not been treated with a botulinum toxin agent within the last 4 months; AND
8. Eptinezumab will not be used in combination with another calcitonin gene-related peptide (CGRP) receptor antagonist indicated for migraine prophylaxis (e.g., erenumab,

fremanezumab, galcanezumab); and if using another CGRP receptor antagonist, the patient will discontinue the other CGRP prior to starting eptinezumab; AND
9. The patient does not have other reasons to explain headache/migraine frequency including history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease; AND
10. If Vyepti 300 mg is requested, the patient has tried and had an inadequate response to the 100 mg strength.

* Adequate trial is defined by a minimum of 4-6 weeks for use of an agent.
**Adherence is defined as the proportion of days covered (PDC) to be 80 percent or greater over the trial period.

Initial authorization: 6 months

Continuation Therapy

Continuation of treatment with eptinezumab-jjmr (Vyepti) beyond 6 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the prevention of migraine when the following criteria are met:

1. The patient continues to meet initial criteria or would have met initial criteria at the time eptinezumab treatment was initiated; AND
2. The patient is using eptinezumab for prevention of migraine; AND
3. The patient has had a positive clinical response with eptinezumab treatment, demonstrated by a decrease from baseline in the number of migraine days per month or migraine frequency; AND
4. The patient has experienced a reduction in the need for migraine rescue medications (i.e. NSAIDs, triptans, ergot derivatives); AND
5. The patient will not be starting therapy with a botulinum toxin agent and has not been treated with a botulinum toxin agent within the last 4 months; AND
6. The patient is not using eptinezumab at the same time as another calcitonin gene-related peptide (CGRP) receptor antagonist indicated for migraine prophylaxis (e.g., erenumab, fremanezumab, galcanezumab); AND
7. If Vyepti 300 mg is requested, the patient has tried and had an inadequate response to the 100 mg strength.

When Eptinezumab-jjmr (Vyepti) is not covered

Eptinezumab-jjmr (Vyepti) is considered **investigational** and therefore not covered when the above criteria are not met, and for all other indications not listed above.

Policy Guidelines

International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine headache include the following:

Headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has the features of migraine headache.

Episodic migraine is described as migraine with or without aura occurring in a headache pattern or <14 days per month.

Features of migraine headache:

- Headache lasts 4 to 72 hours (when untreated or unsuccessfully treated);
- Headache has at least 2 of the following 4 characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
  - Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- During headache, at least one of the following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia

(In ICHD-2, absence of medication overuse was one of the diagnostic criteria for chronic migraine. In the ICHD-3, this criterion was removed from the chronic migraine diagnosis and "medication overuse headache" is now a separate diagnostic category.)

Recommended Pharmacological Treatments for Episodic Migraine Prevention

Antidepressants (amitriptyline, venlafaxine)
Anticonvulsants (divalproex sodium, sodium valproate, topiramate)
Beta-Blockers (atenolol, metoprolol, nadolol, propranolol, timolol)

Botulinum toxin is an approved treatment for prevention of migraine headache. Evidence is lacking to support combination treatment with botulinum toxin and monoclonal antibodies for calcitonin gene-related peptide.

Dosing and Administration

The recommended dose for Vyepti is 100 mg administered as an intravenous infusion over approximately 30 minutes every 3 months. Some patients may benefit from a dose of 300 mg every 3 months.

According to the manufacturer's safety labeling, Vyepti can cause hypersensitivity reactions to include angioedema, urticaria, facial flushing, and rash. Discontinuation of Vyepti should be considered if a hypersensitivity reaction occurs, and appropriate treatment initiated.

Clinical Trial Evidence

The efficacy of eptinezumab was assessed for the prevention of episodic (PROMISE-1; NCT02559895) and chronic (PROMISE-2; NCT02974153) migraine in two randomized, placebo-controlled, multicenter clinical trials, each with 6-month double-blind periods. In each trial, eptinezumab was administered as an intravenous infusion every 3 months, with the primary endpoint measured at 12 weeks.

Episodic Migraine:

Adult patients with a history of episodic migraine (4 to 14 headache days per month, of which at least 4 were migraine days) were included in the PROMISE-1 trial. A total of 665 patients were randomized 1:1:1 to receive eptinezumab 100mg (n=221), eptinezumab 300mg (n=222), or placebo (n=222) every 3 months for 12 months. Patients enrolled in the study were permitted to use concurrent acute migraine or headache medications during the trial, to include migraine-specific medications (i.e., triptans, ergot derivatives). Patients were excluded with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease. The mean migraine frequency at baseline was approximately 8.6 migraine days per month across treatment groups. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over 3 months with eptinezumab 100mg and

300mg compared to placebo (100mg, -3.9 days, p=0.0182; 300mg, -4.3 days; placebo, -3.2 days, p=0.0001). In adult patients with episodic migraine, eptinezumab 100mg and 300mg significantly decreased monthly migraine days at 12 weeks compared with placebo in adults with episodic migraine.

Chronic Migraine:

Adult patients with a history of chronic migraine (15 to 26 headache days per month, of which at least 8 were migraine days) were included in the PROMISE-2 trial. A total of 1072 patients were randomized 1:1:1 to received eptinezumab 100mg (n=356), eptinezumab 300mg (n=350), or placebo (n=366) every 3 months for 6 months. Patients enrolled in the study were permitted to use and continue an established stable acute migraine or headache preventative medication regimen (except onabotulinumtoxin A). Patients with a dual diagnosis of chronic migraine and medication overuse headache attributable to acute medication overuse (triptans, ergot derivatives, or combination analgesics > 10 days per month) were also permitted. However, patients using opioids or butalbital-containing products for greater than 4 days per month were not allowed in the study. Patients were excluded with a history of cardiovascular disease (hypertension, ischemic heart disease), neurological disease, or cerebrovascular disease. The mean migraine frequency at baseline was approximately 16.1 migraine days per month across treatment groups. The primary efficacy endpoint was the change from baseline in mean monthly migraine days over 3 months with eptinezumab 100mg and 300mg compared to placebo (100mg, -7.7 days, p<0.0001 vs placebo; 300mg, -8.2 days, p<0.0001 vs placebo; placebo, -5.6 days). In adults with chronic migraine, eptinezumab 100mg and 300mg significantly decreased the mean monthly migraine days (MMDs) at 12 weeks compared with placebo.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J3032*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Lundbeck Seattle BioPharmaceuticals, Inc. Vyepti (eptinezumab-jjmr) injection for intravenous use. Highlights of prescribing information. February 2020. Available at: https://www.lundbeck.com/upload/us/files/pdf/Products/Vyepti_PI_US_EN.pdf. Last accessed May 2020.

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Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep (2012) 16:86-92. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3258393/pdf/11916_2011_Article_233.pdf. Last accessed May 2020.

Headache Classification Committee of the International Headache Society (HIS). The International Classification of Headache Disorders; 3rd edition. Cephalalgia. 2018 Jan;38(1):1-211. Available at: https://journals.sagepub.com/doi/pdf/10.1177/0333102417738202. Last accessed May 2020.

Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012 Apr 24;78(17):1337-45. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335452/. Last accessed May 2020.

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Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1468-1331.2009.02748.x. Last accessed May 2020.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.29, 12/12/2019

Medical Director review 5/2020

Medical Director review 6/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel 10/2020

Policy Implementation/Update Information

5/12/20 New policy developed. Vyepti may be considered medically necessary for the preventative treatment of migraine in adults (≥ 18 years of age) when specified medical criteria and guidelines are met. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 5/2020. (krc)

6/9/20 Under "When Covered," added the following clarification to initial and continuation sections: "CGRP antagonist indicated for migraine prophylaxis" to clarify intent to allow for concomitant use of one CGRP indicated for acute migraine treatment and one CGRP indicated for migraine prophylaxis. Medical Director review 6/2020. (krc)

6/30/20 Added HCPCS code C9063 to Billing/Coding section effective 7/1/2020. (krc)

9/22/20 Under "When Covered" section, added the following: "The patient has tried and had an inadequate response to both erenumab (Aimovig) AND galcanezumab (Emgality); OR The patient has a clinical contraindication or intolerance to both erenumab (Aimovig) AND galcanezumab (Emgality) that is not expected to occur with eptinezumab; AND".

Medical Director review 7/2020. **Notification given 9/22/2020 for effective date 11/24/2020**. (krc)

10/1/20 Added HCPCS code J3032 to Billing/Coding section effective 10/1/2020 and deleted codes C9063, C9399, J3490, J3590 termed 9/30/2020. **Policy remains on notice for effective date 11/24/2020**. (krc)

11/24/20 Specialty Matched Consultant Advisory Panel review 10/21/2020. No change to policy intent. (krc)

3/9/21 Updated initial authorization length to 6 months. Added the following criteria to initial and continuation sections of "When Covered" section: "If Vyepti 300 mg is requested, the patient has tried and had an inadequate response to the 100 mg strength." **Notification given 3/9/2021 for effective date 5/18/2021**. (krc)