Injectable CGRP Antagonists

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Injectable CGRP Antagonist drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Aimovig (erenumab), Ajovy (fremanezumab), and Emgality (galcanezumab) are the first Food and Drug Administration (FDA) approved Calcitonin Gene-Related Peptide (CGRP) Antagonists indicated for preventive treatment of migraine in adults.

POLICY

Initial Criteria for Approval

A. Aimovig (erenumab), Ajovy (fremanezumab), and Emgality (galcanezumab) may be considered medically necessary for the preventive treatment of chronic migraine in patients 18 years of age and older when ALL of the following criteria are met:
    1. The patient has a diagnosis of chronic migraine defined as a headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has features of a migraine headache
    2. The patient has had a trial of at least TWO of the listed medications from any of the following migraine prophylactic agent classes and or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
        a.) Anticonvulsants (divalproex sodium, sodium valproate, topiramate)
        b.) Beta blockers (atenolol, metoprolol, nadolol, propranolol, timolol)
        c.) Antidepressants (amitriptyline, nortriptyline, venlafaxine)

3. The patient had an adequate trial of both migraine prophylaxis agents as defined by BOTH of the following unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR the patient is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    a.) The trial length was at least 8 weeks at maximum tolerated dose
    b.) The patient was adherent to the prophylaxis agent during the trial
4. The patient has been evaluated for and does not have medication overuse headache (see Appendix B)
5. Other conditions or aggravating factors that are contributing to the development of chronic migraine headaches are being treated when applicable (e.g. dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
6. The patient has not been receiving botulinum toxin injection for headache prophylaxis or plans to discontinue treatment with botulinum toxin injection once therapy with the requested medication has started **AND** will not be initiating botulinum toxin injection for headache prophylaxis while receiving the requested medication.
7. The requested medication will not be used in combination with another CGRP antagonist or inhibitor [e.g., Vyepti (eptinezumab), Nurtec ODT (rimegepant), and Ubrelvy (ubrogepant)]

Approval will be for **3 months**

B. Aimovig (erenumab), Ajovy (fremanezumab), and Emgality (galcanezumab) may be considered medically necessary for the preventive treatment of episodic migraine in patients 18 years of age and older when ALL the following criteria are met:
    1. The patient has a diagnosis of episodic migraine defined as at least 4 and fewer than 15 migraine days per month and fewer than 15 headache days per month on average during the previous 3-month period
    2. The patient has had a trial of at least TWO of the listed medications from any of the following migraine prophylactic agent classes and experienced an inadequate response, has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
        a.) Anticonvulsants (divalproex, valproate, topiramate)
        b.) Beta blockers (atenolol, metoprolol, nadolol, propranolol, timolol)
        c.) Antidepressants (amitriptyline, nortriptyline, venlafaxine)
    3. The patient had an adequate trial of both migraine prophylaxis agents as defined by BOTH of the following unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the alternative migraine prophylactic agents, OR the patient is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
        a.) The trial length was at least 8 weeks at maximum tolerated dose
        b.) The patient was adherent to the prophylaxis agent during the trial
    4. The patient has been evaluated for and does not have medication overuse headache (see Appendix B)
    5. Other conditions or aggravating factors that are contributing to the development of episodic migraine headaches are being treated when applicable (e.g. dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
    6. The requested medication will not be used in combination with another CGRP antagonist or inhibitor [e.g., Vyepti (eptinezumab), Nurtec ODT (rimegepant), and Ubrelvy (ubrogepant)]

Approval will be for **3 months**

C. Emgality (galcanezumab) may be considered medically necessary for the preventive treatment of episodic cluster headache in patients 18 years of age and older when ALL of the following criteria are met:
   1. The patient has a diagnosis of episodic cluster headache defined as severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes, untreated, occurring at least every other day and up to eight times per day (see Appendix A). .
   2. The patient has been evaluated for and does not have medication overuse headache (see Appendix B)

Approval will be for **3 months**

Continuation of Therapy

A. Aimovig (erenumab), Ajovy (fremanezumab) and Emgality (galcanezumab) may be considered medically necessary for the continuation of preventive treatment of chronic migraine or episodic migraine in adults when ALL of the following criteria are met:
   1. The patient's condition has responded to therapy as defined by ONE of the following:
      a.) The patient has achieved or maintained a 50% reduction in monthly headache frequency or severity with requested medication since starting therapy with medical records that support such benefit
      OR
      b.) The patient has had a reduction in headache frequency and/or severity resulting in an improvement in productivity and attendance at school or work since starting therapy with requested medication with medical records that support such benefit
   2. The patient has had a reduction in the number of days of use of acute migraine-specific medications from baseline with medical records that support such benefit
   3. The patient has been evaluated for and does not have medication overuse headache (see Appendix B)
   4. Other conditions or aggravating factors that are contributing to the development of migraine headaches are being treated when applicable (e.g. dental or jaw problems, muscle tension, depression, fibromyalgia, sleep disorders and smoking)
   5. The patient has not been receiving botulinum toxin injection for headache prophylaxis **AND** will not be initiating botulinum toxin headache prophylaxis while using the requested medication
   6. The requested medication will not be used in combination with another CGRP antagonist or inhibitor [e.g., Vyepti (eptinezumab), Nurtec ODT (rimegepant), and Ubrelvy (ubrogepant)]

Approval will be for **12 months**

B. Emgality (galcanezumab) may be considered medically necessary for the continuation of preventive treatment of episodic cluster headache in adults when ALL of the following criteria are met:
   1. The patient's condition has responded to therapy as defined by ONE of the following:
      a.) The patient has achieved or maintained a 50% reduction in weekly cluster headache attack frequency or severity with requested medication since starting therapy with medical records that support such benefit
      OR
      b.) The patient has had a reduction in headache frequency and/or severity resulting in an improvement in productivity and attendance at school or work since starting therapy with requested medication with medical records that support such benefit

2. The patient has had a reduction in the number of days of use of acute medications from baseline with medical records that support such benefit
3. The patient has been evaluated for and does not have medication overuse headache (see Appendix B)

Approval will be for **12 months**

Prior approval is required. Submit a prior approval/treatment request now.

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

- Aimovig 70 mg/mL autoinjector – 1 per 28 days
- Aimovig 140 mg/mL autoinjector – 1 per 28 days
- Ajovy (fremanezumab) 225mg/1.5mL prefilled syringe – 3 syringes/90 days
- Emgality (galcanezumab) 120mg/mL prefilled syringe/pen - 1 autoinjector/28 days
- Emgality (galcanezumab) 100 mg/mL prefilled syringe/pen - 3 autoinjectors/28 days

Appendix

Appendix A

International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for cluster headache

A. At least five attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[1]
C. Either or both of the following:
    1. at least one of the following symptoms or signs, ipsilateral to the headache:
        - – conjunctival injection and/or lacrimation
        - – nasal congestion and/or rhinorrhea
        - – eyelid edema
        - – forehead and facial sweating
        - – miosis and/or ptosis
    2. a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and 8 per day[2]
E. Not better accounted for by another ICHD-3 diagnosis.

Notes

1. During part, but less than half, of the active time-course of 3.1 *Cluster headache*, attacks may be less severe and/or of shorter or longer duration.
2. During part, but less than half, of the active time-course of 3.1 *Cluster headache*, attacks may be less frequent.

Appendix B

International Classification of Headache Disorders (ICHD-3 beta) diagnostic criteria for medication-overuse headache

A. Headache present on >15 days/month
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Headache has developed or markedly worsened during medication overuse
D. One of the following:
    1. Regular intake of ergotamine on ≥10 days per month for >3 months

2. Regular intake of one or more triptans, in any formulation, on ≥10 days per month for >3 months
3. Regular intake of Aspirin on ≥15 days per month for >3 months
4. Regular intake of one or more NSAIDs other than acetylsalicylic acid on ≥15 days per month for >3 months
5. Regular intake of one or more opioids on ≥10 days per month for >3 months
6. Regular intake of acetaminophen on ≥15 days per month for >3 months
7. Regular intake of one or more combination analgesic medications on ≥10 days/month for >3 months
8. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs and/ or opioids on ≥10 days per month for >3 months
9. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs and/or opioids1 on a total of ≥10 days per month for >3 months without overuse of any single drug or drug class alone
10. Regular overuse, on ≥10 days per month for >3 months, of one or more medications other than those described above, taken for acute or symptomatic treatment of headache

CLINICAL RATIONALE

Migraine is a chronic neurological disease that ranks as the second most disabling neurological condition globally in terms of years lost to disability as attacks can significantly impair functional ability at work or school, at home, and in social situations. It involves recurrent attacks of moderate to severe throbbing, often unilateral, head pain and may be associated with nausea, vomiting and sensitivity to light, sound and odors. Diagnoses is based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs). Based on the International Classification of Headache Disorders (ICHD)-3 criteria for Episodic and Chronic Migraine, patients with fewer than 15 MMDs or MHDs have episodic migraine and those with at least 15 MHDs, of which at least 8 are MMDs, have chronic migraine. See Appendix for full ICHD-3 diagnostic criteria.

The severity, frequency, and characteristics of migraine vary among persons resulting in varying treatments that may include acute treatments, preventive treatments, or both. According to the American Headache Society (AHS), a process of trial and error is often necessary before treatment can be optimized with preventive treatments being part of the overall approach for a proportion of people with migraine while avoiding the overuse of acute medications. And typically, those patients with migraine featuring severe, disabling, or frequent attacks, as well as those who cannot tolerate or are nonresponsive to acute treatment, are candidates for preventive therapy.

The use of evidence-based treatments is important to migraine prevention success per AHS. The American Academy of Neurology (AAN) has evaluated the level of evidence for efficacy for preventive migraine medications with antiepileptic drugs (divalproex sodium, valproate sodium, topiramate) and beta-blockers (metoprolol, propranolol, timolol) having established efficacy and antidepressants (amitriptyline, venlafaxine) and beta-blockers (atenolol, nadolol) having probable efficacy. AHS also recommends to give oral preventive treatments an adequate trial of at least 8 weeks at a target or usual effective dose to optimize the possibility of a therapeutic response. If there is no response to treatment after 8 weeks trial, then switching preventive treatments is recommended. If patients have a partial response, they should be counseled that cumulative benefits may occur over 6-12 months of continued use. Any of the following can define the success of migraine prevention: 1) 50% reduction in the frequency of days with headache or migraine 2) significant decrease in attack duration as defined by the patient 3) Significant decrease in attack severity as defined by the patient 4) Improved response to acute treatment 5) Reduction in migraine-related disability and improvements in functioning in important areas of life 6) Improvements in health related quality of life and reduction in psychological distress due to migraine.

Efficacy

In 2018, the FDA approved three parenteral therapies targeting calcitonin gene-related peptide (CGRP). Aimovig (erenumab), Ajovy (fremanezumab), and Emgality (galcanezumab) are indicated for the preventive treatment of migraines in adults. However, the approval was based on phase 2 and phase 3 randomized, placebo-controlled trials demonstrating efficacy and safety in patients with episodic and chronic migraine, not all migraine, with effects occurring over days to weeks in those who have failed prior preventive treatments as well as in those on concurrent oral preventive treatments. The below table summarizes the efficacy of the CGRP antagonists along with other prophylactic agents.

Table 1: Summary of Efficacy of Migraine Prophylactic Agents* Agent

Agent	Reduction in Migraine at 12 weeks (placebo-adjusted reduction per month)		≥ 50% Reduction in Migraine at 12 weeks (placebo-adjusted)	
	EM	**CM**	**EM**	**CM**
Aimovig (erenumab)	1 day to 1.9 days	2.5 days	OR 1.59 to 2.81	OR 2.2 to 2.3
Ajovy (fremanezumab)	1.3 to 1.5 days	1.7-1.8 days	OR 1.7 to 1.9	OR 1.8 to 2.3
Emgality (galcanezumab)	1.8 to 2 days	1.9 to 2.1 days	OR 2.2 to 2.4§	OR 1.6 to 1.8
Botox (onabotulinumtoxinA)	No significant reduction	2.3 attacks	No risk reduction	RR 2.21
topiramate‡	0.99 attacks to 1.20 attacks	1.7 days	RR 1.2 to 2.02	Not available
divalproex‡	1.5 attacks	Not available	RR 2.1 to 2.18	
propranolol‡	1.3 attacks		RR 2.1	
timolol‡	1.7 attacks		RR 1.9	

* All data presented in this table are of Evidence level Ib from randomized, controlled trials or Evidence level Ia from pairwise meta-analyses; doses included in the analyses are generally within the range of the approved doses for migraine prophylaxis
§ Reduction in Migraine at 6 months
‡ Data for oral prophylactic agents were available mostly in patients with fewer monthly migraines or EM
CM = chronic migraine
EM = episodic migraine
Evidence level Ia = meta-analysis
Evidence level Ib = randomized, controlled trial
OR = odds ratio
RR = risk ratio
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Safety

CGRP antagonists were generally well tolerated during clinical trials with the most commonly reported adverse effects pertaining to injection-site pain or reactions in up to 30% of patients. Nasopharyngitis and upper respiratory tract infection were reported in less than 12% of patients.

CGRP and Botox (onabotulinumtoxinA)

Clinical trials for CGRP antagonists excluded the use of Botox (onabotulinumtoxinA). This was likely due to the trial design to ensure outcomes measured were reflective of the drug being studied and not another therapy. The combination of a CGRP antagonist and Botox is not contraindicated but the safety and efficacy has also not been studied. There is no evidence demonstrating an additive effect when combining Botox and a CGRP antagonist nor is there evidence of the safety of the combination therapy. Due to the high cost of dual therapy with both treatments, unknown long-term safety, and no evidence demonstrating that dual therapy is more efficacious than monotherapy, combination therapy with a CGRP antagonist and Botox is not covered.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J3031 - Injection, fremanezumab-vfrm, Ajovy, 1 mg

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POLICY HISTORY

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