Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO025

Description

Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) are subcutaneous injections of monoclonal antibodies that bind to the calcitonin gene-related peptide (CGRP) receptor or ligand. Rimegepant (Nurtec ODT) and atogepant (Qulipta) are orally administered CGRP receptor antagonists.

Length of Authorization

- Initial:
  - **rimegepant (Nurtec ODT)**
    - at a quantity less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine): 12 months
    - at a quantity of 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity): Six months
  - **All other agents**
    - Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
erenumab (Aimovig)	Migraine prophylaxis	70 mg/1 mL autoinjector	1 mL/30 days
		140 mg/1 mL autoinjector	
galcanezumab (Emgality)	Migraine prophylaxis	120 mg/1 mL autoinjector	**Initial:** 2 mL (240 mg)/30 days for one fill **Maintenance:** 1 mL (120mg)/30 days
		120 mg/1 mL prefilled syringe	
	Episodic cluster headache	100 mg/1 mL prefilled syringe	3 mL/30 days
fremanezumab (Ajovy)	Migraine prophylaxis	225 mg/1.5 mL prefilled syringe	1.5 mL/30 days **OR** 4.5 mL per 90-day supply
		225 mg/1.5 mL autoinjector	
rimegepant (Nurtec ODT)	Acute migraine treatment Migraine prophylaxis	75 mg orally disintegrating tablet	8 tablets/30 days
			16 tablets/30 days
atogepant (Qulipta)	Migraine prophylaxis	10 mg tablet	30 tablets/30 days
		30 mg tablet	
		60 mg tablet	

Initial Evaluation

Migraine

I. **Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), and atogepant (Qulipta)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of migraine; **AND**
   B. The member is 18 years of age or older; **AND**
   C. Medications in this policy will not be used in combination with each other (exception: rimegepant (Nurtec ODT) at a dose of less than or equal to 8 tablets per 30 days); **AND**
   D. Medication overuse headache has been ruled out as the cause of, or as an aggravating contributor to, the member's migraines or cluster headaches; **AND**
   E. The provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; **AND**
   F. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently with any agent in this policy (with the exception of rimegepant (Nurtec ODT) at a dose of less than, or equal to, 8 tablets per 30 days); **AND**
   G. The member has a history of four or more monthly migraine days; **AND**
   H. The member has experienced migraine for one year or longer; **AND**
   I. The member has tried and failed, or is intolerant to, prophylactic therapy with at least one specified agent listed in each of the following groups: (Note, if a class of agents is contraindicated, a trial and failure of at least three agents from the remaining groups is required.):
      1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
      2. Group 2: amitriptyline, venlafaxine
      3. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
   J. The patient has tried each of the prophylactic therapies at therapeutic doses for at least three months **OR** the member is intolerant of the therapies; **AND**
   K. Fremanezumab (Ajovy) is being requested; **OR**
      1. Treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated

II. **Rimegepant (Nurtec ODT)** may be considered medically necessary when the following criteria below are met:
   A. The request is for less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine); **AND**
      1. Member is 18 years of age or older; **AND**
      2. Two serotonin 5-HT1 receptor agonists (i.e., sumatriptan, naratriptan, rizatriptan) have been ineffective, contraindicated, or not tolerated; **OR**

B. The request is for 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity); **AND**
    1. Criteria I(A)-I(K) above are met

Cluster Headache Prophylaxis

III. Galcanezumab (Emgality) may be considered medically necessary when the following criteria are met:
    A. Diagnosis of cluster headache; **AND**
    B. The provider attests the diagnosis is confirmed using the International Classification of Headache Disorders (ICHD) criteria for cluster headache; **AND**
    C. The member has had an adequate prophylactic therapy trial and failure (considered to be one month or longer), contraindication, or intolerance to verapamil **and** lithium concurrently or consecutively. (Note, if one is contraindicated, a trial of the other is required.)

IV. Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), rimegepant (Nurtec ODT), and atogepant (Qulipta) are considered investigational when used for all other conditions, including but not limited to:
    A. Use in combination with onabotulinum toxin (e.g., Botox, etc.), with the exception of rimegepant (Nurtec ODT) at a dose of 8 tablets per 30 days
    B. Chronic cluster headache
    C. Episodic cluster headache, with the exception of galcanezumab (Emgality)
    D. Post-traumatic headache
    E. Pediatric headache or migraine
    F. Vasomotor symptoms or hot flashes
    G. Fibromyalgia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
    A. **Diagnosis of migraine**; **AND**

1. Request is for erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), atogepant (Qulipta), or for 9-16 tablets per 30 days of rimegepant (Nurtec ODT); **AND**
    i. The medications in this policy will not be used in combination with each other; **AND**
    ii. The provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; **AND**
    iii. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently; **AND**
    iv. The member has experienced a response to therapy, defined by a reduction of at least two migraine days per month compared to baseline upon first renewal; **OR**
        a. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; **AND**
    v. Fremanezumab (Ajovy) is being requested; **OR**
        a. Treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated; **OR**
2. Request is for less than, or equal to, 8 tablets per 30 days of rimegepant (Nurtec ODT); **AND**
    i. The member has experienced a response to therapy (e.g., reduction in symptoms, severity, or duration of migraine)

B. **Diagnosis of episodic cluster headache**; **AND**
1. The request is for galcanezumab (Emgality) only; **AND**
2. The member has experienced a response to therapy, defined by one of the following:
    i. A reduction in four weekly cluster headache attacks compared to baseline; **OR**
    ii. A complete reduction resolution of attacks (e.g., the member has a baseline of 3-4 attacks per week); **AND**
3. Provider attests the member continues to need therapy for cluster headache (i.e., the cluster period has not passed, or a trial of therapy taper has been attempted and was unsuccessful).

Supporting Evidence

I. There is a lack of safety and efficacy data in pediatrics; however, as of July 2019, clinical trials were underway for injectable CGRP agents in pediatrics.

II. There is lack of safety and efficacy data when CGRP agents are used concurrently. At acute dosing regimens, use of CGRP oral agents in combination with injectables for prophylaxis can be allowed given contraindications and tolerability challenges with triptans. Higher or frequent oral acute doses in combination with injectable CGRPs is not allowed. Combination use shall NOT be granted, nor should quantity exceptions. Historical studies of agents effecting CGRP have failed in clinical trials due to significant hepatotoxic safety concerns. The safety profile of increased CGRP inhibition is unknown with considerable safety risks at this time.

III. Prophylactic dosing of oral and/or injectable CGRPs should not be used in combination with onabotulinum toxin (e.g., Botox, etc.), due to the rationale listed in II. Onabotulinum toxin products have been shown, in part, to play a role in CGRP. The safety profile of combination therapy is unknown at this time with potential significant safety concerns. Additionally, efficacy of combination has not been established in any clinical trials to date or real-world data. Overuse of migraine therapies, acute or prophylactic, may result in medication overuse headache and often results in a prescribing cascade. If adequate reduction in migraine is not achieved from one therapy, it should be discontinued. Another therapy should be initiated after a washout period to ensure the member and provider are realizing baseline migraine frequency and severity.

Acute Migraine Treatment:

IV. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. To which, triptans have an established safety and efficacy profile for the abortive treatment of migraine. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Triptans are not indicated for the continual prophylactic treatment of migraine.

Migraine Prophylaxis:

V. In the pivotal trials for the agents listed in this policy, members had a history of four or more monthly migraine days for at least one year. Migraines may have numerous causes and triggers and may be transient in nature; thus, a strong history of migraine is warranted prior to consideration of coverage for CGRP agents.

VI. Medication overuse headache (MOH) is a chronic daily headache or migraine secondary to acute medication in headache prone patients. In general, MOH presents in patients that use analgesics more than two to three days per week. Often, MOHs are refractory to both pharmacologic and non-pharmacologic therapies. The most effective way to treat MOH is to discontinue the overused medications, allow headaches to come back to baseline in number and severity, and then begin treatment with prophylactic therapy. Some of the agents in this policy have been shown to have efficacy in MOH, and others are under evaluation in clinical trials; however, the same considerations in III apply – the prescribing cascade should not continue with CGRP agents without first attempting to withdraw as many aggravating or unnecessary therapies if possible.

VII. Guidelines recommend select beta blockers, antidepressants, anticonvulsants, and onabotulinum toxin A as efficacious or probably efficacious (Level A and B, respectively) for the

prophylactic treatment of migraine in adults. If onabotulinum toxin A has been listed as a therapy that has been tried and failed, and washed out, this may be used as a qualifier of the three required agents to meet coverage consideration. Agents not listed specifically above in the policy have lower level, conflicting, or negative evidence. This includes, but is not limited to SSRIs, duloxetine, nortriptyline, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, Lisinopril, candesartan, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. Specifically, nortriptyline does not have the same level of efficacy supporting use for migraine prophylaxis as amitriptyline and should not be considered for adequate trials of prophylactic therapy.

VIII. A class review for migraine prophylactic therapies was completed in 2018, with conclusions that are consistent with guideline recommendations. The specific agents listed above, are shown to have the highest level of evidence for safety and efficacy.

IX. Guidelines label a "treatment success" as a 50% reduction in migraine after three months of prophylactic therapy utilization. Additionally, some agents take one-to-three months to begin working. If the prophylactic therapies have not been trialed for three months, this does not constitute an adequate trial of that agent. Of note, adverse effects and contraindications may limit ability to utilize an agent, or class of agents, for three months and this should be taken into consideration when determining if criteria coverage has been met.

X. In the absence of established differences in efficacy and/or safety amongst CGRP products, fremanezumab (Ajovy) has been chosen as the preferred product in this class. Treatment with, or contraindication to, this product is required prior to approval of others in the setting of chronic migraine.

Cluster Headache:

XI. Cluster headaches are defined as severe, strictly unilateral pain, orbital, supraorbital, temporal or any combination of these, lasting 15-180 minutes and occurring from once every other day to eight times per day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness, or agitation. Cluster periods range from two weeks and three months

XII. Diagnostic criteria per ICHD3 include at least five attacks fulfilling the criteria in IX, either or both of the following: a sense of restlessness or agitation AND one of the following: conjunctival injections and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and/or ptosis. Additionally, the diagnosis is not better accounted for by another IDHD3 diagnosis.

- Episodic is defined by the above occurring in periods lasting from seven days to one year, separated by pain free periods of at least three months.
- Chronic is defined as occurring for one year or longer without remission or with remission periods lasting less than three months

XIII. Like migraine therapy, treatment for cluster headaches include acute/rescue therapy and prophylactic therapy; however, contrary to migraine, prophylactic therapy should be initiated without delay once a cluster headache bout begins.

- Acute therapies: Level A evidence includes: Supplemental oxygen, subcutaneous sumatriptan, and nasal zolmitriptan. Level B evidence includes: nasal sumatriptan,

oral zolmitriptan, and sphenopalatine ganglion stimulation (not yet available in the U.S. outside of clinical trials). Therapies with convincing evidence for efficacy: octreotide, dihydroergotamine nasal spray, somatostatin, and corticosteroids.

- Prophylactic therapies: Level A evidence: suboccipital steroid injection as a transitional but not long term therapy. Several other therapies have been evaluated; however, available evidence coupled with expert opinion recommendations state verapamil and lithium should be first-line therapy; however, due to the 1-2 week onset of efficacy, transitional therapy is recommended with oral or subcutaneous steroids.

XIV. Galcanezumab (Emgality) was evaluated for safety and efficacy in episodic cluster headache. One Phase 3, RCT of 106 adult patients was conducted over eight weeks. This included those with episoidic cluster headache in patients not on other therapies for headache prophylaxis. Patients were allowed to use acute/abortive headache treatment regimens (triptans, oxygen, APAP, NSAIDS). Patients with MOH were excluded. Outcomes included mean change from baseline in weekly cluster headache attach frequency from weeks one to three. Secondary endpoints included percentage of patients who achieved a response (50% or greater reduction from baseline in weekly cluster headache attack frequency) at week three, percentage of participants reporting a score of 1 or 2 on the PGI-I scale, and percentage of participants with suicidal behaviors assessed by C-SSRS.

XV. Galcanezumab (Emgality) is indicated for the treatment of episodic cluster headache; however, a requirement of prophylactic therapy is required as prophylactic therapy should be administered without delay in all qualifying patients. Due to lack of long term safety and efficacy data, conventional therapy shall be tried prior to coverage consideration for galcanezumab (Emgality). Although the medication is not FDA approved for chronic cluster headache, there are very limited treatment options in this space beyond the conventional agents listed above. Additionally, there is an increased risk in suicidality in this population. If the medication is providing benefit to the member, as outlined in the criteria, and the clinical paradigm shifts from episodic to chronic cluster - benefits and risks of discontinuation or disapproved payment of the medication should be weighed.

Investigational or Not Medically Necessary Uses

I. The agents listed in this policy are being investigated for safety and efficacy in some the following indications. Safety and efficacy have not yet been established in all of the following:
   A. Any indication in combination with onabotulinum toxin (e.g., Botox, etc.), with the exception of rimegepant (Nurtec ODT) at a dose of 8 tablets per 30 days
   B. Chronic cluster headache
   C. Episodic cluster headache, with the exception of galcanezumab (Emgality)
   D. Post-traumatic headache
   E. Pediatric headache or migraine
   F. Vasomotor symptoms or hot flashes

G. Fibromyalgia

References

1. Emgality [Prescribing Information]. Eli Lilly and Company: Indianapolis, IN. June 2018.
2. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016;56(7):1093-106.
3. International Headache Society. Third edition of the International Classification of Headache Disorder (ICHD-3). Available at: https://ichd-3.org/. Published 2018. Accessed on July 3, 2019.
4. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018;38(8):1442-1454.
5. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018;75(9):1080-1088.
6. Novartis. A study evaluating the effectiveness of AMG 334 injection in preventing migraine in adults having failed other therapies (LIBERTY). Available from: https://clinicaltrials.gov/ct2/show/NCT03096834. NLM identifier: NCT03096834. Accessed June 26, 2018.
7. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018;38(6):1026-1037.
8. Goadsby PJ, Reuter U, Hallström Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017;377(22):2123-2132.
9. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-434.
10. Ajovy [Prescribing Information]. Teva Pharmaceuticals: North Wales, PA. February 2020.
11. S ilberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017;377(22):2113-2122.
12. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018;319(19):1999-2008.
13. Botox [Prescribing Information]. Allergan Inc. Irvine, CA. May, 2018.
14. Aimovig [Prescribing Information]. Amgen Inc. and Novartis Pharmaceuticals Corporation: Thousand Oaks, CA and East Hanover, NJ. May, 2018.
15. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. Headache. 2006;46 Suppl 1:S3-8.
16. Gilmore B, Michael M. Treatment of acute migraine headache. Am Fam Physician. 2011;83(3):271-80.
17. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis. 2015;6(3):115-23.
18. Nurtec ODT [Prescribing Information]. Biohaven Pharmaceuticals. New Haven, CT. March 2020.
19. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397(10268):51-60.
20. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20.
21. Gilmore G., Geffen D., Michael M., et al. Treatment of acute migraine headaches. Am Fam Physician. 2011;83(3):271-280.
22. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache: The Journal of Head and Face Pain*. Published online December 10, 2018:head.13456.
23. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet Neurol. 2020;19(9):727-737.

24. Ailani J, Lipton RB, Goadsby J, et al. Atogepant significantly reduces mean monthly migraine days in the phase 3 trial (ADVANCE) for the prevention of migraine. Migraine Trust Virtual Symposium; October 3-9, 2020. (additionally; data on file from Allergan/Abbvie).
25. Qulipta [Prescribing Information]. Allergan Pharmaceuticals International Limited, an AbbVie company: Dublin, Ireland. September 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval duration to 6 months for all products and to one year for acute treatment setting.	04/2022
Removed trial of triptan agents upon renewal of Nurtec. Restructured Nurtec requirements to improve clarity.	02/2022
Added migraine requirement in Nurtec; Restructured Nurtec requirements breaking down based on treatment setting (acute tx vs phx) in both initial and renewal; Removed age requirement upon renewal.	10/2021
Addition of new product atogepant (Qulipta) into policy, aligning non-preferred CGRP agents	09/2021
Addition of Nurtec ODT into policy (initial and renewal): reviewing coverage/setting of Nurtec via quantity requested; in migraine prophylaxis section aligned Nurtec ODT with non-preferred CGRP agents. Addition of standard language to renewal criteria addressing use of samples. Updates to supporting evidence.	04/2021
Update to require treatment of Ajovy prior to Aimovig or Emgality in the setting of migraines	01/2021
Added Ajovy autoinjector to policy	04/2020
Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market	02/2020
Rearranged formatting for consistency between lines of business	11/2019
Criteria update: Transition from criteria to policy and compilation of all injectable CGRP therapies into one policy. Updated Aimovig quantity limit to 30 days vs 28 to align with other agents. Added comment that these therapies will not be used in combination with one another, clarified prophylactic requirement for migraine indication, reworded renewal criteria. Added Emgality new indication of cluster headache.	07/2019
No changes made	01/2019
Criteria update: Changed onabotulinum toxin requirement to three months versus previous four months of washout. Updated renewal questions to specify a reduction in monthly migraine days by two.	10/2018
Criteria created	10/2018