Health Care Provider Administered (HCPA) Calcitonin Gene-Related Peptide (CGRP) Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
07-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Vyepti® (eptinezumab-jjmr) Intravenous injection	Preventive treatment of migraine in adults		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Migraine and Cluster Headache Management

Migraine is a common disabling primary headache disorder with high prevalence, ranking second globally in terms of years lost to disability.(11) Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Migraines can present with or without aura, unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are most-often followed by headache and associated migraine symptoms.(3)

The International Classification of Headache Disorders 3rd Edition (ICHD-3) Diagnostic Criteria:(3)

Indication	Diagnostic Criteria
Migraine without aura	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has at least TWO of the following: 1. unilateral location 2. pulsating quality 3. moderate to severe pain intensity 4. aggravation by causing avoidance of routine physical activity D. During headache at least ONE of the following:

	1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
Migraine with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least THREE of the following: 1. at least one aura symptom spreads gradually over 5 minutes or more 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
Chronic Migraine	A. Headache (migraine-like or tension-type-like) on greater than or equal to 15 days/month for greater than 3 months AND fulfilling B and C B. Occurring in patient who has had at least 5 attacks fulfilling 1. criteria B-D for migraine without aura (noted above) and/or 2. criteria B and C for migraine with aura (noted above) C. On greater than or equal to 8 days/month for greater than 3 months, fulfilling any of the following: 1. criteria C and D for migraine without aura (noted above) 2. criteria B and C for migraine with aura (noted above)

	3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis
Cluster Headache	A. At least 5 attacks fulfilling criteria B-D B. Severe to very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (untreated) C. At least one of the following: 1. At least one of the following signs or symptoms, ipsilateral to the headache a. conjunctival injection and/or lacrimation b. nasal congestion and/or rhinorrhea c. eyelid edema d. forehead and facial sweating e. miosis and/or ptosis 2. Sense of restlessness or agitation D. Occurring with frequency between one every other day and 8 per day E. Not better accounted for by another ICHD-3 diagnosis
Episodic Cluster Headache	A. Attacks fulfilling criteria for Cluster Headache (noted above) occurring in bouts (cluster periods) B. At least two cluster periods lasting 7 days to 1 years (untreated) and separated by pain-free remission periods of at least 3 months

Migraine Prevention:

The American Headache Society (AHS) position statement update (2024) states that based on ICDH-3, for those with episodic migraine (4-14 monthly migraine days) or chronic migraine (greater than or equal to 15 headache days/month), CGRP-targeting therapies should be considered a first-line migraine prevention treatment option. The guideline states that initiation of CGRP-targeting therapies should not require the prior failure of other migraine preventative drug classes. CGRP-targeting therapies are "migraine-specific" compared to other established preventative therapies. Cumulative evidence supports better efficacy, safety, and tolerability compared to any established first-line migraine prevention therapy. In addition, most CGRP-targeting therapies are labeled for episodic and chronic migraine which aids in decision making if patients spontaneously fluctuate from episodic to chronic migraine.(2) Injectable treatments

(i.e., onabotulinumtoxin A, CGRP) should be evaluated at 4, 8, and 12 weeks after treatment initiation. There is data to support continued improvement beyond 3 months. An adequate trial should be assessed at 3 months for monthly administered CGRPs and 6 months for quarterly treatments. Oral treatments should be used for a minimum of 8 weeks and cumulative benefits should occur within 6-12 months of continued use.(11)

AHS Guidelines:(2)

Diagnosis	Treatments to consider:
Episodic migraine with or without aura (4-14 MMDs) based upon ICHD-3	• Topiramate • Divalproex sodium/valproate sodium • Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Candesartan • Tricyclic antidepressant: amitriptyline, nortriptyline • SNRI: venlafaxine, duloxetine • Other Level A or B treatments according to AAN for classification of evidence • CGRP: erenumab, fremanezumab, galcanezumab, eptinezumab • Gepants: atogepant, rimegepant
Chronic migraine with or without aura (greater than or equal to 15 MHDs) based on ICHD-3	• Topiramate • Divalproex sodium/valproate sodium • Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Candesartan • Tricyclic antidepressant: amitriptyline, nortriptyline • SNRI: venlafaxine, duloxetine • Other Level A or B treatments according to AAN for classification of evidence • Onabotulinumtoxin A • CGRP: erenumab, fremanezumab, galcanezumab, eptinezumab • Gepants: atogepant, rimegepant

The European Headache Federation and WHO consensus article (2019) states the following for episodic migraine prophylaxis:(7)

- Indication for migraine prophylaxis include:
  - Attacks cause disability on two or more days per month, and
  - Acute therapy has been optimized but does not prevent this, or is poorly tolerated, or there is a risk of over-frequent use of acute therapy, even when it is effective, and
  - Patient is willing to take daily medication

- Failure of acute therapy is an indication for migraine prophylaxis
- For children, frequent absence from school is an additional indication for prophylaxis

- Migraine prophylaxis agents may take 2-3 months to show efficacy
- Onabotulinumtoxin A is not effective in episodic migraine and not recommended
- When prophylaxis therapy fails:
  - May be due to subtherapeutic dosage or duration of therapy
  - Failure of one therapy does not predict the failure of another therapy in a different class
  - Review of the following are recommended:
    - Diagnosis
    - Adherence
    - Other medications, especially for MOH causes
  - The prophylaxis therapy should be discontinued if it fails to show clear benefit
  - If all prophylaxis therapies fail, a specialist should be referred

Acute Migraine Treatment:

The AHS guidelines recommend the following indications for initiating treatment acute treatment with gepants and ditans agents:(11)

- Prescribed by a licensed clinician
- Patient is at least 18 years of age
- Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
- Either of the following:
  - Contraindication to or inability to tolerate triptans
  - Inadequate response to two or more oral triptans, as determined by either of the following:
    - Validated acute treatment patient-reported outcoming questionnaire:
      - Migraine Functional Impact Questionnaire (mTOQ)
      - Migraine Assessment of Current Therapy (Migraine-ACT)
      - Patient Perception of Migraine Questionnaire-Revised (PPMQ-R)
      - Functional Impairment Scale (FIS)
      - Patient Global Impression of Change (PGIC)
    - Clinician attestation
- At least three attacks should be treated to evaluate response and assess clinical improvement

The European Headache Federation and WHO consensus article (2019) states the following regarding the treatment of acute migraine headaches:(7)

- Treatment should be approached in a step wise manner and should treat three attacks at each step before moving to the next step if needed:
  - Step 1:
    - Use non-opioid analgesics, plus an antiemetic when needed
  - Step 2 for adults:
    - Use triptan products
    - Triptans should not be used regularly for 10 or more days per month to avoid the risk of MOH
    - Triptan efficacy is highly variable between individuals, so patients should try different triptans and formulations. Sumatriptan subcutaneous injection should be considered when all other triptans are ineffective.
    - When vomiting is present, zolmitriptan nasal spray or sumatriptan subcutaneous injection may be preferred

	○ Step 2 for children and adolescents: ▪ Failure of Step 1 in children should lead to specialist referral. No specific anti-migraine drugs have shown efficacy in children under 12 years of age. ▪ Failure of Step 2 in adolescents (12-17 years of age), the following have shown efficacy and are approved: • Sumatriptan nasal spray • Zolmitriptan nasal spray The Medical Letter Treatment Guidelines (2023) state that a triptan is the drug of choice for moderate to severe migraine. The short-acting oral serotonin (5-HT1B/1D) receptor agonists (triptans) sumatriptan (IMITREX, and others), almotriptan (Axert, and generics), eletriptan (RELPAX), rizatriptan (Maxalt, and generics), and zolmitriptan (Zomig, and generics) are similar in efficacy. Onset of pain relief generally occurs 30-60 minutes after administration. The longer-acting oral triptans naratriptan (Amerge, and generics) and frovatriptan (Frova, and generics) have a slower onset of action and lower initial response rate than other triptans, but they are better tolerated. Patients with migraine who have nausea or vomiting may not be able to take an oral triptan. Intranasal triptan formulations have a more rapid onset of action than oral tablets, but their efficacy is partially dependent on GI absorption of the portion of the dose that is swallowed. Use of sumatriptan nasal powder (ONZETRA Xsail) results in a faster rise in sumatriptan plasma concentrations and higher peak concentrations than use of a similar dose of sumatriptan nasal spray, suggesting that a larger portion of the dose is absorbed intranasally with the powder. Subcutaneously administered sumatriptan relieves pain faster (in about 10 minutes) and more effectively than other triptan formulations, but it causes more adverse effects.(13) AHS (2018, updated 2021): Triptans are effective (Level A) and considered by AHS guidelines to be the gold standard for acute treatment of moderate to severe migraine headaches. Dihydroergotamine is recommended for use as a second- or third-line therapy for select patients or for those with refractory migraine. Intranasal dihydroergotamine has strong evidence of effectiveness but more adverse effects than triptans because of its decreased receptor specificity. An assessment of new migraine treatments by the AHS lists triptans, dihydroergotamine, the oral gepants (Nurtec ODT [rimegepant] and UBRELVY [ubrogepant]), and REYVOW (lasmiditan) as effective treatment of moderate or severe acute attacks and mild to moderate attacks that respond poorly to non-specific nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin/acetaminophen/caffeine).(11) **Cluster Headache:** Cluster headache (CH) is the most common primary headache disorder and considered the most severe due to extreme pain, autonomic symptoms and high frequency of attacks.(14) The International Headache Society (IHS) notes that cluster periods usually last between 2 weeks and 3 months.(3) The American Academy of Neurology (AAN) Guidelines (2010, re-reviewed 2016): For acute treatment, sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen remain the treatments with a Level A recommendation. For transitional and prophylactic therapy, suboccipital steroid injections is the only treatment with a Level A recommendation. Verapamil is the prophylactic therapy of choice, and because suboccipital corticosteroid injections are typically used for transitional prophylaxis, lithium and verapamil have the highest evidence among preventative therapies. Oral corticosteroids are commonly used for transitional prophylaxis and considered first or second line. Melatonin is another prophylactic treatment with favorable adverse effect profile.(14) The European Academy of Neurology Guidelines (2023): For the acute treatment of CH attacks, high flow oxygen and 6mg subcutaneous sumatriptan are still highly recommended. For prophylaxis of CH, verapamil at a daily dose of at least 240 mg (or

	maximum dose based on efficacy and tolerability) is recommended. Corticosteroids show efficacy for cluster headache while lithium, topiramate, and galcanezumab (only for episodic cluster headache) are recommended as alternative treatment options.(4)
	
	The European Headache Federation and WHO consensus article (2019) states the following for CH management:(7)
	
	• Cluster Headache management:
	  ○ Acute therapies include:
	  ▪ Triptans:
	  • Sumatriptan subcutaneous injection
	  • Sumatriptan nasal spray
	  • Zolmitriptan nasal spray
	  ▪ Oxygen
	  ○ Transition and maintenance therapies include:
	  ▪ Prednisone
	  ▪ Greater occipital nerve blockade
	  ▪ Verapamil
	  ▪ Lithium carbonate
	  ▪ Topiramate
	  ○ Neuromodulation is another treatment option
	  ○ Failure of one prophylactic therapy does not predict the failure of other therapies
	  ○ Combination prophylaxis therapy can be considered though the potential for toxicity is high
	  ○ Long-term prophylaxis therapy may need to be continued
	
	Combination of therapies:
	
	• Migraine Prophylaxis Therapies:
	  ○ The European Headache Federation guideline states the following on combining migraine prophylaxis therapy:(8)
	  ▪ In episodic migraine, guidelines suggest to stop oral prophylaxis migraine agents before starting CGRPs, unless the patient previously had chronic migraine prior to prophylaxis. In such patients, the suggestion is to add CGRP to the ongoing oral prophylaxis therapy
	  ▪ In chronic migraine, guidelines suggest to add CGRP to ongoing oral prophylaxis therapy
	  ▪ In chronic migraine patients on onabotulinumtoxin A therapy and are receiving inadequate treatment response, guidelines suggest to stop onabotulinumtoxin A therapy before starting CGRPs
	  ▪ In patients with chronic migraine who are on treatment with CGRP and may benefit from additional prevention, guidelines suggest to add on oral preventative agents
	  ▪ In patients with medication overuse, guidelines suggest to use CGRPs before or after withdrawal of acute medications
	  ○ The clinical trials referenced in FDA labeled package inserts for the preventative CGRP agents excluded patients that had received botulinum toxin within 4 months prior to receiving the CGRP agent.(16,17,18) However, the 2021 AHS consensus statement states that CGRP monoclonal antibody treatment (e.g., eptinezumab-jjmr, erenumab, fremanezumab, galcanezumab) may be added to greater than or equal to one established preventative treatment, based on clinical judgement, in adults who meet the ICHD-3 criteria for migraines.(3,11)
	• Acute Use Therapies:
	  ○ Literature supports the use of gepants and triptans in combination for acute migraine therapy. All studies showed co-administration of these medications were well tolerated with a favorable safety profile.

	▪ Ubrogepant when co-administered with sumatriptan showed healthy patients tolerated these medications well and the slight alterations in pharmacokinetic parameters had minimal clinical relevance. Pooled Phase 3 ACHIEVE trials safety assessment supported use of optional second dose of a rescue medication for the treatment of moderate to severe headache starting 2-48 hours after initial dose of study medication. Rescue medication included triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). Overall frequency of treatment-related adverse effects was similar among patients that took ubrogepant along with patients that took ubrogepant and a triptan rescue medication.(19) ▪ Concomitant administration of oral rimegepant and subcutaneous sumatriptan in healthy adults showed no hemodynamic or pharmacokinetic interactions suggesting it is safe and well tolerated.(20) ▪ The pharmacokinetic and pharmacodynamic interactions between zavegepant and triptans in healthy adults showed no statistically significant difference when co-administered compared to sumatriptan alone.(5) o Lasmiditan with a triptan or gepant used in combination is not recommended(11,13) o Triptans and ergots used in combination is contraindicated(13) o The safety, tolerability, and efficacy of co-administering of the following agents has not been assessed or supported in literature: ▪ Two acute use CGRPs ▪ Acute use CGRP with ergotamine
Medication overuse headache (MOH)	The European Headache Federation and WHO consensus article (2019) states the following:(7) • In adults and children, regular high frequency use (greater than 2 day/week) of acute medication risks the development of MOH • Prevention is preferred • The four objectives of management are: o Stop the overused medication o Recovery from MOH o Review and reassess the underlying headache disorder o Prevent relapse while allowing acceptable use of medications • Comorbidities may require management
Safety	Vyepti is contraindicated in patients with serious hypersensitivity to eptinezumab-jjmr or to any of the excipients.(1)

REFERENCES

Number	Reference
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Number	Reference
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POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J3032	Vyepti	eptinezumab-jjmr iv soln	100 MG/ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Vyepti	eptinezumab-jjmr iv soln	100 MG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Indication	Preferred Target Agent(s)	Non-Preferred Target Agent(s)
	Preferred and non-preferred target agents - to be determined by client	Preferred and non-preferred target agents - to be determined by client
Chronic Migraine Prophylaxis	Aimovig AJOVY Emgality	Vyepti
Episodic Migraine Prophylaxis	Aimovig AJOVY Emgality	Vyepti

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

      1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
      2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. The requested agent is being used for migraine prophylaxis AND ALL of the following:
      1. ONE of the following:
         A. The patient has had at least 15 headache days per month of migraine-like or tension-like headache for a minimum of 3 months (chronic migraine) AND BOTH of the following:
            1. The patient has had at least 8 migraine headache days per month for a minimum of 3 months **AND**
            2. The requested agent is FDA labeled for chronic migraine prophylaxis **OR**
         B. BOTH of the following:
            1. The patient has 4-14 monthly migraine days (episodic migraine) **AND**
            2. The requested agent and strength are FDA labeled for episodic migraine prophylaxis **AND**

Module	Clinical Criteria for Approval
	2. ONE of the following: A. The patient has ONE of the following: 1. Has tried and had an inadequate response to TWO preferred agents used for migraine prophylaxis **OR** 2. Has tried and had an inadequate response to ONE preferred agent and an intolerance or hypersensitivity to ONE preferred agent used for migraine prophylaxis **OR** 3. Has an intolerance or hypersensitivity to TWO preferred agents used for migraine prophylaxis **OR** B. The patient has an FDA labeled contraindication to ALL preferred agents used for migraine prophylaxis **AND** 3. The patient will NOT be using the requested agent in combination with another prophylactic use CGRP **AND** 4. Medication overuse headache has been ruled out **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. ALL of the following: 1. The requested agent is being used for migraine prophylaxis **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with another prophylactic use CGRP **AND** 4. Medication overuse headache has been ruled out **OR** B. The patient has a diagnosis other than migraine prophylaxis AND has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months

