BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/16/19
LAST REVIEW DATE: 8/15/19
LAST CRITERIA REVISION DATE: 8/15/19
ARCHIVE DATE:

DIHYDROERGOTAMINE MESYLATE injection 1 mg/mL ampule
DIHYDROERGOTAMINE MESYLATE nasal spray 4 mg/mL
MIGRANAL® (dihydroergotamine mesylate) nasal spray 4 mg/mL

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy**: Migranal (dihydroergotamine mesylate) nasal spray, generic Dihydroergotamine mesylate nasal spray, or generic Dihydroergotamine mesylate injection is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is **ONE** of the following:
   - A Neurologist
   - A licensed professional authorized by his or her license to prescribe Migranal (dihydroergotamine mesylate) nasal spray, generic Dihydroergotamine mesylate nasal spray or generic Dihydroergotamine mesylate injection **and ONE** of the following:
     - Is prescribing in consultation with a Neurologist or Pain Specialist
     - Is certified as a headache specialist by the United Council for Neurologic Subspecialties (UCNS)
     - Has earned a Certificate in Added Qualifications (CAQ) in Headache Medicine from the National Headache Foundation

2. Individual is between 18-65 years of age

3. A confirmed diagnosis of moderate to severe migraine headaches with or without aura of **ONE** of the following severity:
   - Moderate migraine: a headache that inhibits many daily activities, the migraine pain is more noticeable and uncomfortable but it is not incapacitating
   - Severe migraine: a headache that is incapacitating such that patient is no longer able to engage in normal daily activities

4. Individual has failure, contraindication, or intolerance to **TWO** abortive agents from each of the following category of preferred step therapy:
   - NSAIDs: aspirin 500 mg, diclofenac 50 mg, ibuprofen 200 mg or naproxen 500 mg
   - Triptans: naratriptan, rizatriptan, sumatriptan, and zolmitriptan

5. Individual has failure, contraindication, or intolerance to **EITHER** Aimovig (erenumab-aooe) or Emgality (galcanezumab)

6. **Additional criteria for dihydroergotamine mesylate injection only**:
   - Individual has failure, contraindication, or intolerance to **BOTH** Migranal (dihydroergotamine mesylate) nasal spray and generic dihydroergotamine mesylate nasal spray

7. Uses and is adherent with **ONE** of the following migraine prophylactic medications:
   - Beta-blocker such as metoprolol, propranolol, or timolol
   - Antidepressant such as amitriptyline or venlafaxine
   - Anticonvulsant such as valproate, divalproex, or topiramate

8. Use is not for medication overuse headache or rebound headache or medication withdrawal headache

9. Will not be used for chronic daily administration

10. There are **NO** contraindications
    - Contraindications include:
      - Concurrent use with potent CYP450 3A4 inhibitor
      - Ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia)
      - Coronary artery vasospasm, including Prinzmetal's variant angina
      - Uncontrolled hypertension
      - Hemiplegic or basilar migraine
      - Concurrent use (within 24 hours) with 5HT1 agonists (sumatriptan, naratriptan, zolmitriptan, etc.), ergotamine-containing or other ergot-type medications or methysergide
      - Known peripheral arterial disease
      - Following vascular surgery
      - Sepsis
      - Severe hepatic impairment
      - Severe renal impairment
      - Pregnancy
      - Woman who is nursing an infant or child
      - Previous hypersensitivity to ergot alkaloids
      - Concurrent use with peripheral and central vasoconstrictors

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request)**: Migranal (dihydroergotamine mesylate) nasal spray, generic Dihydroergotamine mesylate nasal spray, or generic Dihydroergotamine mesylate injection is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by **ONE** of the following:
   - Neurologist
   - A licensed professional authorized by his or her license to prescribe Migranal (dihydroergotamine mesylate), generic Dihydroergotamine mesylate, or generic Dihydroergotamine mesylate injection **and ONE** of the following:
     - Is prescribing in consultation with a Neurologist or Pain Specialist
     - Is certified as a headache specialist by the UCNS
     - Has earned a CAQ in Headache Medicine from the National Headache Foundation

2. Individual's condition responded while on therapy Individual's condition has not worsened while on therapy
   - Response is defined as:
     - At least a 50% reduction in the number of migraine days per month from baseline
     - A reduction in the number of days of use of acute migraine-specific medications from baseline

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- No emergency visits for acute migraine treatment

3. Individual has been adherent with the medication

4. Uses at least one migraine prevention/prophylactic agent

5. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section
   - Significant adverse effect such as:
     - Pleural and retroperitoneal fibrosis
     - Cardiac valvular fibrosis
     - Acute myocardial infarction
     - Life-threatening cardiac dysrhythmia
     - Cerebral hemorrhage, subarachnoid hemorrhage, stroke, or transient ischemic attack
     - Any vasospastic phenomenon
     - Ischemic bowel
     - Raynaud's syndrome
     - Ergotism

6. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Migranal (dihydroergotamine mesylate) nasal spray, generic dihydroergotamine mesylate nasal spray, or generic dihydroergotamine mesylate injection is indicated for the acute treatment of migraine headaches with or without aura. Migranal (dihydroergotamine mesylate) nasal spray, generic dihydroergotamine mesylate nasal spray, or generic dihydroergotamine mesylate injection is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine. Migranal (dihydroergotamine mesylate) nasal spray, generic dihydroergotamine mesylate nasal spray, or generic dihydroergotamine mesylate injection should only be used where a clear diagnosis of migraine headache has been established.

Dihydroergotamine binds with high affinity to 5-HT1Dα and 5-HT1Dβ receptors. It also binds with high affinity to serotonin 5-HT1A, 5-HT2A, and 5-HT2C receptors, noradrenaline α2A, α2B and α1 receptors, and dopamine D2L and D3 receptors. The therapeutic activity of dihydroergotamine in migraine is generally attributed to the agonist effect at 5-HT1D receptors. Two current theories have been proposed to explain the efficacy of 5-HT1D receptor agonists in migraine. One theory suggests that activation of 5-HT1D receptors located on intracranial blood vessels, including those on arterio-venous anastomoses, leads to vasoconstriction, which correlates with the relief of migraine headache. The alternative hypothesis suggests that activation of 5-HT1D receptors on sensory nerve endings of the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release. In addition, dihydroergotamine possesses oxytocic properties.

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Migraine is a common episodic disorder, the hallmark of which is a disabling headache generally associated with nausea, and/or light and sound sensitivity. Migraine with aura refers to the occurrence of transient visual, sensory, language, or motor disturbance that is followed by a migraine headache. The exact mechanisms of migraine are unknown, but currently it is believed to initiate from a primary neuronal dysfunction that leads to a sequence of intracranial and extracranial changes accounting for migraine, including the four phases of premonitory symptoms, aura, headache and post-drome. Specifically, activation of the trigeminovascular system, cortical spreading depression, and neuronal sensitization all seem to play a role.

Selection of medication for acute treatment is directed by the severity of the attacks, presence of associated nausea and vomiting, treatment setting, and patient-specific factors. Abortive treatments are usually more effective if they are given early in the course of the headache (within in the first hour if possible). The 2015 updated guideline assessment published by the American Headache Society lists the following medications as Level A (established as effective) for acute migraine treatment: all triptan drugs, NSAIDs (naproxen, ibuprofen, aspirin, diclofenac), combination of sumatriptan and naproxen, acetaminophen/aspirin/caffeine, acetaminophen (for acute treatment of non-incapacitating migraine), and dihydroergotamine nasal spray.

Prophylactic headache treatment is indicated if the headaches are frequent, long lasting, or account for a significant amount of total disability. A number of drug classes are used for the prevention of migraine. Medications that are effective in controlled trials include: beta blockers (metoprolol, propranolol, and timolol); anticonvulsants (valproate, divalproex, and topiramate); and antidepressants (amitriptyline and venlafaxine).

Definitions:

Identification of headache type: migraine, tension, or cluster			
	Migraine	**Tension**	**Cluster**
Location	Unilateral	Bilateral	Supraorbital/temporal
Pain intensity[1]	Moderate to severe	Mild to moderate	Severe
Duration	4–72 hours	30 minutes to 7 days	15–180 minutes
Characterization of pain	Pulsing	Pressure/squeezing	Boring/stabbing
Sensitivity to light/sound	One or both may be present	Both are absent or only one is present	No
Nausea/vomiting	One or both may be present	No	One or both may be present
Aggravated by routine activity	Yes	No	No
Aura	May be present	No	No
Associated symptoms	None	None	Miosis, ptosis, rhinorrhea

1 Pain intensity
- Mild—Patient is aware of a headache, but is able to continue daily routine with minimum alterations.
- Moderate—The headache inhibits daily activities, migraine pain is more noticeable but is not incapacitating.
- Severe—The headache is incapacitating such that patient is no longer able to engage in normal activities.

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2013 Canadian Headache Society (CHS) – medications for acute migraine:

2013 Canadian Headache Society (CHS) Summary of Recommendations*		
Recommended For Use in Episodic Migraine (Use)**		
	Recommendation	
Drug	**Recommendation Strength**	**Quality of Evidence**
Almotriptan	Strong	High
Eletriptan	Strong	High
Frovatriptan	Strong	High
Naratriptan	Strong	High
Rizatriptan	Strong	High
Sumatriptan	Strong	High
Zolmitriptan	Strong	High
Aspirin	Strong	High
Diclofenac	Strong	High
Ibuprofen	Strong	High
Naproxen	Strong	High
Acetaminophen	Strong	High
Domeridone	Strong	Low
Metoclopramide†	Strong	Moderate
Dihydroergotamine	Weak	Moderate
Ergotamine	Weak, not recommended for routine use	Moderate
Opioid containing compounds	Weak, not recommended for routine use	Low
Tramadol containing compounds	Weak, not recommended for routine use	Moderate
Not Recommended for Use in Episodic Migraine (Do not use***)**		
Butalbutal containing compounds	Strong	Low
Butorphanol	Strong	Low
*Utilizing Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria **Migraine with headache on less than 15 days a month *** Except under exceptional circumstances † Metoclopramide strongly recommended for use when necessary		

Resources:

Migranal. Package Insert. Revised by manufacturer 08/2017. Accessed 05-03-19.

Migranal (dihydroergotamine mesylate) nasal spray product information accessed 07-19-19 at DailyMed

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Dihydroergotamine mesylate nasal spray product information accessed 07-19-19 at DailyMed

Dihydroergotamine mesylate injection product information accessed 07-19-19 at DailyMed

Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015; 55:3-20

Worthington I, Pringsheim T, Gawel MJ, et al.: Targeted Review: Medications for Acute Migraine Treatment. Can J Neurol Sci 2013; 40: Suppl 3: S10-S32

UpToDate: Acute treatment of migraines in adults. Current through Apr 2018.

UpToDate: Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. Current through Apr 2018.

UpToDate: Preventive treatment of migraine in adults. Current through Apr 2018.

UpToDate: Preventive treatment of migraine in children. Current through Jul 2017