



Ergotamine/Dihydroergotamine Products

Policy # 00582

Original Effective Date: 01/01/2018

Current Effective Date: 03/11/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Migranal[®] (dihydroergotamine mesylate nasal spray), generic dihydroergotamine mesylate nasal spray, Trudhesa[™] (dihydroergotamine nasal spray), DHE 45[®] (dihydroergotamine 1 mg/mL injection), generic dihydroergotamine 1 mg/mL injection, Ergomar[®] (ergotamine), Cafergot[®] (ergotamine/cafeine), generic ergotamine/cafeine, and generic migergot[®] (ergotamine/cafeine) to be **eligible for coverage**** when the patient selection criteria are met for the requested drug.

Patient Selection Criteria

Coverage eligibility for Migranal (dihydroergotamine mesylate nasal spray), generic dihydroergotamine mesylate nasal spray, Trudhesa (dihydroergotamine nasal spray), DHE 45 (dihydroergotamine 1 mg/mL injection), generic dihydroergotamine 1 mg/mL injection, Ergomar (ergotamine), Cafergot (ergotamine/cafeine), generic ergotamine/cafeine, and generic migergot (ergotamine/cafeine) will be considered when the following criteria are met for the requested drug:

- Migranal nasal spray:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists ("triptans"); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); AND
 - Patient has tried and failed (e.g. intolerance or inadequate response) generic dihydroergotamine mesylate nasal spray after at least 6 months of use.

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- dihydroergotamine mesylate nasal spray:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID).
- Trudhesa:
 - Medication will be used for the acute treatment of migraine; AND
 - Patient is greater than or equal to 18 years of age; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to at least one small molecule calcitonin gene related peptide inhibitor (“gepants”) (e.g., Ubrelvy[®] [ubrogepant], Nurtec ODT[®] [rimegepant]).
- DHE 45 injection:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); AND
 - Patient has tried and failed (e.g. intolerance or inadequate response) generic dihydroergotamine mesylate injection after at least 6 months of use; OR
 - Patient has a diagnosis of acute cluster headache; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); AND
 - Patient has tried and failed (e.g. intolerance or inadequate response) generic dihydroergotamine mesylate injection after at least 6 months of use.

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- dihydroergotamine 1 mg/mL injection:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); OR
 - Patient has a diagnosis of acute cluster headache; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan).
- Ergomar tablet:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); OR
 - Patient has a diagnosis of cluster headache; AND
 - If patient is using for the acute treatment of an attack, patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); OR
 - If patient is using for the prevention of nocturnal cluster headaches, patient has a contraindication, intolerance, or inadequate response to oral generic verapamil after a trial of at least 2 weeks.
- Cafergot tablet:
 - Patient has a diagnosis of acute migraine; AND

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- Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); AND
- Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); AND
- Patient has tried and failed (e.g. intolerance or inadequate response) generic ergotamine/caffeine after at least 6 months of use; OR
- Patient has a diagnosis of cluster headache; AND
 - Patient has tried and failed (e.g. intolerance or inadequate response) generic ergotamine/caffeine after at least 6 months of use; AND
 - ❖ If patient is using for the acute treatment of an attack, patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); OR
 - ❖ If patient is using for prevention of nocturnal cluster headaches, patient has a contraindication, intolerance, or inadequate response to oral generic verapamil after a trial of at least 2 weeks.
- ergotamine/caffeine tablets:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, rizatriptan, zolmitriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic prescription non-steroidal anti-inflammatory drug (NSAID); OR
 - Patient has a diagnosis of cluster headache; AND
 - If patient is using for acute treatment of an attack, patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); OR

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- If patient is using for the prevention of nocturnal cluster headaches, patient has a contraindication, intolerance, or inadequate response to oral generic verapamil after a trial of at least 2 weeks.
- migergot suppository:
 - Patient has a diagnosis of acute migraine; AND
 - Patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); AND
 - Patient has a history of failure, contraindication, or intolerance to a combination of a generic triptan and a generic non-steroidal anti-inflammatory drug (NSAID); OR
 - Patient has a diagnosis of cluster headache; AND
 - If patient is using for the acute treatment of an attack, patient has a history of failure, contraindication, or intolerance to at least TWO generic 5HT-1 receptor antagonists (“triptans”) (e.g., sumatriptan, zolmitriptan, rizatriptan); OR
 - If patient is using for the prevention of nocturnal cluster headaches, patient has a contraindication, intolerance, or inadequate response to oral generic verapamil after a trial of at least 2 weeks.

*(Note: The patient selection criteria that requires use of alternative products prior to the requested product are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

(Note: The patient selection criteria requires use of alternative products unless there is clinical evidence or patient history that suggests the use of the alternative products will be ineffective or cause an adverse reaction to the patient)

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Migranal (dihydroergotamine mesylate nasal spray), generic dihydroergotamine mesylate nasal spray, Trudhesa (dihydroergotamine nasal spray), DHE 45 (dihydroergotamine 1 mg/mL injection), generic dihydroergotamine 1 mg/mL injection, Ergomar (ergotamine), Cafergot (ergotamine/cafeine),

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generic ergotamine/cafeine, and generic migergot (ergotamine/cafeine) when a patient has not tried and failed the above listed standard therapy for the requested drug to be **not medically necessary**.**

Based on review of available data, the Company considers the use of Ergomar (ergotamine tablet), Cafergot (ergotamine/cafeine tablet), generic ergotamine/cafeine tablet, and generic migergot (ergotamine/cafeine suppository) for the prevention of migraine headaches to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers Migranal (dihydroergotamine mesylate nasal spray), generic dihydroergotamine mesylate nasal spray, Trudhesa (dihydroergotamine nasal spray), DHE 45 (dihydroergotamine 1 mg/mL injection), generic dihydroergotamine 1 mg/mL injection, Ergomar (ergotamine), Cafergot (ergotamine/cafeine), generic ergotamine/cafeine, and generic migergot (ergotamine/cafeine) for any indication other than treatment or prevention of migraine or cluster headache attacks (EXCEPT where noted as **not medically necessary****in the above section) to be **investigational**.*

Background/Overview

Currently available ergot alkaloids include ergotamine and dihydroergotamine. Ergotamine is available as brand Ergomar sublingual tablets and in combination with caffeine as brand Cafergot tablets, generic ergotamine/cafeine tablets, and generic migergot suppositories. Dihydroergotamine is available as brand Migranal nasal spray, brand Trudhesa nasal spray, generic dihydroergotamine mesylate nasal spray, DHE 45 injection, and generic dihydroergotamine 1 mg/mL injection. Both agents have erratic and low absorption from the GI tract and are therefore commonly administered via non-oral dosage forms. Although the mechanism of these agents is not fully understood, it is known that they bind to the serotonin receptors 5-HT₁ and 5-HT₂ as well as to α and dopamine receptors leading to vasoconstriction and potentially inhibition of pro-inflammatory neuropeptide release. The ergotamine products are indicated for treatment or prevention of vascular headaches including migraine and cluster headache, however their use as preventive therapy is no longer routinely recommended due to the side effects, drug interactions, and dosing limits of the

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medication. The dihydroergotamine products are indicated for the acute treatment of migraine or cluster headache (injection only).

Both ergotamine and dihydroergotamine are associated with significant drug interactions and contain a black box warning contraindicating their use with CYP3A4 inhibitors such as macrolide antibiotics, “azole” antifungals, or protease inhibitors. This combination can lead to serious or life-threatening cerebral and/or peripheral ischemia. These agents also contain a risk for pleural and retroperitoneal fibrosis, myocardial ischemia or other cardiovascular complications in patients with pre-existing cardiovascular disease, and significant blood pressure elevation.

Treatment of acute migraine attack depends on the severity of the headaches. Mild to moderate migraines can be managed with non-specific pain relievers such as NSAIDs, acetaminophen, or combination analgesics, but moderate to severe migraines require treatment with the migraine-specific agents including triptans, gepants, and ergotamine derivatives. Many clinicians prefer triptans to ergotamine derivatives due to the better safety profile and higher quality of evidence. If the migraines are associated with nausea and vomiting, non-oral formulations should be used. There is some evidence that the combined use of a triptan and an NSAID is more effective than using either drug class alone.

Cluster headaches are short-lasting, severe headaches that typically recur frequently for a period of time before subsiding for a period of remission. The average length of a cluster period is 6-12 weeks with remissions lasting 12 months or longer. Treatment of an acute attack depends on the setting of the patient. When available, inhaled 100 percent oxygen is the first line of treatment for an acute attack. If oxygen is unavailable or ineffective, subcutaneous or intranasal triptans should be used. If neither of these is effective, alternative treatments include oral ergotamine and intravenous dihydroergotamine. However, none of the alternative treatments are supported by high quality evidence. During a cluster headache bout, prophylactic therapy should be initiated. The drug of choice is high-dose oral verapamil (up to 960 mg per day), but this may take up to 2 weeks of dose titration to take effect. During this time, oral glucocorticoids or oral ergotamine may be useful to prevent cluster headache attacks. As an alternative, some experts recommend daily administration of ergotamine or ergotamine/caffeine to prevent attacks at night since ergotamine has a faster onset than verapamil and a longer duration of action than triptans. However, there is no high quality evidence demonstrating efficacy of these products and their safety profile and dosing limits often preclude this use.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The patient selection criteria presented in this policy take into consideration clinical evidence or patient history that suggests the first line treatment agents for acute migraine or cluster headache are contraindicated, ineffective, or will cause an adverse reaction to the patient. Based on a review of the data, if these factors are not present, there is no advantage of using dihydroergotamine or ergotamine products over the generic triptans, generic NSAIDs, gepants (where applicable), or generic verapamil (where applicable). The purpose of this policy is to assure that these products are being used appropriately and that the most clinically appropriate and cost effective products are tried and failed prior to the utilization of the requested product.

References

1. Migranal [package insert]. Valeant. Costa Mesa, CA. Updated 2014.
2. DHE 45 [package insert]. Valeant. Costa Mesa, CA. Updated Nov 2007.
3. Ergomar [package insert]. TerSera Therapeutics LLC. Cedar Rapids, IA. 2016
4. Cafergot [package insert]. Sandoz. Princeton, NJ. 2012
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6. UpToDate. Cluster Headache: Treatment and Prognosis. Accessed 8/2017.
7. UpToDate. Acute Treatment of Migraine in Adults. Accessed 8/2017.
8. Trudhesa [package insert]. Impel NeuroPharma, Inc. Seattle, WA. 2021.

Policy History

Original Effective Date: 01/01/2018

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09/07/2017 Medical Policy Committee review

09/20/2017 Medical Policy Implementation Committee approval. New policy.

09/06/2018 Medical Policy Committee review

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09/19/2018	Medical Policy Implementation Committee approval. No change to coverage.
09/05/2019	Medical Policy Committee review
09/11/2019	Medical Policy Implementation Committee approval. No change to coverage.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021	Medical Policy Committee review
09/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Added new product, Trudhesa, to policy with relevant criteria and background information.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged

Next Scheduled Review Date: 02/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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