**Medication Policy Manual**

**Topic:** Ergot alkaloid products

**Policy No:** dru477

**Date of Origin:** December 16, 2016

**Committee Approval Date:** December 16, 2016

**Next Review Date:** December 2017

**Effective Date:** May 1, 2017

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Ergotamine alkaloids (i.e. dihydroergotamine, ergotamine) are a rescue treatment for immediate pain relief of an acute migraine headache attack or cluster headaches.

This policy applies to all ergot alkaloid products (brand or generic).
Policy/Criteria

I. Most contracts require prior authorization approval of ergot alkaloid products (as listed in Appendix 1) prior to coverage.

A. **Lower-cost ergot products** (as listed in Appendix 1) may be considered medically necessary when generic sumatriptan AND one other low-cost triptan (as listed in Appendix 1) have been ineffective, not tolerated, or all are contraindicated.

OR

B. **High-cost ergot products** (as listed in Appendix 1) may be considered medically necessary when generic sumatriptan AND one other low-cost triptan AND one low-cost ergot product (as listed in Appendix 1) have been ineffective, not tolerated, or all are contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers all ergot alkaloid products to be self-administered medications.

B. When criteria IA. or IB. above are met and prior authorization is approved, ergot alkaloid products may be authorized in the following quantities (Table 1):

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>dihydroergotamine nasal spray (generic, Migranal)</td>
<td>8 unit-of-use ampules/month</td>
</tr>
<tr>
<td>dihydroergotamine injection (generic, D.H.E. 45)</td>
<td>10 vials/month</td>
</tr>
<tr>
<td>ergotamine tartrate sublingual tablet (Ergomar)</td>
<td>10 tablets/month</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine oral tablet (generic, Cafergot)</td>
<td>20 tablets/month</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine rectal suppository (Migergot)</td>
<td>12 suppositories/month</td>
</tr>
</tbody>
</table>

C. Ergot alkaloids in higher quantities, as listed in Table 2 below, may be considered medically necessary for treatment of cluster or migraine headaches when criteria IA or IB above is met AND either criterion 1 or 2 below is met.

1. Diagnosis of **cluster headache**

OR

2. Diagnosis of migraine headache and both criteria a. and b. below are met.

   a. Prophylaxis with medications from three of the different therapy classes listed in Appendix 2 has been ineffective, not tolerated, or all are contraindicated.
AND

b. There is documentation of migraine prophylaxis continuously for the last four months.

Table 2:

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>dihydroergotamine nasal spray (generic, Migranal)</td>
<td>16 unit-of-use ampules/month</td>
</tr>
<tr>
<td>dihydroergotamine injection (generic, D.H.E. 45)</td>
<td>20 vials/month</td>
</tr>
<tr>
<td>ergotamine tartrate sublingual tablet (Ergomar)</td>
<td>20 tablets/month</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine oral tablet (generic, Cafergot)</td>
<td>40 tablet/month</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine rectal suppository (Migergot)</td>
<td>24 suppositories/month</td>
</tr>
</tbody>
</table>

D. Quantities exceeding the quantity limits in Table 1 and Table 2 in any combination of ergot alkaloid products or dosage forms are considered not medically necessary.

E. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

II. Dihydroergotamine injection (generic, D.H.E. 45) is considered investigational when administered intravenously (IV) by a healthcare provider, such as in an emergency department (ED), in an infusion center, or as part of an inpatient hospital stay.

III. Dihydroergotamine injection (generic, D.H.E. 45) is considered not medically necessary when administered subcutaneously (SC) by a healthcare provider, such as in an emergency department (ED), in an infusion center, or as part of an inpatient hospital stay.

Position Statement

Summary – Ergot Alkaloids

- The intent of this policy is to encourage the use of the lowest-cost and most effective products for the acute treatment of migraine headaches, as well as ensure appropriate use of all ergot alkaloids, to minimize the risk of medication overuse headache.

- Simple analgesics (e.g. NSAIDs), triptans, ergot alkaloids are all considered effective for reducing headache pain. Although there is no definitive treatment algorithm, the general strategy is to start with the lowest-cost medications first.
- Triptans are considered first-line abortive treatment for moderate to severe migraine, or mild attacks that have not responded to nonprescription analgesics. Although all triptans are effective and relatively safe, generic sumatriptan is the best-value option, along with other relatively low-cost generic triptans (naratriptan, rizatriptan, and zolmitriptan tablets). Generic triptans are available in a variety of dosage forms, including non-oral options when severe nausea and/or vomiting is present.

- Poor response to one triptan does not mean that all triptans will be ineffective. A patient who does not respond to one triptan, may have a favorable response with a different triptan. Patients who fail to respond to standard of care triptans may receive benefit from an ergot alkaloid.

- There is no evidence demonstrating that ergot alkaloids provide superior headache relief compared to triptans. However, triptans are generally easier to use with fewer adverse effects compared with ergot alkaloids.

- Within the ergot alkaloid class, dihydroergotamine is considered to be more effective than ergotamine. Ergotamine has poor bioavailability (i.e. only a small amount of drug reaches systemic circulation), and clinical studies evaluating ergotamine alone have not consistently demonstrated a benefit.

- However, ergotamine may be considered an appropriate option for patients with prolonged duration of attacks (e.g. greater than 48 hours) and possibly frequent headache recurrence.

- Frequent use of abortive therapies, including ergot alkaloids, may lead to medication overuse headache. Limiting the number of doses per month can help minimize the risk.

Summary - Provider-administered dihydroergotamine injection (generic, D.H.E. 45)

- There is insufficient evidence to establish the safety or efficacy of provider-administered dihydroergotamine repetitive IV infusion (generic, D.H.E. 45) for treatment of acute migraines (status migrainosus), such as the Raskin protocol for repetitive IV infusion.

- Dihydroergotamine injection subcutaneous (SC) (generic, D.H.E. 45) may be self-administered by a patient, per the FDA-approved labeling and the OmedaRx Self-Administered Injectables Policy. The administration by a healthcare provider is considered not medically necessary. [1,2]

- Guidelines do not uniformly and conclusively support the use of provider-administered dihydroergotamine IV; however, outpatient, self-administered dihydroergotamine SC may be a treatment option for some patients.

Clinical Efficacy - Ergots

- Dihydroergotamine is considered an effective treatment for acute migraine. There is less certainty that ergotamine-containing products offer a considerable benefit.

* A high quality systematic review evaluated the evidence for ergot alkaloids relative to placebo and demonstrated that dihydroergotamine provides superior headache relief for the acute treatment of moderate to severe migraine. [14]
* The level of evidence for ergotamine is lower; and therefore, there is less certainty in the potential benefit provided. There are concerns around the poor bioavailability of ergotamine and the fact that most placebo-controlled trials of oral ergotamine alone have failed to show efficacy in the relief of migraine. It is unclear if ergotamine itself or the other ingredients (e.g. caffeine) in the combination product provide the most effect.

* Ergotamine may be considered an appropriate option for patients with prolonged duration of attacks (e.g. greater than 48 hours) and possibly frequent headache recurrence.

- There is no evidence demonstrating that ergot alkaloids are more effective than triptans for the acute treatment of migraine.

Clinical Efficacy - Provider-administered dihydroergotamine injection (generic, D.H.E. 45)

- Although the use provider-administered dihydroergotamine IV, also known as “IV DHE protocols,” seems to be an accepted treatment by headache specialists, the majority of the evidence to support its use is from retrospective case series and is considered inconclusive.

- Specifically, the use of dihydroergotamine repetitive IV infusion every 8 hours for migraines (the “Raskin protocol”) is considered investigational. The evidence is limited one small trial of 48 hour infusions, along with retrospective cases. [4-6]

- The evidence to support the use of dihydroergotamine IV is summarized in one systematic review, which includes two randomized controlled trials (up to 48 hours treatment) and two large retrospective case series in patients with medication overuse headache (MOH) (up to 7.4 day inpatient stay), along with one newer large retrospective case series (n=114) which used a 5-day treatment course. [8] There is no new randomized controlled trial evidence to support the use of dihydroergotamine IV or the specific protocols since the publication of the systematic review in 2005.

- Additional, high quality (large, prospective randomized controlled) clinical trials are needed to establish the safety and efficacy of dihydroergotamine IV, whether repetitive or continuous, in the treatment of severe migraine or other types of headache.

- The efficacy of dihydroergotamine SC is supported by a large high quality systematic review. Dihydroergotamine SC provides superior headache relief for the acute treatment of moderate to severe migraine relative to placebo and can be self-administered by that patient. [9]
Clinical Guidelines

- The American Headache Society (AHS) guidelines for the treatment of acute migraines recognize the use of dihydroergotamine nasal spray as effective (Level A). However, ergotamine (oral, rectal), and dihydroergotamine SC, IM, or IV are all Grade B, “scientific support was not optimal,” based on the American Academy of Neurology (AAN/AHS) 2000 guidelines. Use of provider-administered dihydroergotamine IV in combination with antiemetics as a lower level recommendation (Grade C, based on expert consensus). [9,10] A more recent review of treatment of acute migraines in the emergency department (ED) (2016) concluded no recommendation can be made regarding the role of injectable dihydroergotamine (Level U, very low confidence in the evidence). [11]

- Similarly, the Canadian Headache Society (CHS) guidelines do not endorse the use of provider-administered dihydroergotamine IV; however, these guidelines do endorse the use of outpatient, self-administered dihydroergotamine SC, limited to patients who do not adequately respond to use of NSAIDs, triptans, or combination therapy (weak recommendation, based on moderate quality evidence). [12]

- The European Federation of Neurological Societies (EFNS) do not recognize the use of provider-administered dihydroergotamine IV as a treatment option. Recognized medication options for status migrainosus include corticosteroids and dihydroergotamine (nasal spray or suppositories), based on expert opinion and supported by open label studies. Oral NSAIDs, oral triptans, oral metoclopramide, and oral domperidone are recommended for acute migraines, with IV acetylsalicylic acid and sumatriptan SC for very severe attacks. [13]

Safety

Preventative (Prophylactic) Therapy [10,16,17]

- Patients who suffer very severe of frequent migraine attacks may benefit from preventative therapy.

- Current medical literature suggests that preventative therapy should be considered in patients experiencing greater than two migraine attacks per month.

- Preventative medication can help most people decrease the number of migraine headaches by half.

- Consultation with a specialist experienced in the evaluation and treatment of refractory headache patients may be beneficial when three or more successive preventive drugs have not been effective.

- The American Academy of Neurology (AAN) states that preventive medication may be indicated when a patient is experiencing one or more migraines per week. Severe may be defined as headache causing work loss.

- Frequent use of quick-relief ("abortive") medication may cause medication overuse headache (MOH), including triptans, NSAIDs, acetaminophen and opioids.

- Many experts limit quick-relief therapy to two headaches per week on a regular basis.

Patients with medication overuse headache should use preventative medication.
- The American Academy of Neurology suggests the best evidence for preventative drug efficacy is for amitriptyline, propranolol, timolol, and divalproex sodium. Evidence of efficacy also exists for other beta-blockers, tricyclic antidepressants (TCAs), and venlafaxine (see Appendix 2).
- Ergot alkaloids do not prevent migraines.

Maximum Quantities \cite{17,18}
- Frequent use of quick relief medications can lead to medication overuse headache and eventually chronic daily headache. Medication overuse headache is defined as headache frequency of more than 15 days per month after the frequent intake of quick relief medications for a minimum of three months.
- Frequent use of ergot alkaloids can lead to medication overuse headache.
- Medication overuse headache is the most common factor in patients referred to tertiary headache clinics.
- The dosage of ergotamine sublingual tablet (Ergomar) should not exceed three tablets in any 24-hour period or 10 mg in any week.
- The dosage of ergotamine/caffeine oral tablet (Cafergot) should not exceed six tablets per attack or ten tablets per week.
- The dosage of ergotamine/caffeine rectal suppository (Migergot) should not exceed two suppositories per attack or five suppositories per week.
- The dosage of dihydroergotamine nasal spray (generic, Migranal) should not exceed more than 3 mg in a 24-hour period and 4 mg in a 7-day period.
- The dosage of dihydroergotamine injection (generic, D.H.E. 45) should not exceed more than 6 mL in a 7-day period and only when self-administered by the patient.
Appendix 1: Ergots covered in this policy: [18]

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Dosage Form</th>
<th>Doses per Headache</th>
<th>Max Doses/Month</th>
<th>Strengths Available</th>
<th>Doses per package</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOWER-COST ERGOT PRODUCTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ergotamine options</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ergotamine tartrate (Ergomar®)</td>
<td>sublingual tablet</td>
<td>1 a</td>
<td>20</td>
<td>2 mg</td>
<td>20 tablets</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine (generic, Cafergot®)</td>
<td>oral tablet</td>
<td>1 b</td>
<td>40</td>
<td>1 mg</td>
<td>100 tablets</td>
</tr>
<tr>
<td>ergotamine tartrate/caffeine (Migergot®)</td>
<td>rectal suppository</td>
<td>1 c</td>
<td>20</td>
<td>2 mg/100 mg</td>
<td>12 suppositories</td>
</tr>
<tr>
<td><strong>Dihydroergotamine options</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dihydroergotamine mesylate (generic)</td>
<td>injection</td>
<td>1 d</td>
<td>24</td>
<td>1 mg/mL</td>
<td>10</td>
</tr>
<tr>
<td><strong>HIGH-COST ERGOT PRODUCTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dihydroergotamine mesylate (D.H.E. 45®)</td>
<td>injection</td>
<td>1 d</td>
<td>24</td>
<td>1 mg/mL</td>
<td>10</td>
</tr>
<tr>
<td>dihydroergotamine mesylate (generic)</td>
<td>nasal solution</td>
<td>1 e</td>
<td>8</td>
<td>4 mg/mL</td>
<td>8</td>
</tr>
<tr>
<td>dihydroergotamine mesylate (Migranal®)</td>
<td>nasal solution</td>
<td>1 e</td>
<td>8</td>
<td>4 mg/mL</td>
<td>8</td>
</tr>
<tr>
<td><strong>LOW-COST TRIPHTANS (step therapy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>naratriptan</td>
<td>oral tablet</td>
<td>1 to 2</td>
<td>4 to 8</td>
<td>1 mg, 2.5 mg</td>
<td>9 tablets</td>
</tr>
<tr>
<td>rizatriptan</td>
<td>oral tablet, ODT</td>
<td>1 to 3 f</td>
<td>4 to 12</td>
<td>5mg, 10mg</td>
<td>various</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>oral tablet</td>
<td>1 to 2 f</td>
<td>4 to 8</td>
<td>25mg, 50mg, 100mg</td>
<td>9 tablets; multidose bottles</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>nasal Spray</td>
<td>1 to 2 f</td>
<td>4 to 8</td>
<td>5mg, 20mg</td>
<td>6 sprays</td>
</tr>
<tr>
<td>sumatriptan</td>
<td>injection</td>
<td>1</td>
<td>4</td>
<td>6mg/0.5ml</td>
<td>2 syringes, vial, cartridges</td>
</tr>
<tr>
<td>zolmitriptan</td>
<td>oral tablet, ODT</td>
<td>1</td>
<td>4</td>
<td>2.5mg, 5mg</td>
<td>1, 3 or 6 tabs</td>
</tr>
</tbody>
</table>

a. Another tablet can be taken at 30-minute intervals following the first dose, if necessary. Dosage must not exceed 3 tablets in any 24-hour period or 10 mg in any 1 week.
b. May be repeated every 30 minutes as needed; maximum of 6 tablets per attack; do not exceed 10 tablets per week.
c. A second dose may be given after 1 hour, if needed; max of 2 suppositories per attack; do not exceed 5 suppositories per week.
d. Dose may be repeated, as needed, at 1-hour intervals to a total dose of 3 mL in a 24-hour period; maximum 6 mL per week.
e. Dose may be repeated 15 minutes later, for a total dosage for 4 sprays (2 mg); maximum 3 mg in a 24-hour period and 4 mg in a 7-day period.
f. Dose may be repeated if first dose was not completely effective.

ODT: orally dissolving tablet
Appendix 2: Migraine Prophylaxis Drug Therapy Classes \[10\]

The following are examples of medication classes used for migraine prophylaxis:

- Anticonvulsants (a.k.a. anti-epileptic drugs, AEDs) (e.g. divalproex sodium, topiramate).
- Beta Blockers (e.g. propranolol, atenolol, metoprolol).
- Antidepressants (TCAs, e.g. amitriptyline; venlafaxine).
- Other antihypertensives (ACEIs, ARBs, alpha-agonists) [e.g. candesartan, clonidine (Catapres®), guanfacine, lisinopril]

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; TCAs: tricyclic antidepressants.

Appendix 3: Cluster Headache Diagnostic Criteria \[19\]

1. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes untreated.

AND

2. Headache is associated with at least one of the following signs on the pain side:
   a. Conjunctival injection and/or Lacrimation
   b. Nasal congestion and/or Rhinorrhea
   c. Eyelid edema
   d. Forehead/facial sweating
   e. Forehead/facial flushing
   f. Sensation of fullness in the ear
   g. Miosis and/or Ptosis

AND

3. Current frequency of attack is at least 1 every other day.

AND

4. At least five attacks have occurred fulfilling the criteria listed above.

Cross References

Triptan products, Medication Policy Manual, Policy No. dru475
Self-Administered Injectables, Medication Policy dru110

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References


Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/16/2016</td>
<td>New policy</td>
</tr>
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