Clinical Pharmacy Program Guidelines for Migranal

<table>
<thead>
<tr>
<th>Program</th>
<th>Prior Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Migranal (dihydroergotamine mesylate) nasal spray</td>
</tr>
<tr>
<td>Pharmacy and Therapeutics Approval Date</td>
<td>11/2016</td>
</tr>
<tr>
<td>Effective Date</td>
<td>1/2017</td>
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1. **Background:**

**Indications**

**Migraine headaches with or without aura**

Is indicated for the acute treatment of migraine headaches with or without aura. Migranal Nasal Spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

**Clinical Practice Guidelines**

**British Association for the Study of Headache (2010) [10]**

Among first-line agents for migraine prophylaxis, BASH includes atenolol, metoprolol, propranolol LA, and amitriptyline. Second-line agents include topiramate and valproic acid. Third-line agents include gabapentin.

Limited trial evidence is available for verapamil. Fluoxetine and the SSRIs are of uncertain value. While lisinopril may have a potential benefit, further trials are recommended before being recommended. Oral contraceptives may be beneficial in hormone-associated migraines (menstrual migraines).

**American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine (2004) [3]**

Six recommendations are offered under the AAFP-ACP-ASIM guidelines.

1. NSAIDs should be given as first line therapy for acute migraine headaches. The evidence is favored for aspirin, ibuprofen, naproxen, and tolmentin. The combination of caffeine with acetaminophen or aspirin is also effective; however, benefits of acetaminophen use alone appear lacking.

2. Second line acute therapy includes migraine specific agents, such as triptans and DHE. Few data is available confirming the superiority of one particular triptan over the others. Opiate and butorphanol are also acceptable options provided abuse potential and sedation are not of concern.

3. Use of antiemetics in combination with a migraine agent may be appropriate in patients suffering from nausea and/or vomiting as part of their symptom profile. Non-oral routes are preferred.

4. Preventive therapy should be considered in patients presenting with the following:
a. greater than or equal to 2 acute headache attacks per month which produce disability lasting greater than or equal to 3 days
b. contraindications, failure, or intolerance to acute treatments
c. use of abortive therapeutic agents greater than or equal to 2 times per week
d. migraines presenting with uncommon symptoms, such as hemiplegic migraine, migraine with prolonged aura, or migrainal infarct

5. First line preventive treatments include: propranolol, timolol, divalproex, amitriptyline, or sodium valproate

6. Educate and involve patients in a management plan with regular re-evaluation of therapy (e.g. headache diary)

Evidence was inconsistent to support efficacy of ergotamine or ergotamine-caffeine, and the studies documented frequent adverse effects.

DHE nasal spray is safe and effective for the treatment of acute migraine attacks and should be considered for use in patients with moderate to severe migraine (Grade A: multiple well-designed randomized clinical trials yielded a consistent pattern of findings).

Frequent use of acute medications (ergotamine [not DHE], opiates, triptans, simple analgesics, and mixed analgesics containing butalbital, caffeine, or isomeethptene) is generally thought to cause medication-overuse headache. Many experts limit acute therapy to two headache days per week on a regular basis. Patients with medication overuse should use preventive therapy.

Triptans are effective and relatively safe for the acute treatment of migraine headaches are appropriate initial treatment choice in patients with moderate to severe migraine who have not contraindications for its use (Grade A).

Ergotamine PO/PR (and caffeine combination) may be considered in the treatment of selected patients with moderate to severe migraine (Grade B).

Grade A: Multiple well-designed randomized clinical trial, directly relevant to the recommendation, yielded a consistent pattern of findings.

Grade B: Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation.

United States Headache Consortium (2000) [8]
The use of DHE nasal spray is an appropriate treatment choice and should be considered for use in patients with moderate-to-severe migraine (Grade A: multiple well-designed randomized clinical trials). Because of their inability to tolerate or take oral medications, patients with nausea and vomiting may be given intranasal DHE (Grade C: consensus on the recommendation in the absence of relevant randomized controlled trials). Initial treatment with DHE nasal spray is a reasonable choice when:

a. the headache is moderate-to-severe, or
b. an adequate trial of NSAIDs or other non-opiate analgesics (including combination analgesics as acetaminophen plus aspirin plus caffeine) has failed to provide adequate relief in the past (Grade C).

Triptans are effective and relatively safe for the acute treatment of migraine headaches. To date, no evidence supports their use during the aura phase of a migraine attack. Triptans are an appropriate choice and may be considered for use in patients with moderate to severe migraine who have no contraindications for its use (Grade A, see definition in American Academy national guideline).

Evidence was inconsistent to support efficacy of ergotamine PO/PR (and caffeine combination) for the treatment of migraine. Studies documented a higher incidence of adverse events with ergot as compared with placebo, sumatriptan, isometheptene, NSAIDs, or dextropropoxyphene compounds. Ergotamine is recommended in the treatment of selected patients with moderate-to-severe migraine (Grade B, see definition in American Academy national guideline).

**International Headache Society (IHS) [9]**
The IHS defines ergotamine overuse according to the following guidelines:

a. Headache present greater than or equal to 15 days per month and fulfilling the following criteria:
   (1) headache that has developed or markedly worsened with triptan overuse
   (2) headache resolves or returns to its previous pattern with 2 months after stopping triptan therapy

b. Ergotamine intake on greater than or equal to 10 days per month on a regular basis for at least 3 months

The IHS also states that acute migraines may progress to chronic migraines, and this transition may occur more rapidly with triptans than with ergotamine overuse.

2. **Coverage Criteria:**
A. **Migranal nasal spray**

1. Confirmed diagnosis of migraine headaches with or without aura. [1]

   -AND-

2. History of failure, contraindication, or intolerance to two formulary 5-HT1 receptor agonist (triptan) alternatives [eg, Imitrex (sumatriptan), Maxalt or Maxalt-MLT (rizatriptan)]

**Authorization will be issued for 12 months.**

B. **Migranal nasal spray- Quantity Limit**

1. Quantity requests exceeding the limited amount per month for frequently occurring migraines will be approved by a clinical pharmacist based on all of the following:
   a. Confirmed diagnosis of migraine headaches with or without aura

   -AND-

   b. Prescribed by or in consultation with a neurologist or pain management specialist

   -AND-

   c. Currently receiving prophylactic therapy with at least one of the following agents in patients experiencing two or more headaches monthly: [2-4, 10, A]
      - Antidepressants [eg, Elavil (amitriptyline)*, Effexor (venlafaxine)] [A]
      - Antihistamines (eg, cyproheptadine*) [B]
      - Antiepileptics [eg, Depakote/Depakote ER (divalproex sodium), Topamax (topiramate)]
      - ACE Inhibitors [eg, Zestril (lisinopril)]
      - Angiotensin receptor blockers [eg, Atacand (candesartan)]
      - Alpha-agonists (eg, clonidine*, guanfacine*) [C]
      - Beta-blockers [eg, Inderal (propranolol), timolol, Toprol XL (metoprolol)]

   -AND-

   d. Both of the following:
      1. One of the following:
         a. Higher dose or quantity is supported by the manufacturer's
prescribing information

-OR-

(b) Higher dose or quantity is supported by one of following compendia:
   • American Hospital Formulary Service Drug Information
   • Micromedex DRUGDEX ® System
   • Clinical Pharmacology

-OR-

(c) Physician provides evidence to support safety and additional efficacy at higher than maximum doses as documented in published biomedical literature demonstrating safety and efficacy of doses/quantities greater than those approved by the FDA for the diagnosis indicated

-AND-

(2) Physician acknowledges that the potential benefit outweighs the risk associated with the higher dose or quantity

Authorization will be issued for 12 months.

NOTES: *Amitriptyline and cyproheptadine are recommended only for patients less than 65 years old.

NOTE TO PRESCRIBER: A common cause of chronic daily headaches is excessive use of the following medications: analgesics (such as acetaminophen or ibuprofen), narcotics, triptans, or ergotamines.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Description</th>
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<tbody>
<tr>
<td>Migranal Nasal Spray [1] - Migraine with or without aura</td>
<td>One spray (0.5 mg) administered in each nostril. Fifteen minutes later, an additional one spray (0.5 mg) should be administered in each nostril, for a total dosage of four sprays (2.0 mg). Studies have shown no additional benefit from acute doses greater than 2.0 mg for a single migraine administration. The safety of doses greater than 3.0 mg in a 24 hour period and 4.0 mg in a 7 day period has not been established. Migranal should not be used for chronic daily administration. Prior to administration, the pump must be primed (i.e., squeeze 4 times) before use. Once the nasal spray applicator has been prepared, it should be discarded (with any remaining...</td>
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3. **Endnotes:**

A. Migraine prevention should be considered for patients with the following: 1) two or more attacks per month that produce disability lasting 3 or more days; 2) contraindication to, or failure of, acute treatments; 3) the use of abortive medication more than twice per week; 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migraineous infarction. [3]

B. Amitriptyline, a tricyclic antidepressant (TCA), is part of the Beer’s Criteria for potentially inappropriate medication use in older adults (independent of diagnoses or condition) because of its strong anticholinergic and sedation properties. [12] However, amitriptyline has been more frequently studied than the other agents, and is the only antidepressant with fairly consistent support for efficacy in migraine prevention. Other TCAs are clinically efficacious based on consensus and clinical experience, but lack scientific evidence of efficacy. [3, 4]

C. Cyproheptadine is included on the 2011 Health Plan Employer Data and Information Set (HEDIS) list of high-risk medications in the elderly (greater than or equal to 65 years old). [11]

D. Cafergot (ergotamine-caffeine) products were not added as a formulary alternative to the Migranal guidelines due to lack of efficacy and adverse effects. [3, 4, 8]

4. **References:**


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<tr>
<th>Program</th>
<th>Program type - Migranal (dihydroergotamine mesylate) nasal spray</th>
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<tbody>
<tr>
<td><strong>Change Control</strong></td>
<td></td>
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<tr>
<td><strong>Date</strong></td>
<td><strong>Change</strong></td>
</tr>
<tr>
<td>3/2015</td>
<td>New policy</td>
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<tr>
<td>10/2016</td>
<td>Updated quantity limit section to closely align with Triptans quantity limit section. Updated policy template.</td>
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