

## Pharmacy Policy Bulletin

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**Title:** Acute Migraine Agents

**Policy #:** Rx.01.56

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***Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.***

***This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.***

***Members are advised to use participating pharmacies in order to receive the highest level of benefits.***

### **Intent:**

The intent of this policy is to communicate the medical necessity criteria for **Maxalt® [MLT]** , **Tosymra®**, **sumatriptan/naproxen (Treximet®)**, **zolmitriptan nasal spray, Zomig® [ZMT]** , **Relpax®**, **Amerge®**, **Imitrex®**, **Frova®**, **Onzetra Xsail®**, **Zembrace®**, **dihydroergotamine mesylate injection (D.H.E.45®)**, **dihydroergotamine mesylate nasal spray (Migranal®)**, **Reyvow™**, **Ubrelyv™**, and **Nurtec™ ODT** as provided under the member's prescription drug benefit.

### **Description:**

**Migraine headaches** are believed to result from the dilatation of blood vessels and inflammation in the brain and stimulation of sensory neurons resulting in the sensation of pain.

### **Mechanism of Action**

The class of anti-migraine agents, known as 'Triptans' provide agonist action on the 5-HT-1 sub-type of serotonin receptors resulting in cerebral vasoconstriction and reduction in neurogenic inflammation. This mechanism of action allows the Triptans to provide pain relief during a migraine. These drugs bind to specific areas on the blood vessels and nerves and stop the inflammation and pain. While they are very effective in relieving migraine headaches for most individuals, they are not indicated for prophylactic use as they do not prevent or reduce the number of migraine headaches.

**Maxalt® [MLT]** , **Tosymra®**, **sumatriptan/naproxen (Treximet®)**, **zolmitriptan nasal spray, Zomig® [ZMT]**, **Relpax®**, **Amerge®**, **Imitrex®**, **Frova®**, **Onzetra Xsail®**, and **Zembrace®** are indicated for the treatment of acute migraine headache, to be taken at the first signs of onset and not as prophylactic therapy.

Dihydroergotamine is a drug that exerts its action on the 5HT-1 serotonin receptor sub-type, resulting in cerebral vasoconstriction. Additionally, in contrast to the triptans, Dihydroergotamine also stimulates dopaminergic and adrenergic receptors.

**D.H.E. 45® (dihydroergotamine)** is indicated for the acute treatment of cluster headache episodes and migraine headaches.

**Migranal® (dihydroergotamine)** is indicated for the acute treatment of migraine headaches with or without aura and is not intended for use as prophylactic therapy

Reyvow® (lasmiditan) binds with high affinity to the 5-HT<sub>1F</sub> receptor. Lasmiditan presumably exerts its therapeutic effects in the treatment of migraine through agonist effects at the 5-HT<sub>1F</sub> receptor; however, the precise mechanism is unknown.

Nurtec™ ODT and Ubrelvy™ are calcitonin gene-related peptide receptor antagonists.

**Nurtec™ ODT (rimegepant), Reyvow® (lasmiditan), and Ubrelvy™ (ubrogepant)** are indicated for the acute treatment of migraine with or without aura in adults and is not intended for use as prophylactic therapy.

**Policy:**

**INITIAL CRITERIA:** Brand Maxalt®/Maxalt® MLT, Amerge®, Frova®, Imitrex®, Tosymra®, Relpax®, Onzetra® Xsail, Zembrace® Symtouch, zolmitriptan nasal spray, Zomig®/Zomig® ZMT, Nurtec™ ODT, Reyvow™, or Ubrelvy™ is approved when ALL of the following inclusion criteria are met:

- A. Diagnosis of migraine headache; and
- B. Use in the age group shown in the table below; and
- C. Inadequate response or inability to tolerate two generic triptans (e.g. eletriptan, naratriptan, rizatriptan, zolmitriptan, sumatriptan) as appropriate for the member's age; and
- D. Inadequate response or inability to tolerate BOTH of the following (applies to Reyvow™ only):
  - a. Nurtec™ ODT; and
  - b. Ubrelvy™

**Drug**

<b>Drug</b>	<b>Age recommendation</b>
Rizatriptan (Maxalt®/Maxalt® MLT)	Age 6 and up
Zolmitriptan (Zomig®/Zomig® ZMT)	Age 12 and up
Eletriptan (Relpax®)	Age 18 and up
Naratriptan (Amerge®)	Age 18 and up
Sumatriptan (Imitrex®, Onzetra® Xsail, Zembrace® Symtouch, Tosymra®)	Age 18 and up
Frovatriptan (Frova®)	Age 18 and up
Lasmiditan (Reyvow™)	Age 18 and up
Ubrogepant (Ubrelvy™)	Age 18 and up
Rimegepant (Nurtec™ ODT)	Age 18 and up

**INITIAL CRITERIA:** Sumatriptan/naproxen (Treximet®) is approved when ALL of the following are met:

- A. Diagnosis of migraine headache; and
- B. Member is 12 years of age or older; and
- C. Inadequate response or inability to tolerate three generic triptans (e.g. eletriptan, naratriptan, rizatriptan, zolmitriptan, sumatriptan); and
- D. Inadequate response to concurrent administration of sumatriptan and naproxen as separate products

**INITIAL CRITERIA:** Dihydroergotamine mesylate (D.H.E. 45®) injection is approved when ALL of the following inclusion criteria are met:

- A. Prescribed by or in consultation with a neurologist or headache specialist; and
- B. Diagnosis of migraine or cluster headaches; and
- C. Member is 18 years of age or older; and
- D. Member has been instructed on proper preparation, injection, and disposal of medication; and
- E. ONE of the following:
  - 1. Inadequate response or inability to tolerate an injectable triptan; or
  - 2. Triptan overuse, defined as using triptans greater than 8 days per month
- F. Inadequate response or inability to tolerate generic dihydroergotamine injection or it is not available (applies to D.H.E. 45)

**INITIAL CRITERIA:** Dihydroergotamine mesylate (Migranal®) is approved when ALL of the following are met:

- A. Diagnosis of moderate to severe migraine headache with or without aura; and
- B. Inadequate response or inability to tolerate TWO, oral or nasal, triptans; and
- C. Prescribed by or in consultation with a neurologist or pain specialist

Initial authorization: 2 years

**REAUTHORIZATION CRITERIA:** Brand Maxalt®/Maxalt® MLT, Amerge®, Frova®, Imitrex®, Tosymra®, Relpax®, Onzetra® Xsail, Zembrace® Symtouch, zolmitriptan nasal spray, Zomig®/Zomig® ZMT, Nurtec™ ODT, Reyvow™, Ubrelvy™, sumatriptan/naproxen (Treximet®), dihydroergotamine mesylate (D.H.E 45®) injection or dihydroergotamine mesylate (Migranal®) nasal spray is approved when there is documentation of positive clinical response to therapy.

Reauthorization: 2 years

**Black Box Warning as shown in the drug Prescribing Information:**

**Treximet®**

Cardiovascular Risk: TREXIMET may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk

Gastrointestinal Risk: TREXIMET® contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

**D.H.E. 45 ®, Migranal® (dihydroergotamine mesylate)**

Serious and/or life-threatening peripheral ischemia. D.H.E. 45 has been associated with peripheral ischemia with co-administration of potent CYP3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Therefore, concomitant use of these medications is contraindicated.

**Guidelines:**

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

**BENEFIT APPLICATION**

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

**References:**

Amerge® (naratriptan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline. December 2016. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=13f4a8ec-75a3-4c51-b3bc-6244f3c79e95&type=display>. Accessed July 16, 2021.

D.H.E. 45® (dihydroergotamine mesylate) [package insert] Bridgewater, NJ. Valeant Pharmaceuticals. November 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fe826e6a-75c8-43ed-9c36-f8263ec35aff>. Accessed July 16, 2021.

Frova® (frovatriptan) [package insert]. Malvern, PA: Endo Pharmaceuticals; August 2018. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c0703630-9ce8-4259-841e-71fd2019fa66&type=display>. Accessed July 16, 2021.

Imitrex® injection (sumatriptan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; August 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=fee7d073-0b99-48f2-7985-0d8cf970894b&type=display>. Accessed July 16, 2021.

Imitrex® tablets (sumatriptan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=584abe73-8290-4484-ff8e-5890831c095e&type=display>. Accessed July 16, 2021.

Imitrex® spray (sumatriptan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=cc11b09d-e6cc-4cf8-1495-5ac64d5aae5f&type=display>. Accessed July 16, 2021.

Maxalt®/ Maxalt® MLT® (rizatriptan) [package insert]. Whitehouse station, NJ: Merck & Co., Inc.; September 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d93286f5-99f7-4dc5-aa9d-ad73ab8490db&type=display>. Accessed July 16, 2021.

Migranal® (dihydroergotamine mesylate spray) [package insert]. Bridgewater NJ: Bausch Health US, LLC. July 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a24bfa8-b952-48ac-942a-379585250782>. Accessed July 16, 2021

Nurtec® ODT (rimegepant) [prescribing information]. New Haven, CT: Biohaven Pharmaceuticals, Inc.; March 2020. Available at: <https://www.nurtec.com/pi>. Accessed July 16, 2021.

Onzetra® (sumatriptan nasal powder) [package insert]. Aliso Viejo, CA. Avanir Pharmaceuticals, Inc. December 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=08234d7d-5972-4384-99a5-599140aa215d&type=display>. Accessed July 16, 2021.

Relpax® (eletriptan) [package insert]. New York, NY: Pfizer; March 2020. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=85745375-fcb6-4edc-b6db-a77b4a5f3e8c&type=display>. Accessed July 16, 2021.

Reyvow™ (lasmiditan) [package insert]. Indianapolis, IN: Lilly USA, LLC; January 2021. Available at: <https://uspl.lilly.com/reyvow/reyvow.html#pi>. Accessed July 16, 2021.

Tosymra™ (sumatriptan nasal spray) [package insert]. Promius Pharma LLC (per FDA), Princeton, NJ, July 2019. Available at <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=7260d567-3824-230d-836d-8065302baaec&type=display>. Accessed July 16, 2021.

Treximet® (sumatriptan/naproxen) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2019. Available at: <http://www.treximet.com/areas/hcp/contents/pdf/prescribing-information.pdf>. Accessed July 16, 2021.

Ubrelyv™ (ubrogepant) [package insert]. Madison, NJ: Allergan USA, Inc; March 2021. Available at: [https://media.allergan.com/products/Ubrelyv\\_pi.pdf](https://media.allergan.com/products/Ubrelyv_pi.pdf). Accessed July 16, 2021

Zembrace® (sumatriptan succinate) [package insert]. San Diego, CA: Dr. Reddy's Laboratories Limited. July 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d565763d-b740-411d-bbb4-13536017d634&type=display>. Accessed July 16, 2021.

Zomig® spray (zolmitriptan) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=84b51cb9-83f3-4a49-7fa3-1adc0f963658&type=display>. Accessed July 16, 2021.

Zomig®/ Zomig® ZMT® tablets (zolmitriptan) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=df93b636-103f-4fb5-26b6-50f639e29b1d&type=display>. Accessed July 16, 2021.

Bajwa MD, Smith, MD. Acute treatment of migraine in adults. Post TW, ed. UpToDate. Updated October 2020. Waltham, MA: UpToDate Inc. <http://www.uptodate.com.proxy1.lib.tju.edu/>. Accessed on July 16, 2021.

#### Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

#### Brand Name

Amerge®  
D.H.E. 45®, Migranal®  
Frova®  
Imitrex®  
Maxalt®/ Maxalt MLT®  
Onzetra Xsail  
Relpax®  
Reyvow™  
Tosymra®  
Treximet®  
Ubrelvy™  
Zembrace® Symtouch  
Zomig®/ Zomig ZMT®  
Nurtec® ODT

#### Generic Name

Naratriptan  
dihydroergotamine mesylate  
Frovatriptan  
Sumatriptan  
Rizatriptan  
Sumatriptan  
Eletriptan  
Lasmiditan  
Sumatriptan  
sumatriptan/naproxen  
Ubrogepant  
Sumatriptan  
Zolmitriptan  
Rimegepant

This list is subject to change as new products are introduced to the market.

#### Cross References:

RX. 01.2 Applicable Age Edits

RX. 01.76 Quantity Level Limits for Pharmaceuticals Covered Under the Pharmacy Benefit

RX.01.33 Off-Label Use

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<b>Policy Version Number:</b>	25.00
<b>P&amp;T Approval Date:</b>	June 10, 2021
<b>Policy Effective Date:</b>	October 01, 2021
<b>Next Required Review Date:</b>	March 18, 2022

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The Policy Bulletins on this web site were developed to assist the Company in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Company, please refer

to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Company does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of the Company. If you have a specific medical condition, please consult with your doctor. The Company reserves the right at any time to change or update its Policy Bulletins.

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