

## Pharmacy Policy Bulletin

---

**Title:** Migraine Agents  
**Policy #:** Rx.01.56

---

***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] , Treximet®, Zomig® [ZMT] , Axert®, Relpax®, Amerge®, Imitrex®, Sumavel® DosePro®, Frova®, Onzetra Xsail®, Zembrace®, and D.H.E.45® 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 'Tryptans' 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 Tryptans 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] , Treximet®, Zomig® [ZMT] , Axert®, Relpax®, Amerge®, Imitrex®, Sumavel® DosePro®, 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 migraine headaches and is not intended for use as prophylactic therapy.

**Policy:**

Brand Maxalt®/Maxalt® MLT, Amerge®, Frova®, Imitrex®, Sumavel® DosePro, Axert®, Treximet®, Relpax®, Onzetra® Xsail, Zembrace® Symtouch, or Zomig®/Zomig® ZMT are approved when ALL of the following inclusion criteria are met:

- A. Diagnosis of migraine headache
- B. Use in the age group shown in the table below
- C. Inadequate response or inability to tolerate two generic triptans (e.g. eletriptan, naratriptan, rizatriptan, zolmitriptan, sumatriptan) as appropriate for the patient’s age

Drug	Age recommendation
Rizatriptan (Maxalt®/Maxalt® MLT)	Age 6 and up
Sumatriptan/naproxen (Treximet®)	Age 12 and up
Zolmitriptan (Zomig®/Zomig® ZMT)	Age 12 and up
Almotriptan (Axert®)	Age 12 and up
Eletriptan (Relpax®)	Age 18 and up
Naratriptan (Amerge®)	Age 18 and up
Sumatriptan (Imitrex®, Sumavel® DosePro, Onzetra® Xsail, Zembrace® Symtouch)	Age 18 and up
Frovatriptan (Frova®)	Age 18 and up

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

- 1. Prescribed by or in consultation with a neurologist or headache specialist; and
- 2. Diagnosis of migraine or cluster headaches; and
- 3. Member is 18 years of age or older; and
- 4. Member has been instructed on proper preparation, injection, and disposal of medication; and

5. ONE of the following:

- a. Inadequate response or inability to tolerate an injectable triptan; or
- b. Triptan overuse, defined as using triptans greater than 8 days per month

6. Inadequate response or inability to tolerate generic dihydroergotamine injection or it is not available (applies to D.H.E. 45)

▸ **Black Box Warning:**

**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 (see WARNINGS: Cardiovascular Effects).

**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 (see WARNINGS: Risk of Gastrointestinal Ulceration, Bleeding, and Perforation With Nonsteroidal Anti-inflammatory Drug Therapy).

**D.H.E. 45®** (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 (see: CONTRAINDICATIONS and WARNINGS).

▸ **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 November 26, 2018.

Axert (almotriptan) [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. May 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=a8479ec0-204e-11e1-aa3f-a3c74724019b&type=display>. Accessed November 26, 2018.

D.H.E. 45® (dihydroergotamine mesylate) [package insert] Bridgewater, NJ: Valeant Pharmaceuticals. November 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fe826e6a-75c8-43ed-9c36-f8263ec35aff>. Accessed November 13, 2018.

Frova® (frovatriptan) [package insert]. Malvern, PA: Endo Pharmaceuticals; October 2013. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=c0703630-9ce8-4259-841e-71fd2019fa66&type=display>. Accessed November 26, 2018.

Imitrex® injection (sumatriptan) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=fee7d073-0b99-48f2-7985-0d8cf970894b&type=display>. Accessed November 26, 2018.

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 November 26, 2018.

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 November 26, 2018.

Maxalt®/ Maxalt® MLT® (rizatriptan) [package insert]. Whitehouse station, NJ: Merck & Co., Inc.; March 2015. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d93286f5-99f7-4dc5-aa9d-ad73ab8490db&type=display>. Accessed November 26, 2018.

Onzetra® (sumatriptan nasal powder) [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc. January 2016. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=08234d7d-5972-4384-99a5-599140aa215d&type=display>. Accessed November 26, 2018.

Relpax® (eletriptan) [package insert]. New York, NY: Pfizer; November 2013. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=85745375-fcb6-4edc-b6db-a77b4a5f3e8c&type=display>. Accessed November 26, 2018.

Sumavel® (sumatriptan) [package insert]. Malvern, PA: Endo Pharmaceuticals; October 2013. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=5e9a0861-a802-4580-bb34-f84f0ee4ac07&type=display>. Accessed November 26, 2018.

Treximet® (sumatriptan/naproxen) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2016. Available at: <http://www.treximet.com/areas/hcp/contents/pdf/prescribing-information.pdf>. Accessed November 26, 2018.

Zembrace® (sumatriptan succinate) [package insert]. San Diego, CA: Dr. Reddy's Laboratories Limited. March 2017. Available at:

<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d565763d-b740-411d-bbb4-13536017d634&type=display>. Accessed November 26, 2018.

Zomig® spray (zolmitriptan) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2016. Available at:


<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=84b51cb9-83f3-4a49-7fa3-1adc0f963658&type=display>. Accessed November 26, 2018.

Zomig®/ Zomig® ZMT® tablets (zolmitriptan) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2016.. Available at:

<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=df93b636-103f-4fb5-26b6-50f639e29b1d&type=display>. Accessed November 13, 2018.

Bajwa MD, Smith, MD. Acute treatment of migraine in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com.proxy1.lib.tju.edu>. Accessed on November 13, 2018.

#### 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	Generic Name
Amerge®	naratriptan
Axert®	almotriptan
D.H.E. 45®	dihydroergotamine mesylate
Frova®	frovatriptan
Imitrex®	sumatriptan
Maxalt®/ Maxalt MLT®	rizatriptan
Onzetra Xsail	sumatriptan
Relpax®	eletriptan
Sumavel DosePro®	sumatriptan
Treximet®	sumatriptan/naproxen
Zembrace® Symtouch	sumatriptan
Zomig®/ Zomig ZMT®	zolmitriptan

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

#### Cross References:

RX. 01.2 Age Edits

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

Policy Version Number:

18.00

P&T Approval Date:

October 11, 2018

**Policy Effective Date:**

January 1, 2019

**Next Required Review Date:**

October 11, 2019

---

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.