

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru054

Topic: Frova[®], frovatriptan

Date of Origin: April 22, 2002

Revised/Effective Date: November 14, 2008

Next Review Date: November 2009

IMPORTANT REMINDER

This Medical 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 medical policy is to provide a guide to coverage. Medical 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

Frovatriptan (Frova[®]) is a rescue treatment for immediate pain relief of an acute migraine headache attack.

Policy/Criteria

I. Most contracts require prior authorization approval of frovatriptan prior to coverage of quantities greater than 13 tablets per month. Frovatriptan in quantities up to 12 tablets per month may be considered medically necessary in patients with migraine or cluster headaches and may be covered without prior authorization.

II. Frovatriptan, alone or in combination with other triptans, may be considered medically necessary for either of the following conditions, when the following criteria are met.

A. Migraine headaches

1. Formulary/preferred medications have been ineffective or not tolerated (see Appendix 2).

AND

2. Prophylaxis with medications from three of the different therapy classes listed in Appendix 1 has been ineffective, not tolerated, or contraindicated.

AND

3. There is documentation of migraine prophylaxis within the last four months.

OR

B. Cluster Headaches

1. Diagnosis is made by a neurologist.

OR

2. All criteria (1 through 4) listed in Appendix 3 are met.

III. Administration, Quantity Limitations and Authorization Period

A. Regence considers frovatriptan to be a self-administered medication.

B. When prior authorization is approved, frovatriptan may be authorized in quantities of 13 to 24 tablets per month. Quantities exceeding 24 tablets per month are considered investigational.

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

Position Statement

Summary

- For the treatment of migraine headache, the preferred triptan medications sumatriptan (Imitrex[®]), rizatriptan (Maxalt[®]), eletriptan (Relpax[®]), and zolmitriptan (Zomig[®]) are the best value and have the best evidence of effectiveness.
- There is reliable evidence that almotriptan (Axert[®]) stops migraines, but it has no proven additional benefit over formulary options to justify the higher cost.
- Frovatriptan is used for the acute treatment of migraine headaches.
- All triptans are effective and relatively safe for the acute treatment of moderate to severe migraine headaches. [1-8, 22, 29, 33-34]
- There is reliable evidence that preventive medications help gain control of migraine headaches by reducing how often they occur and the severity.

Clinical Efficacy

- The evidence for the preferred nasal and oral triptans is reliable for the acute treatment of migraine attacks. [1-7] There is not reliable evidence for the treatment of other types of headaches. [1-8]
- Sumatriptan (Imitrex[®]) injection has the best evidence for the treatment of cluster headaches. [1]
- Among the available triptans, there is no evidence that almotriptan, frovatriptan (Frova[®]) or naratriptan (Amerge[®]) offer additional clinical benefits: [17-21, 26-28]
 - * in headache relief at two hours.
 - * in headache recurrence rates.
- There is some evidence that eletriptan (Relpax[®]) has a lower migraine recurrence rate at two hours than oral sumatriptan. [31-32]

- There is reliable evidence that almotriptan, sumatriptan, rizatriptan, eletriptan, and zolmitriptan abort migraine headaches and treat the associated symptoms. Approximately three to five patients need to be treated for one to have a response.
- The clinical value of naratriptan, frovatriptan and sumatriptan/naproxen (Treximet™) is uncertain because there is not reliable evidence to determine how well they treat migraines.
- Because migraines are often accompanied by nausea, products with multiple dosage forms such as oral disintegrating tablets, nasal sprays and injectables provide additional clinical value for patients who can not tolerate swallowing tablets.
- There is insufficient evidence that demonstrates that one triptan is more efficacious than another in the treatment of migraine headache.
- A triptan taken at the first sign of a migraine yields the best response (elimination or significant reduction of pain).
- There is no reliable evidence that the addition of naproxen to sumatriptan is effective.

Safety

PREVENTIVE (PROPHYLACTIC) THERAPY

- Patients who suffer very severe or frequent migraine attacks may benefit from preventative therapy.^[10]
- Current medical literature suggests that preventative therapy should be considered in patients experiencing greater than two migraine attacks per month.^[10, 11]
- Preventative medication can help most people decrease the number of migraine headaches by half. Approximately one in ten patients become migraine free with preventative medication.^[11, 14]
- Consultation with a specialist experienced in the evaluation and treatment of refractory headache patients may be beneficial when three or more successive preventative drugs have not been effective.^[14]
- The American Academy of Neurology states that preventative 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 medication may cause medication overuse headache.
- Many experts limit quick relief therapy to two headaches per week on a regular basis. Patients with medication overuse headache should use preventative medication.^[15]

- The American Academy of Neurology has suggested the best evidence for preventative drug efficacy is for amitriptyline, propranolol, timolol, and divalproex sodium. Evidence of efficacy also exists for other beta-blockers, tricyclics, and verapamil. ^[15]
- Triptans do not prevent migraines. ^[1-8, 22, 29, 33-34]

MAXIMUM QUANTITIES

- Most people who have migraine headaches need fewer than 12 tablets per month.
- Approximately 85% of patients with migraine headaches suffer fewer than three to four attacks per month. ^[9] The median frequency of migraine attacks among migraine sufferers is 1.5 per month. ^[11]
- 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). ^[10]
- Frequent use of triptans may lead to medication overuse headache. ^[12, 13]
- Medication overuse headache is the most common factor in patients referred to tertiary headache clinics. ^[14]
- The safety of treating more than four headaches with almotriptan, naratriptan, sumatriptan, frovatriptan, rizatriptan, or zolmitriptan (nasal spray) in a 30-day period has not been established. ^[1-7, 34-35]
- The safety of treating more than three headaches with zolmitriptan tablets or eletriptan in a 30-day period has not been established. ^[4, 33]
- The safety of treating an average of more than 5 migraine headaches in a 30-day period has not been established for sumatriptan/naproxen. ^[38]
- The manufacturer's recommended dose for sumatriptan/naproxen is one tablet. The efficacy of taking a second dose has not been established. ^[38]
- The prescribing information states not to take more than two sumatriptan/naproxen tablets in 24 hours. ^[38]

Appendix 1: Migraine Prophylaxis Drug Therapy Classes

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

| | |
|---|--|
| - | Anticonvulsants (divalproex sodium). |
| - | Beta Blockers (propranolol, atenolol, metoprolol). |
| - | Calcium Channel Blockers (verapamil). |
| - | Tricyclic Antidepressants (amitriptyline). |

Appendix 2: Product Availability

| Brand Name | Generic Name | Dosage Form | Doses per Headache | Doses per Month (4 headaches) ^[b] | Strengths Available | Doses per package |
|--|--------------------------|-------------|-----------------------|--|----------------------|-------------------------|
| FORMULARY/PREFERRED TRIPTANS | | | | | | |
| Maxalt [®] , Maxalt MLT [®] | rizatriptan | Tablet | 1 to 3 ^[a] | 4 to 12 | 5mg, 10mg | 6 tablets |
| Imitrex [®] | sumatriptan | Tablet | 1 to 2 ^[a] | 4 to 8 | 25mg, 50mg, 100mg | 9 tablets |
| Imitrex [®] | sumatriptan | Nasal Spray | 1 to 2 ^[a] | 4 to 8 | 5mg, 20mg | 6 sprays |
| Imitrex [®] | sumatriptan | Injection | 1 | 4 | 6mg/0.5ml | 2 syringes |
| Relpax [®] | eletriptan | Tablet | 1 to 2 ^[a] | 4 to 8 | 20mg, 40mg | 6 tablets 12 tablets |
| Zomig [®] | zolmitriptan | Nasal Spray | 1 to 2 | 4 to 8 | 5mg | 6 sprays |
| Zomig [®] , Zomig ZMT [®] | zolmitriptan | Tablet | 1 | 4 | 2.5mg, 5mg | 6 tablets 3 tablets |
| NON-FORMULARY/NON-PREFERRED TRIPTANS | | | | | | |
| Amerge [®] | naratriptan | Tablet | 1 to 2 ^[a] | 4 to 8 | 1mg, 2.5mg | 9 tablets |
| Axert [®] | almotriptan | Tablet | 1 | 4 | 6.25mg, 12.5mg | 6 tablets 12 tablets |
| Frova [®] | frovatriptan | Tablet | 1 to 3 ^[a] | 4 to 12 | 2.5mg | 9 tablets |
| Treximet [™] | sumatriptan/ naproxen | Tablet | 1 to 2 ^[a] | 5 to 10 | 85mg/500mg | 9 tablets |
| a. Dose may be repeated if first dose was not completely effective. | | | | | | |
| b. Headache recurs in less than 46% of patients within 24 hours. ^[16] | | | | | | |

Appendix 3: Cluster Headache Diagnostic Criteria

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|------------|---|
| 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 |
| b. | Lacrimation |
| c. | Nasal congestion |
| d. | Rhinorrhea |
| e. | Forehead/facial sweating |
| f. | Miosis |
| g. | Ptosis |
| h. | Eyelid edema |
| 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. |

References

1. Imitrex[®] Tablets (sumatriptan) prescribing information. GlaxoSmithKline; Research Triangle Park, NC; April 2007.
2. Imitrex[®] Nasal Spray (sumatriptan) prescribing information. GlaxoSmithKline; Research Triangle Park, NC; April 2007.
3. Amerge[®] Tablets (naratriptan) prescribing information. GlaxoSmithKline; Research Triangle Park, NC; April 2007.

4. Zomig[®] Tablets (zolmitriptan) prescribing information. AstraZeneca Pharmaceuticals LP; Wilmington, DE; January 2007.
5. Axert[®] Tablets (almotriptan) prescribing information. Ortho-McNeil Pharmaceuticals, Inc; Raritan, NJ; May 2007.
6. Frova[®] Tablets prescribing information. Elan Pharmaceuticals South San Francisco, CA. April 2007.
7. Maxalt[®] Tablets (rizatriptan) prescribing information. Merck and Co., Inc.; Whitehouse Station, NJ; August 2007.
8. Imitrex[®] Injection (sumatriptan) prescribing information. GlaxoSmithKline; Research Triangle Park, NC; April 2007.
9. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001; 41:646-57.
10. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the diagnosis and management of migraine in clinical practice. Canadian Headache Society. *CMAJ*. 1997; 156:1273-87.
11. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. *N Engl J Med*. 2002;346:257-70.
12. Katsarava Z, Fritsche G, Muessig M, et al. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology*. 2001;57:1694-8.
13. Fritsche G, Eberl A, Katsarava Z, et al. Drug-induced headache: long-term follow-up of withdrawal therapy and persistence of drug misuse. *Eur Neurol*. 2001;45:229-35.
14. Noble SL, Moore KL. Drug treatment of migraine: Part II. Preventive therapy. *Am Fam Physician*. 1997;56:2279-86.
15. Silberstein SD, et al. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report on the Quality Standards Subcommittee of the American Academy of Neurology. *Neurol* 2000; 55:754-63.
16. Welch KMA. A 27 year-old woman with migraine headaches. *JAMA* 1997;278:322-328
17. Ferrari MD, Roon KI, Lipton R, Goadsby PJ. Oral triptans (serotonin 5-HT 1b-1d agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001 Nov;358:1668-75.
18. Ryan R, Geraud G, Golstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo controlled studies. *Headache* 2002 April;42(Suppl2):S84-92.
19. Geraud G, Spierings LH, Keywood C. Tolerability and safety of frovatriptan with short and long term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002 April;42(Suppl2):S93-9.

20. Speirings ELH, et al. Oral almotriptan vs sumatriptan in the abortive treatment of migraine. A double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001 June;58:944-50.
21. Pascual J, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia* 2000:588-96.
22. Zomig[®] Nasal Spray (zolmitriptan) prescribing information. AstraZeneca Pharmaceuticals LP; Wilmington, DE; January 2007.
23. Syrett N, Abu-Shakra S, Yates R. zolmitriptan nasal spray: advances in migraine treatment. *Neurology* 2003;61(suppl 4):S27-S30.
24. Dowson AJ, Charlesworth BR, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs* 2003;17(11):839-51.
25. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003;17(9):653-67.
26. Dalhof C, Winter P, Whitehouse H, Hassani H. Randomized, double-blind, placebo controlled comparison of oral naratriptan and oral sumatriptan in acute treatment of migraine. *Neurology* 1997;48:A85.
27. Mathew NT, Asgharnejad M, Peykamain M, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. *Neurology* 1997 Nov;49(6):1485-90.
28. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. *Headache* 1997 Nov/Dec:640-5.
29. Relpax[®] (eletriptan) prescribing information. Pfizer, Inc.; New York, NY; April 2007.
30. Fuseau E, et al. Effect of encapsulation on absorption of sumatriptan tablets: data from healthy volunteers and patients during migraine. *Clin Therapeutics* 2001 Nov 1;23(1):127-45.
31. Sandrini G et al. Eletriptan vs sumatriptan; a double blind, placebo-controlled, multiple migraine attack study. *Neurology* 2002;59(8):1210-7.
32. Mathew NT, Schoenen J, Winner P, Muirhead N, Kikes CR. Comparative efficacy of eletriptan 40mg versus sumatriptan 100mg. *Headache* 2003;43:214-22.
33. Frova[®] Tablets (frovatriptan) prescribing information. Elan Pharmaceuticals; San Francisco, CA; June 2006.

34. International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. [cited 2004 Oct 11]; Available at: <http://www.i-h-s.org>.
35. Marcus DA, Furman JM. Prevention of motion sickness with rizatriptan: a double-blind, placebo controlled pilot study. *Med Sci Monit.* 2006;12(1):PI1-7.
36. Rapoport AM, Mathew NT, Silberstein SD, Dodick D, Tepper SJ, Sheftell FD, Bigal ME. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology.* 2007 Aug 28;69(9):821-6.
37. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. *Arch Neurol.* 2006 Nov;63(11):1537-42.
38. Treximet™ (sumatriptan and naproxen sodium) Tablets Prescribing Information. July 2008. GlaxoSmithKline, Research Triangle Park, NC.

| Cross References |
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| Amerge® , naratriptan dru052 |
| Axert® , almotriptan dru053 |
| Imitrex® , sumatriptan dru055 |
| Maxalt®/Maxalt MLT® , rizatriptan dru056 |
| Relpax® , eletriptan dru092 |
| Treximet™ , sumatriptan/naproxen dru165 |
| Zomig®/Zomig ZMT® , zolmitriptan dru057 |

| Codes | Number | Description |
|-------|--------|-------------|
| N/A | | |