



CIGNA HEALTHCARE COVERAGE POSITION

Subject Antimigraine Therapy –
Serotonin-1 Receptor Agonist: Almotriptan (Axert®), Eletriptan (Relpax®), Frovatriptan (Frova™), Naratriptan (Amerge®), Rizatriptan (Maxalt®, Maxalt-MLT®), Sumatriptan (Imitrex®), Zolmitriptan (Zomig®, Zomig-ZMT®)

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INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

Coverage Position

CIGNA HealthCare covers serotonin-1 receptor agonists for the treatment of migraine headache for certain quantities without prior authorization. (Please refer to table 2 in the background section).

CIGNA HealthCare covers additional quantities of serotonin-1 receptor agonists as medically necessary when ANY of the following indications are met:

- treatment and prophylactic of migraine **AND** one of the following:
 - patient is currently being treated with migraine prophylaxis medication (beta-blockers, calcium channel blockers, tricyclic antidepressants, or Anticonvulsant medications) for a minimum of two months)
 - failure, contraindication, or intolerance to two migraine prophylaxis medications: beta-blockers, calcium channel blockers, tricyclic antidepressants or anticonvulsant medications
- for treatment of acute cluster headache (sumatriptan [Imitrex®] injection **ONLY**)

CIGNA HealthCare does not cover for the following indications because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- tension headache
- migraine prophylaxis
- basilar artery migraine
- hemiplegic migraine
- cluster headache (for all above therapies, except sumatriptan [Imitrex®] injection)

General Background

Seven triptans, selective 5-hydroxy-triptamine 1 (5-HT₁) receptor agonist, are available in the United States at present: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. All of the agents are U.S. Food and Drug Administration (FDA)-approved for the abortive treatment of migraine headache. Triptans are not approved for the prevention of migraine headache. Subcutaneous sumatriptan is also labeled for the abortive treatment of cluster headache. Table 1 provides the dosage forms, normal dose and the maximum daily dose of the available triptans.

Table 1

5-HT ₁ Receptor Agonists		Dosage Forms Available	Normal Dose	Maximum Daily Dose
Generic	Brand			
almotriptan	Axert	Tablets: 6.25 and 12.5 mg	6.25 mg or 12.5 mg May repeat after two hours	25 mg
eletriptan	Relpax	Tablets: 20 and 40 mg	20 mg or 40 mg May repeat after two hours	80 mg
frovatriptan	Frova	Tablets: 2.5 mg	2.5 mg May repeat after two hours	7.5 mg
naratriptan	Amerge	Tablets: 1 and 2.5 mg	1 mg or 2.5 mg May repeat after four hours	5 mg
rizatriptan	Maxalt	Tablets: 5 and 10 mg ODT: 5 and 10 mg	5 mg or 10 mg May repeat after four hours	30 mg
sumatriptan	Imitrex	Tablets: 25, 50, and 100 mg Nasal Spray: 5 and 20 mg per spray Injection: 6 mg/0.5 mL prefilled syringe	Tablets: 25 mg, 50 mg, or 100 mg May repeat in two hours Nasal Spray: 5 mg, 10 mg, or 20 mg May repeat in 2 hours Injection = 6 mg May repeat once in one hour	Tablets: 200 mg Nasal spray: 40 mg Injection: 12 mg
zolmitriptan	Zomig	Tablets: 2.5 and 5 mg ODT: 2.5 and 5 mg Nasal Spray: 5 mg per spray	Tablets: 1 mg, 2.5 mg, or 5 mg ODT: 2.5 mg Nasal Spray: 5 mg May repeat in two hours	10 mg

Abbreviations: ODT = orally disintegrating tablets

While members of the triptan family are similar in many ways, there are significant differences in time to peak blood concentration and half-life. Subcutaneously injectable sumatriptan reaches peak blood concentrations faster than any other migraine-specific medications (in approximately 15 minutes) and has been shown to be effective in 70–82% of patients. The oral form of rizatriptan reaches peak concentration in 60 to 90 minutes, compared with two to three hours for most other triptans. The longest half-life of the triptans belongs to naratriptan. In general, if recurrence happens with use of the triptans, it takes place within eight to 12 hours and can be relieved with a second dose of the medication.

The evidence-based migraine headache treatment guidelines are established by the U.S. Headache Consortium, a multidisciplinary team consisting of members from seven organizations, including the American Academy of Family Physicians (AAFP) and the American Academy of Neurology. Based on their recommendations, frequent use of acute medications (including but not limited to opiates, triptans, simple analgesics, and mixed analgesics containing butalbital, caffeine, or isometheptene) is generally thought to cause medication-overuse headache. To decrease the risk of medication-overuse headaches, the consortium suggests limiting acute therapy for patients who have more than two headache days per week on a regular basis. Following is the background information supporting the maximum quantity criteria:

- Approximately 85% of patients with migraine headaches suffer fewer than three to four attacks per month. The median frequency of migraine attacks among migraine sufferers is 1.5 per month.
- Frequent use of abortive therapies can lead to medication-overuse headaches (MOH) and eventually chronic daily headache (MOH is defined as headache frequency of more than 15 days per month after the frequent intake of abortive therapies for a minimum of three months).
- Medication-overuse headache has been associated with triptans.
- The safety of treating more than four headaches for Axert, Amerge, Imitrex, Frova, Maxalt, or Zomig (nasal spray) in a 30-day period has not been established, according to the FDA-approved prescribing information.
- The safety of treating more than three headaches with Zomig tablets or Relpax in a 30-day period has not been established, according to the FDA-approved prescribing information.
- Medication-overuse headache is the most common factor in patients referred to tertiary headache clinics.
- Patients who suffer very severe or frequent migraine attacks may benefit from prophylactic therapy.

Migraine Headache

All of the triptans are effective for the treatment of migraine headache. Triptan effectiveness is dose-dependent, and varies between individual agents. Time to response and duration of response also varies between agents. Many comparative trials between the triptans do not compare equivalent doses of the agents. The most important comparison between agents is between the highest labeled doses of each, since triptan dosage may be increased if ineffective at lower doses. Of the 21 trials that compared the triptans, nine compared the highest labeled doses of the different agents. In these trials, both eletriptan and rizatriptan were significantly more effective than naratriptan and sumatriptan in separate clinical trials. Each triptan is also effective in producing 24-hour sustained headache response for patients with migraine headache. Only 10 of the comparative trials reported statistical comparisons between groups for this outcome. No statistical comparisons were reported for almotriptan or frovatriptan.

Both rizatriptan and zolmitriptan are available as orally disintegrating tablets (ODT). Two open-label, patient preference trials comparing rizatriptan 10 mg ODT to sumatriptan 50 mg conventional oral tablets were identified. Efficacy outcomes were secondary endpoints in both trials. When contrasted against data from other active-control triptan trials, the percentage of patients achieving headache response (one, two, and 24 hours) appear much greater than the other oral dosage forms. However, two placebo-controlled, double-blind trials of zolmitriptan ODT produced results for all major efficacy endpoints that fell within the range of the other triptans.

Zolmitriptan ODT was compared to sumatriptan 50 mg tablets for patient preference in one trial. No other comparative trials are available for zolmitriptan ODT. The ODT formulations of both rizatriptan and zolmitriptan were preferred by more patients than sumatriptan 50 mg tablets (57–64% versus vs. 36–43%, $p < 0.05$).

Eight trials were located comparing various triptans to other agents. Individual triptans were more effective than ergotamine plus caffeine, aspirin plus metoclopramide, and dihydroergotamine in achieving headache response. Sumatriptan is the only agent compared to each treatment group. Almotriptan, frovatriptan, and naratriptan have not been compared to other agents used for the treatment of migraine headache.

Cluster Headache

No trials have evaluated the comparative efficacy of triptans for the treatment of cluster headache. Sumatriptan, given subcutaneously, was compared to placebo for the treatment of cluster headache in two trials. In these trials, sumatriptan was more effective than placebo in reducing the pain associated with cluster headache. More patients had mild or no pain in 15 minutes compared to placebo (75–80% vs. 26–35%, $p < 0.001$). Sumatriptan 6 mg was as effective as a 12 mg dose. Two descriptive case series evaluated the efficacy of sumatriptan over 12–24 months. In both of these trials, the efficacy of sumatriptan did not decline over time.

Zolmitriptan was compared to placebo in one trial. Each patient treated three headaches with zolmitriptan 5 mg, 10 mg, or placebo (i.e., each patient took each treatment option in a blinded fashion over the course of three headaches). More patients with episodic cluster headache reported a headache response, defined as a two-point or greater improvement in headache intensity, with zolmitriptan 10 mg than placebo (46.8% vs. 28.9%, $p = 0.02$). Zolmitriptan 5 mg was no different than placebo. The response to each treatment intervention was similar for patients with chronic cluster headache.

Prophylactic Therapy

Key points regarding migraine's prophylactic therapy:

- Current medical literature suggests that preventative therapy should be considered in patients experiencing greater than two migraine attacks per month.
- On average, about two-thirds of patients on prophylactic therapy will have a 50% reduction in frequency of migraines, even though less than 10% of patients become headache-free on prophylactic therapy.
- Failure with three or more successive prophylactic drugs is unusual, and such patients may benefit from a consultation with a specialist experienced in the evaluation and treatment of refractory headache patients.
- The American Academy of Neurology (AAN) states that prophylaxis may be indicated when a patient is experiencing one or more severe migraines per week. Severe may be defined as headache causing work loss.
- Frequent use of acute medication is generally thought to cause medication-overuse headache.
- Many experts limit acute therapy to two headaches per week on a regular basis. Patients with medication overuse should use preventive medication.
- The AAN has recently suggested the best evidence for prophylactic drug efficacy is for amitriptyline, propranolol, timolol, and divalproex sodium. Evidence also exists for other beta-blockers, tricyclics, and verapamil.
- None of the triptans are indicated for prophylaxis of migraine.

The triptans are associated with a similar rate of adverse events and chest-related symptoms. Adverse effects were dose-related, being more common with high doses. Few trials made statistical comparisons between the agents but, in those that did, almotriptan 12.5 mg was associated with fewer chest symptoms compared to sumatriptan 50 mg (0.3% vs. 2.25%, $p < 0.001$) and rizatriptan 5 mg was associated with fewer chest symptoms compared to sumatriptan 100 mg (1% vs. 6%, $p < 0.01$).

Almotriptan and naratriptan require dosage adjustment in patients with renal and hepatic dysfunction. Naratriptan is contraindicated in patients with severe renal dysfunction. Eletriptan, naratriptan, and sumatriptan are contraindicated in patients with severe hepatic impairment. In addition, contraindications to their use include ischemic vascular conditions, vasospastic coronary disease, uncontrolled hypertension, or other significant cardiovascular disease.

The drug interaction profiles for each of the triptans are similar. All of the triptans are contraindicated within 24 hours of an ergot-containing medication or another triptan. Eletriptan is the only agent with an additional contraindication within 72 hours of a potent cytochrome P450 3A4 (CYP3A4) inhibitor (e.g., ketoconazole). Rizatriptan, sumatriptan, and zolmitriptan are contraindicated within two weeks of a monoamine oxidase (MAO) inhibitor.

Patients may prefer a particular dosage form over another (e.g., ODT versus injection or nasal spray). Please note that rizatriptan, sumatriptan, and zolmitriptan are the only agents with additional dosage forms (i.e., ODT – rizatriptan, zolmitriptan; nasal spray – sumatriptan, zolmitriptan; injection – sumatriptan).

CIGNA HealthCare covers serotonin-1 receptor agonists for the treatment of migraine headache in the following quantities without prior authorization, consistent with the FDA-approved manufacturer product information. According to the manufacturer, the safety of treating an average of more than 3–4 migraine headaches in a 30-day period with serotonin-1 receptor agonists has not been established.

Table 2

Drug	Dose	How Supplied	Quantity (QTY) Allowed per Month or Script	Copays	Maximum Monthly Dose
Amerge	1 mg	One pack of nine tablets	Two packs or 18 tablets	one per script	20 mg
	2.5 mg	One pack of nine tablets	One pack or nine tablets	one per script	
Axert	6.25 mg	One pack of nine tablets	Two packs or 18 tablets	one per script	100 mg
	12.5 mg	One pack of 12 tablets	One pack or 12 tablets	one per script	
Frova	2.5 mg	One pack of 9 tablets	Two packs or 18 tablets	one per script	30 mg
Imitrex tablets	25 mg	One pack of 9 tablets	Three packs or 27 tablets	one per script	800 mg
	50 mg	One pack of nine tablets	Two packs or 18 tablets	one per script	
	100 mg	One pack of nine tablets	One pack or nine tablets	one per script	
Imitrex nasal	5 mg	One box of six sprays	Two boxes of 12 sprays	one per script	160 mg
	20 mg	One box of six sprays	Two boxes of 12 sprays	one per script	
Imitrex injection kits/refills	6 mg (12mg/mL)	two prefilled syringe/cartridge	Two pen kits	one per script	48 mg
Imitrex Cartridge	6 mg/0.5 mL	One case of two pens	Two cases	one per script	48 mg
	4 mg/0.5 mL	one case of two pens	Two cases	one per script	48 mg
Imitrex pen	4 mg/0.5 mL	one case of two pens	Two cases	one per script	48 mg
Imitrex, vials	6mg/0.5 mL	6 mg single-dose vials in carton of five vials	Five vials	one per script	48 mg
Maxalt, Maxalt-MLT	5 mg	one pack of six tabs	Two packs or 12 tablets	one per script	120 mg
	5mg	one pack of nine tabs	Two packs or 18 tablets	one per script	
	10 mg	one pack of six tabs	Two packs or 12 tablets	one per script	
	10 mg	one pack of nine tabs	Two packs or 18 tablets	one per script	
	5 mg	case of two with three inside	Two packs or 12 tablets	one per script	
	5 mg	case of three with three inside	Two packs or 18 tablets	one per script	
	10 mg	case of two with three inside	Two packs or 12 tablets	one per script	
Relpax	20 mg	three pack of six tablets	Two packs or 12 tablets	one per script	240 mg
	40 mg	one pack of six tablets	One pack or six tablets	one per script	
Zomig, Zomig ZMT	2.5 mg	one pack of six tablets	Two packs or 12 tablets	one per script	30 mg
	5 mg	one pack of three tablets	Two packs or six tablets	one per script	
Zomig, Nasal Spray	5 mg	one pack of six sprays	Two packs or 12 sprays	one per script	40 mg

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT ^{®*} Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description

HCPCS Codes	Description

ICD-9-CM Diagnosis Codes	Description

*Current Procedural Terminology (CPT[®]) © 2004 American Medical Association: Chicago, IL.

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