



Antimigraine Agents, Triptans Therapeutic Class Review (TCR)

August 1, 2019

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
almotriptan ¹	generic	Acute treatment of migraine attacks with or without aura in adults and in adolescents 12 to 17 years of age whose attacks usually last 4 hours or more
eletriptan (Relpax®) ²	generic, Pfizer	Acute treatment of migraine attacks with or without aura in adults
frovatriptan (Frova®) ³	generic, Endo	
naratriptan (Amerge®) ⁴	generic, GlaxoSmithKline	
rizatriptan (Maxalt®, Maxalt-MLT®) ⁵	generic, Merck	Acute treatment of migraine attacks with or without aura in adults and in pediatric patients 6 to 17 years of age
sumatriptan (Imitrex®) ^{6,7,8}	generic, GlaxoSmithKline	Acute treatment of migraine attacks with or without aura in adults (all formulations) Injection: Acute treatment of cluster headache episodes in adults
sumatriptan (Onzetra® Xsail®) ⁹	Avanir	Acute treatment of migraine attacks with or without aura in adults
sumatriptan (Sumavel® DosePro®) ¹⁰	Endo	Acute treatment of migraine attacks with or without aura in adults Acute treatment of cluster headache episodes in adults
sumatriptan (Tosymra™) ¹¹	Promius/Upsher-Smith	Acute treatment of migraine with or without aura in adults
sumatriptan (Zembrace® SymTouch®) ¹²	Promius	Acute treatment of migraine with or without aura in adults
sumatriptan/naproxen (Treximet®) ¹³	generic, Pernix	Acute treatment of migraine attacks with or without aura in those ≥ 12 years of age
sumatriptan; camphor/menthol* (Migranow™) ¹⁴	Puretek	Acute treatment of migraine attacks with or without aura in adults
zolmitriptan (Zomig®, Zomig-ZMT®) ^{15,16}	generic, Impax	Acute treatment of migraine attacks with or without aura in adults†

*Migranow kit contains sumatriptan tablets (approved as a therapeutic equivalent of Imitrex) co-packaged with Camphotrex™ pain relieving gel (camphor/menthol), an analgesic indicated for the temporary relief of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains, bruises, and sprains.

† Zomig nasal spray is approved in patients ≥ 12 years of age.

For all agents in this review, use only after a clear diagnosis of migraine has been established.

Endo announced discontinuation of Sumatriptan injection with needle-free delivery system (Sumavel DosePro) 4 mg/0.5 mL (in 2016) and 6 mg/0.5 mL (in February 2018) due to business reasons.^{17,18}

OVERVIEW

Headache is one of the most common complaints by patients when presenting to a physician. Migraine accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (U.S.).^{19,20} The American Migraine Study 2 found that migraine causes decreased productivity and absenteeism from work for many patients, which creates a large economic impact for the U.S.²¹ Sixty-four percent of physician-diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bed rest due to their migraine symptoms. In addition, 18% of women, 6% of men, and 10% of children experience migraine, an epidemiologic profile that has remained stable over many years.^{22,23} Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month.²⁴ However, over 4 million people experience at least 15 migraine days per month.²⁵ The median frequency of migraine attacks among migraine sufferers is 1.5 per month.²⁶

Migraine headache must be differentiated from tension-type headache. Key criteria for the diagnosis of migraine headache is an episodic headache lasting from 4 to 72 hours with at least 2 of the following symptoms: (1) unilateral pain, (2) throbbing, (3) aggravated by routine physical activity, and (4) pain of moderate to severe intensity.²⁷ During the headache at least 1 of the following are present: (1) nausea and/or vomiting, or (2) photophobia and phonophobia. The American Headache Society continues to recognize non-opioid analgesia with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or caffeinated combinations as first-line therapy for patients with mild to moderate migraine pain.²⁸ Migraine-specific agents (triptans, dihydroergotamine [DHE]) should be used in patients who experience moderate to severe migraine attacks. Due to well-established efficacy, the triptans have become the drugs of choice for treating acute migraine attacks.

In 2000, the US Headache Consortium, a multidisciplinary panel of several professional organization, including the American Academy of Family Physicians, American Academy of Neurology (AAN), American Headache Society (AHS) American College of Emergency Physicians, American Osteopathic Association, National Headache Foundation, and the American College of Physicians – American Society of Internal Medicine, recognized that the triptans are effective agents for the acute treatment of migraine.^{29,30} Data reviewed for the guidelines did not demonstrate that any 1 triptan was superior. These groups indicated that therapy with any triptan for a patient with moderate to severe migraine pain in whom no contraindications exist is appropriate. If a patient does not experience adequate relief or experiences intolerable adverse reactions with 1 triptan, treatment with another agent in the class may be effective.^{31,32,33,34} However, multiple agents within this class were not available at the time of these publications.

In their 2012 practice guidelines, pharmacologic treatment for episodic migraine prevention in adults, the AAN and the AHS advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention; frovatriptan is established for short-term menstrually associated migraine (MAM) prevention.³⁵ Naratriptan, zolmitriptan, antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention; but no triptan is approved for the prevention of migraines. This guideline was reaffirmed in July 2015.

A publication from the AHS in 2015 assessed the evidence for the acute treatment of migraine in adults from 1998 to 2013.³⁶ The AHS concluded that all available triptans (almotriptan; eletriptan; frovatriptan; naratriptan; rizatriptan; sumatriptan oral, nasal, injectable, and transdermal; and zolmitriptan oral and

nasal) are effective treatments (Level A evidence, defined as ≥ 2 well-designed, double-blind, randomized, placebo-controlled studies). Dihydroergotamine (nasal, inhaler), acetaminophen, NSAIDs, select opioids, sumatriptan/naproxen, and acetaminophen/aspirin/caffeine were also rated as effective with Level A evidence. No recommendation was offered regarding an advantage of 1 triptan over another.

In 2019 the AHS published its position statement on integrating new migraine treatments into clinical practice; there were no changes in recommended usage or place in therapy for agents in this class from previous guidelines.³⁷ The AHS included recommendations regarding use non-triptan, injectable agents, including onabotulinumtoxinA (Botox[®]) and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) (fremanezumab [Ajovy[®]], galcanezumab [Emgality[®]]) or the CGRP receptor (erenumab [Aimovig[®]]) for migraine prevention in patients who experience episodic (CGRP agents only) or chronic (both classes) migraine; these agents are not discussed in this therapeutic class review.

PHARMACOLOGY^{38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54}

Receptor Binding

Drug	High Binding Affinity	Weak Binding Affinity
almotriptan	5-HT _{1B} , 5-HT _{1D} , 5-HT _{1F}	5-HT _{1A} , 5-HT ₇
eletriptan (Relpax)	5-HT _{1B} , 5-HT _{1D} , 5-HT _{1F}	5-HT _{1A} , 5-HT _{1E} , 5-HT _{2B} , 5-HT ₇
frovatriptan (Frova)	5-HT _{1B} , 5-HT _{1D}	--
naratriptan (Amerge)	5-HT _{1B} , 5-HT _{1D}	--
rizatriptan (Maxalt, MLT)	5-HT _{1B} , 5-HT _{1D}	5-HT _{1A} , 5-HT _{1E} , 5-HT _{1F} , 5-HT ₇
sumatriptan (Imitrex, Migranow, Onzetra Xsail, Sumavel DosePro, Tosymra, Treximet, Zembrace SymTouch)	5-HT _{1B} , 5-HT _{1D}	5-HT _{1A} , 5-HT _{5A} , 5-HT ₇
zolmitriptan (Zomig, ZMT)	5-HT _{1B} , 5-HT _{1D}	5-HT _{1A}

Migraine pain is believed to result from activity within the trigeminovascular system. This activity results in a release of vasoactive neuropeptides with subsequent vasodilation, dural plasma extravasation, and perivascular inflammation.⁵⁵ The therapeutic activity of the triptan derivatives can be attributed to agonist effects on the vascular and neuronal serotonin (5-hydroxytryptamine, 5-HT₁) receptor subtypes in the trigeminal system. Relief of migraine headache may result from (1) intracranial vessel constriction via stimulation of vascular 5-HT_{1B} receptors; (2) inhibition of vasoactive neuropeptide release through stimulation of presynaptic 5-HT_{1D} receptors; and (3) interruption of pain signal transmission within the brainstem through stimulation of 5-HT_{1D} receptors.

All serotonin agonists in this class are selective 5-HT₁ receptor agonists, acting at subset 5-HT_{1D} and most also at 5-HT_{1B}. When activated, these receptors are believed to mediate the symptoms associated with a migraine attack.^{56,57}

Naproxen is an NSAID that inhibits the synthesis of inflammatory mediators and has analgesic properties.

Camphor and menthol are topical analgesics. The mechanisms of analgesia of these agents are not well defined but are thought to be associated with an antipruritic effect, cooling sensation, irritant/counter-irritant effect, and/or vasodilation.

PHARMACOKINETICS^{58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73}

Drug	Bioavailability (%)	Half-Life (hrs)	Tmax (hrs)	Time to Onset of Effect (hrs) ⁷⁴	Active Metabolites	Excretion (%)
almotriptan	70	3–4	1–3	0.5–2	None	Urine: 75 Feces: 13
eletriptan (Relpax)	50	4	1.5–2	1–2	N-demethylated metabolite	Predominantly non-renal
frovatriptan (Frova)	20 in men 30 in women	26	2–4	2–4	One with minor activity	Urine: 32 Feces: 62
naratriptan (Amerge)	70	6	3–4	1–3	None active	Urine: 80
rizatriptan (Maxalt, MLT)	45	2–3	1–1.5* 1.6-2.5 [†]	0.5–2	N-monodesmethyl-rizatriptan (activity similar to parent)	Urine: 82 Feces: 12
sumatriptan injection (Imitrex, Sumavel DosePro, Zembrace SymTouch)	97	1.9	12 minutes	0.17–0.25	None	Urine: 60
sumatriptan nasal powder (Onzetra Xsail)	19	3	0.75	--	None	Urine: 45
sumatriptan nasal spray (Imitrex)	15	2.5	2.5	0.25–0.33	None	Urine: 45
sumatriptan nasal spray (Tosymra)	87	2.4	5–23 minutes	--	None	Urine: 60
sumatriptan tablet (Imitrex, Migranow)	15	2.5	2	0.5–1.5	None	Urine: 60 Feces: 40
sumatriptan/ naproxen (Treximet)	15	2	1.5	--	None 6-O-desmethyl naproxen	Urine: 60 Feces: 40
	95	12–19	1			Urine: 95
zolmitriptan (Zomig, ZMT)	40	3	1.5* 3 [†]	0.75–1	N-desmethyl metabolite (potency is 2 to 6 times that of the parent)	Urine: 65 Feces: 30
zolmitriptan nasal spray (Zomig)	102 (versus oral tablet)	3	3	0.25–0.33		Predominantly renal

hr = hours

*Regular tablets

[†]Orally disintegrating tablets

Subcutaneous administration of sumatriptan typically provides the fastest and most complete migraine symptom relief, but is associated with a higher incidence of adverse effects. Oral formulations are most commonly used, but may not be appropriate for some patients, particularly those who experience nausea and vomiting.

Pharmacokinetic studies show that drug delivery of sumatriptan nasal spray (Imitrex) was greatest anterior to the nasal valve and in the lower posterior region (floor) of the nasal cavity, while delivery of sumatriptan nasal powder (Onzetra Xsail), using the breath powered deliver device, was deposited beyond the nasal valve, an area that may allow for greater drug absorption.⁷⁵ The results suggest that, with the nasal spray a significant amount of drug is swallowed, leading to a dual serum peak pattern.⁷⁶ Compared to the nasal spray, the nasal powder was reported to have an earlier and more pronounced peak plasma concentration, suggesting that a larger proportion of the dose is absorbed intranasally rather than in the gastrointestinal (GI) tract.

The intranasal formulation of sumatriptan, Tosymra, contains the permeation enhancer 1-O-n-Dodecyl- β -D-maltopyranoside (DDM), and a pharmacokinetic study compared this formulation to the other sumatriptan nasal spray, Imitrex 20 mg.⁷⁷ It was demonstrated that Tosymra 10 mg had faster absorption than Imitrex intranasal with the time to maximum concentrations of 15 minutes for a single dose and 10.2 minutes for multidoses (at least 5 days between treatments) compared with 2 hours for Imitrex.

CONTRAINDICATIONS/WARNINGS^{78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93}

Triptan use is contraindicated in patients with known hypersensitivity to any component of the product. Injectable products may contain latex; use with caution in latex-sensitive individuals.

Sumatriptan/naproxen has Boxed warnings regarding serious cardiovascular and gastrointestinal (GI) events. NSAIDs increase the risk of potentially fatal myocardial infarction and stroke. NSAIDs also increase the risk of serious GI inflammation, bleeding, ulceration, and perforation. NSAID-containing products are contraindicated in the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery (CABG). Long-term administration of NSAIDs can also lead to hepatic and/or renal dysfunction, skin reactions, such as Stevens-Johnson syndrome, and premature closure of the ductus arteriosus in late pregnancy. Sumatriptan/naproxen is also contraindicated in patients with certain cardiac and vascular conditions (as described above); stroke, transient ischemic attacks, or related conditions; ischemic bowel disease; use during the third trimester of pregnancy; and history of asthma, urticaria, or allergic-type reactions with components. Anemia and other hematologic toxicities have been reported with NSAIDs. NSAID-containing products, like Treximet, may also mask the signs and symptoms of inflammation and fever. Laboratory monitoring should be considered in patients using long-term NSAIDs due to the risk of GI bleeding, hepatotoxicity, and renal injury.

While the incidence is rare, the triptans have been associated with angina (including Prinzmetal's variant angina), myocardial infarction, cardiac arrhythmias, hypertension, or stroke, particularly when they were used in patients with vascular risk factors. Triptans should be used with extreme caution in these patients or those with a suspected history of coronary artery disease. Triptans should not be used in patients with uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, cerebrovascular disease, or ischemic bowel disease. Patients with these or other significant underlying cardiovascular diseases should not receive sumatriptan/naproxen (Treximet), nor should patients who have undergone coronary artery bypass graft surgery as this is contraindicated. Triptans may cause

sensations of chest, throat, neck, or jaw pain or tightness, which is generally non-cardiac; however, a cardiac evaluation is warranted in high-risk patients. Other vasospasm reactions (e.g., peripheral vascular ischemia, GI or splenic infarction, Raynaud's syndrome) have also been reported with triptans.

Triptans should not be used in patients with severe hepatic impairment or diseases that impair absorption, metabolism, and excretion of these products. Naratriptan (Amerge) and sumatriptan/naproxen should not be used in patients with severe renal impairment (creatinine clearance [CrCl] < 15 mL/min). Rizatriptan (Maxalt) should be used with caution in patients with moderate hepatic insufficiency.

In a Public Health Advisory, the Food and Drug Administration (FDA) cautioned that serotonin syndrome could occur if triptans are used in combination with selective serotonin reuptake inhibitor (SSRI) or selective serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants.⁹⁴ All triptan-containing products include this warning in their labeling.

Seizures have been reported with use of triptans; use caution in patients with an epilepsy history or in conditions with a lowered seizure threshold.

Overuse of ergotamines, triptans, and opioids has been associated with the exacerbation of headache (medication overuse headache) in susceptible patients. Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Withdrawal of the treatment may be necessary.

Phenylketonuric patients should be advised that the oral disintegrating tablet formulations contain phenylalanine (Maxalt-MLT, Zomig-ZMT).

Both nasal spray formulations of sumatriptan (Imitrex and Tosymra) carry the potential for local irritation. Only a small percentage of these cases were considered to be severe (~1% for Imitrex, 0.5% for Tosymra).

If excessive irritation develops after using menthol/camphor gel (a component of the Migranow kit) or the condition worsens, the patient should contact his or her prescriber. This product should not be used on wounds or damaged skin, and the patient should avoid contact with eyes or mucous membranes.

DRUG INTERACTIONS^{95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110}

All agents from this class should not be given within 24 hours of ergot alkaloids or another triptan.

Rizatriptan (Maxalt), sumatriptan (Imitrex, Onzetra Xsail, Migranow, Sumavel DosePro, Tosymra, Treximet, Zembrace SymTouch), and zolmitriptan (Zomig) should not be given within 2 weeks of a monoamine oxidase inhibitor (MAOI) due to increased exposure of these select triptans.

Concurrent use of almotriptan or eletriptan (Relpax) with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, nelfinavir) can significantly increase the exposure of the triptan. Initial dose of almotriptan should be at the lower end of the recommended range (6.25 mg) and the maximum dose within a 24-hour period should not exceed 12.5 mg. Concurrent use of almotriptan and a potent CYP3A4 inhibitor should be avoided in patients with renal or hepatic impairment. Eletriptan (Relpax) should not be used within 72 hours of the following a potent CYP450 3A4 inhibitor.¹¹¹

Concurrent use of rizatriptan and propranolol can increase exposure to the triptan by 70%; therefore, rizatriptan total daily dose should be limited when administered concurrently with propranolol.¹¹²

NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors. Concomitant use of aspirin or bisphosphonates and NSAIDs is not generally recommended because of the potential for GI ulceration. The effects of warfarin and NSAIDs on GI bleeding are synergistic, thereby increasing the risk of serious GI bleeding when used together. There is an increased bleeding risk when NSAIDs are given with selective SSRIs, as well. The effects of NSAIDs on renal prostaglandin synthesis may alter the effects of cyclosporine, lithium, and various diuretics.

Caution should be used when co-administering triptans with other serotonergic medications (e.g., SSRIs, SNRIs) due to the risk of serotonin syndrome.

Concurrent use of sumatriptan/naproxen (Treximet) can result in an increased risk for cardiovascular events based upon a pharmacodynamic study demonstrating lower dose naproxen interferes with the antiplatelet effect of low-dose aspirin. Consider use of an NSAID that does not interfere with the antiplatelet effects of aspirin in patients who are taking low-dose aspirin for cardioprotection who require intermittent analgesics.¹¹³

Drug interactions with menthol/camphor gel (within the Migranow kit) are unknown.

ADVERSE EFFECTS^{114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129}

Drug	Paresthesia	Pain and Pressure Sensations	Flushing/ Palpitations	Nausea	Dizziness	Somnolence	Unusual Taste/ Nasal Irritation
almotriptan	1	< 1	< 1	1-2	< 1	< 1	nr
eletriptan (Relpax)	3-4	1-2	2 / < 2	4-8	3-7	3-7	nr
frovatriptan (Frova)	4	3 / reported	4 / nr	> 2	8	> 2	nr
naratriptan (Amerge)	1-2	2-4	nr	4-5	1-2	1-2	nr
rizatriptan tablet (Maxalt, MLT)	3-4	6-9	> 1 / > 1	4-6	4-9	4-8	nr
sumatriptan injection (Imitrex, Sumavel DosePro, Zembrace SymTouch)	5-14	7	7 / < 1	< 1	12	3	nr
sumatriptan nasal powder (Onzetra Xsail)	nr	nr	nr	nr	nr	nr	20
sumatriptan nasal spray (Imitrex)	0.4-1.4	< 1	< 1	11-13.5	1-1.4	< 1	13.5-24.5 / 2.5-3.8
sumatriptan tablet (Imitrex, Migranow)	3-5	6-8	nr	nr	> 1	> 1	nr
sumatriptan/naproxen (Treximet)	2	3	> 1	3	4	3	nr
zolmitriptan tablet (Zomig, ZMT)	5-9	13-22	1-2	4-9	6-10	5-8	nr
zolmitriptan nasal spray (Zomig)	10	10	reported	4	3	4	21 / 3

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive.

nr = not reported.

In clinical studies, ear, nose, and throat discomfort was reported in 2.5% to 3.8% of patients treated with sumatriptan nasal spray (Imitrex) versus 2.4% with placebo. Nasal discomfort was reported in 1% to 3% of patients treated with zolmitriptan nasal spray compared to 2% with placebo. Common adverse effects reported with sumatriptan nasal powder (Onzetra Xsail) included nasal discomfort (11% versus 1% for placebo) and rhinorrhea (5% versus 2% for placebo). Local irritative symptoms occurred in about 46% of patients who received sumatriptan nasal spray (Tosymra) during an open-label study with repeated administration over the course of 6 months. The most common symptoms in this study were burning sensation in the nose, dysgeusia, and throat irritation.

SPECIAL POPULATIONS^{130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145}

Pediatrics

Almotriptan, sumatriptan/naproxen (Treximet), and zolmitriptan nasal spray (Zomig) are approved for adolescents 12 to 17 years of age, whereas rizatriptan (Maxalt, Maxalt MLT) carries approval for pediatric patients 6 to 17 years of age whose attacks usually last 4 hours or more. The other products in this class have not been approved for use in pediatric populations (< 18 years of age).

There are data to suggest that other agents may be effective in the treatment of migraine headaches in adolescents; all measure triptan efficacy against placebo. In general, even if statistically significant differences are demonstrated, the response rates for placebo are high. This is true for almotriptan, as well as zolmitriptan nasal spray (Zomig).^{146,147} Several studies in patients ages 12 to 17 years showed efficacy for sumatriptan (Imitrex) nasal spray.^{148,149,150}

Pregnancy

All triptans in this review currently are or were previously considered Pregnancy Category C. The labels for frovatriptan (Frova), naratriptan (Amerge), sumatriptan (Imitrex, Zembrace SymTouch), and zolmitriptan (Zomig, Zomig ZMT) have been updated to remove the Pregnancy Category C indicator in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). The label for sumatriptan nasal spray (Tosymra) also complies with the PLLR. Data is not adequate to establish guidance on the use of naratriptan in pregnant women. Products containing NSAIDs (Treximet) should not be used in pregnant women during the third trimester due to risk of premature closure of the ductus arteriosus (Category X).

Renal Impairment

Although no significant change in clearance of eletriptan was observed, blood pressure elevations were reported in those with mild to severe renal impairment. Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan.

Dose adjustments are recommended for patients taking almotriptan with severe renal impairment and patients taking naratriptan with mild to moderate impairment. Naratriptan is contraindicated in patients with severe renal impairment (CrCl < 15 mL/min).

Little clinical effect on sumatriptan or frovatriptan is expected in those with renal impairment since it is largely metabolized to an inactive substance.

Elimination of naproxen is decreased in patients with severe renal impairment. Sumatriptan/naproxen (Treximet) is contraindicated in patients with CrCl < 30 mL/min.

In studies, clearance of zolmitriptan was decreased by 25% in those with severe renal impairment.

Hepatic Impairment

Triptans should not be used in patients with severe hepatic impairment or diseases that impair absorption, metabolism, and excretion of these products. Rizatriptan should be used with caution in patients with moderate hepatic insufficiency. Dosage adjustments are required for almotriptan and naratriptan for those with mild to moderate impairment. The maximum single dose for oral formulations of sumatriptan is 50 mg in patients with moderate impairment. Use of lower dosages of zolmitriptan is recommended in patients with moderate to severe hepatic impairment.

DOSAGES^{151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166}

Drug	Availability	Single Initial Dose	Minimum Time Before Repeat Dose (hr)	Maximum Dose in 24 Hours (mg)	Package Size
almotriptan	6.25 mg, 12.5 mg tablets	6.25 mg or 12.5 mg	2	25	1, 6 (6.25 mg only), 12 (12.5 mg only)
eletriptan (Relpax)	20 mg, 40 mg tablets	20 mg or 40 mg	2	80	1, 6, 12 (40 mg only)
frovatriptan (Frova)	2.5 mg tablet	2.5 mg	2	7.5	1, 9 (brand only)
naratriptan (Amerge)	1 mg, 2.5 mg tablets	1 mg or 2.5 mg	4	5	1, 9 (generic only)
rizatriptan (Maxalt, MLT)	5 mg, 10 mg tablets	5 mg or 10 mg (pediatrics weight based: 5 mg < 40 kg; 10 mg ≥ 40 kg)	2 (adults); Subsequent redosing not established in children	30 (adults), 5 to 10mg (children)	Tablets: 5 mg (generic only): 1, 12, 18, 30 10 mg: 1, 12, 18, 30 MLTs (orally disintegrating tablets [ODTs]): 5 mg: 1, 3, 9, 12, 18 10 mg: 1, 3, 9, 12, 18
sumatriptan injection (Imitrex)	4 mg, 6 mg injection	4 mg, 6 mg SC	1	12	Injection: 4 or 6 mg/0.5 mL Injection kit STATdose system® (2 prefilled cartridges + 1 pen); STATdose cartridges (2 prefilled cartridges for refill) Vials: 6 mg injections only (5 single-dose vial cartons)
sumatriptan injection (Sumavel DosePro)	4 mg, 6 mg injection (needle-free system)	4 mg, 6 mg SC	1	12	Two 4 or 6 mg/0.5 mL single-dose pre-filled units*

MLT = Maxalt orally disintegrating tablet

*In 2016, Endo made a business decision to discontinue the 4 mg strength of Sumavel DosePro; in March 2018 Endo announced that the 6 mg formulation will also be discontinued for business reasons. Product may be available until product expiry is reached.

Dosages (continued)

Drug	Availability	Single Initial Dose	Minimum Time Before Repeat Dose (hr)	Maximum Dose in 24 Hours (mg)	Package Size
sumatriptan injection (Zembrace SymTouch)	3 mg injection	3 mg SC	1 may be given \geq 1 hour after a dose of another sumatriptan product	12	Four 3 mg/0.5 mL prefilled auto-injectors
sumatriptan nasal powder (Onzetra Xsail)	11 mg per single-use nosepiece	22 mg (2 nosepieces)	2	44	8 doses (16 nose-pieces) per kit
sumatriptan nasal spray (Imitrex)	5 mg, 20 mg per spray	5 mg or 10 mg (1 to 2 sprays) or 20 mg (1 spray)	2	40	6
sumatriptan nasal spray (Tosymra)	10 mg per single-dose nasal spray device	10 mg (1 spray in 1 nostril)	1	30	6
sumatriptan tablet (Imitrex)	25 mg, 50 mg, 100 mg tablets	25 mg to 100 mg	2	200	1, 9, 36, 90, 100
sumatriptan/naproxen (Treximet)	10 mg/60 mg (brand only), 85 mg/500 mg tablets	Pediatric: 10/60 mg Adult: 85/500 mg	2	Pediatric: 1 tablet of 85/500 mg Adult: 2 tablets of 85/500 mg	9
sumatriptan; camphor/menthol (Migranow Kit)	50 mg sumatriptan tablets; 4% camphor/10% menthol gel	Tablets: 25 mg to 100 mg; Gel: using liberal amount, apply directly on affected area (avoiding eyes or mucous membranes)	Tablets: 2; Gel: no time interval specified	Tablets: 200; Gel: 3 to 4 uses/day	1-kit: nine 50 mg sumatriptan tablets co-packaged with 3 oz (85 g) of Camphotrex Extra Strength gel (4% camphor/10% menthol) with roll-on applicator
zolmitriptan (Zomig, ZMT)	2.5 mg, 5 mg tablets and ODTs	2.5 mg or 5 mg	2	10	Tablets: 2.5 mg: 1, 6 5 mg: 1, 3 ZMT (ODT): 2.5 mg: 1, 6 5 mg: 1, 3
zolmitriptan nasal spray (Zomig)	2.5 mg, 5 mg per spray	2.5 mg	2	10	6-single dose nasal spray units in 2 mg or 5 mg strengths (brand only)

TDS = transdermal system; ZMT = Zomig orally disintegrating tablet

Dosing Considerations

Renal Impairment

The recommended starting dose of almotriptan in patients with severe renal impairment is 6.25 mg. The maximum daily dose should not exceed 12.5 mg over a 24-hour period. In patients with mild to moderate renal impairment, the maximum daily dose of naratriptan should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered. Naratriptan should not be used in patients with severe renal impairment. Sumatriptan/naproxen sodium is not recommended in patients with CrCl < 30 mL/min.

The safety of treating, on average, more than 3 headaches in a 30-day period has not been established for eletriptan tablets and zolmitriptan tablets and orally disintegrating tablets; more than 4 headaches in a 30-day period for almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan tablets and nasal spray, nasal powder, and zolmitriptan nasal spray; and more than 5 headaches in a 30-day period for sumatriptan/naproxen.

Hepatic Impairment

The recommended starting dose of almotriptan in patients with hepatic impairment is 6.25 mg. The maximum daily dose should not exceed 12.5 mg over a 24-hour period. In patients with mild or moderate hepatic impairment, the maximum daily dose of naratriptan should not exceed 2.5 mg over a 24-hour period and a lower starting dose should be considered. The use of naratriptan is contraindicated in patients with severe hepatic impairment (Child-Pugh C). Use of sumatriptan is not recommended, but if treatment is deemed advisable in the presence of liver disease, the maximum single oral dose, in general, should not exceed 50 mg. Sumatriptan/naproxen sodium is contraindicated in patients with hepatic impairment. Patients with moderate or severe hepatic impairment have decreased clearance of zolmitriptan, and significant elevation in blood pressure has been observed in some patients. Use of zolmitriptan doses < 2.5 mg of an alternate formulation with blood pressure monitoring is recommended.

Drug Interactions

Eletriptan (Relpax) should not be used within 72 hours of CYP450 3A4 inhibitors.¹⁶⁷ The recommended starting dose of almotriptan is 6.25 mg in patients taking a potent CYP3A4 inhibitor; maximum dose within a 24-hour period should not exceed 12.5 mg in these patients. Avoid concurrent use of almotriptan and a potent CYP3A4 inhibitor in patients with renal or hepatic impairment.

Rizatriptan dose should not exceed 5 mg (up to a maximum of 3 doses in any 24-hour period in adults and a single dose of 5 mg for pediatric patients weighing greater or equal to 40 kg) when administered concurrently with propranolol.¹⁶⁸

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human

participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Randomized, double-blind, comparative trials meeting criteria are not available for frovatriptan (Frova); however, its efficacy has been assessed in placebo-controlled and open-label trials.^{169,170} Likewise, large, randomized, double-blind, comparative trials meeting inclusion criteria have not been published for sumatriptan injections (Imitrex, Sumavel DosePro, Zembrace SymTouch), rizatriptan ODT (Maxalt-MLT), or zolmitriptan nasal spray (Zomig) but their efficacy has been described.^{171,172,173,174,175,176,177} The prescribing information for the Migranow kit, which contains sumatriptan tablets and topical camphor/menthol, contains the same efficacy studies included in the prescribing information for sumatriptan tablet (Imitrex).¹⁷⁸ No randomized, controlled studies of this kit are available.

The sumatriptan nasal spray, Tosymra, was approved via the 505(b)(2) pathway, and an efficacy study was not required for approval as efficacy was based on that previously established with the reference drug sumatriptan injection.¹⁷⁹ However, a pharmacokinetic study was required and demonstrated the bioavailability of the 10 mg nasal spray was found to be 87% (95% confidence interval [CI], 82 to 94) of that observed following 4 mg of sumatriptan administered subcutaneously.^{180,181,182} In addition, a long-term safety study evaluating the intranasal local toxicity of the nasal spray formulation was required by the FDA.^{183,184} The overall safety profile for the nasal spray formulation was found to be similar to that of the reference product; however, adverse effects related to local toxicity were observed and are therefore described in the product's labeling.

almotriptan versus sumatriptan (Imitrex)

A randomized, double-blind trial comparing the efficacy and safety of almotriptan 12.5 mg and oral sumatriptan 50 mg enrolled 1,173 patients with migraine.¹⁸⁵ Efficacy was evaluated at 2 hours for headache relief (decrease in pain to little or no pain), headache freedom (decrease to no pain), use of rescue medications, and headache recurrence. At 2 hours, almotriptan and sumatriptan provided headache relief in 58% and 57.3% of patients, respectively. Almotriptan provided headache freedom in 17.9% of patients, and 24.6% of the sumatriptan group reported headache freedom ($p=0.005$). All other efficacy variables were similar for both treatment groups. Adverse effects were reported less frequently in the almotriptan group (15.2%) compared to the sumatriptan group (19.4%; $p=0.06$) although the difference was not statistically significant.

In a study to evaluate patient satisfaction with antimigraine therapy, 1,173 patients were randomized to almotriptan 12.5 mg or sumatriptan 50 mg oral in a double-blind manner.¹⁸⁶ Diaries were evaluated for satisfaction of pain relief, side effects, functional status, and health-related quality of life (HRQOL). No difference was seen between the groups for satisfaction with pain relief, functional status, or HRQOL results. Almotriptan patients reported being less bothered by side effects.

In a randomized, single-dose, placebo-controlled, double-blind study, almotriptan and sumatriptan were compared for efficacy and safety in the treatment of migraine.¹⁸⁷ Patients (n=668) were randomized to almotriptan 12.5 or 25 mg, sumatriptan 100 mg, or placebo and evaluated for pain relief at 2 hours following dosing. All active therapies had equivalent response rates that were significantly superior to placebo. Almotriptan was tolerated best and similar to placebo. Almotriptan 25 mg and sumatriptan 100 mg had similar incidence of adverse effects.

almotriptan versus zolmitriptan (Zomig)

In a multicenter, double-blind, randomized trial, 532 adult migraineurs received almotriptan 12.5 mg and 530 adult migraineurs received zolmitriptan 2.5 mg for the treatment of a single migraine attack.¹⁸⁸ For blinding purposes, both drugs were encapsulated. The primary endpoint was sustained pain-free patients with no adverse events. Other endpoints included pain relief and pain-free at several time points, sustained pain free, headache recurrence, use of rescue medication, functional impairment and time lost because of migraine, treatment acceptability, and overall treatment satisfaction. No significant differences were seen in the percentage of patients that were sustained pain-free with no adverse events (almotriptan 29.2% and zolmitriptan 31.8%; p=0.357) or the other efficacy endpoints measured including pain-relief and pain-free at 2 hours. The incidence of triptan-associated adverse events and triptan-associated central nervous system adverse events was significantly lower for patients receiving almotriptan compared to zolmitriptan (p=0.03).

eletriptan (Relpax) versus sumatriptan (Imitrex)

In a randomized, double-blind, parallel-group trial, eletriptan and sumatriptan were compared for efficacy, safety, and tolerability in the acute treatment of migraine in 692 patients.¹⁸⁹ Patients were randomized to placebo, sumatriptan 100 mg, or eletriptan 20 mg, 40 mg, or 80 mg. At 2 hours, headache response rates were 24% for placebo, 55% for sumatriptan, 54% for eletriptan 20 mg, 65% for eletriptan 40 mg, and 77% for eletriptan 80 mg. At 2 hours, there was a difference between sumatriptan 100 mg and eletriptan 80 mg in headache response rate (p<0.001). All doses of eletriptan were significantly different from placebo for headache response rate (p<0.001). Headache-free rates at 2 hours for eletriptan 80 mg were superior to sumatriptan 100 mg (37% versus 23%; p<0.05). All therapies were well tolerated. Eletriptan 80 mg is not currently available in the U.S., nor is the 80 mg dose FDA-approved.

Eletriptan and sumatriptan were compared in a single migraine attack study enrolling 2,113 patients.¹⁹⁰ Patients were randomized to eletriptan 40 mg, sumatriptan 100 mg, or placebo in the double-blind, parallel-group trial involving patients with moderate migraine headaches. After 2 hours, the headache response rate was 67% for eletriptan, 59% for sumatriptan, and 26% for placebo, both statistically significant differences in favor of eletriptan (p<0.001, p<0.0001). Eletriptan patients also reported less nausea, photophobia, and phonophobia compared with sumatriptan after 2 hours. Overall, the incidence of adverse effects was low for the 2 active treatment groups, with nausea being the most commonly reported in all groups.

Eletriptan and sumatriptan were compared for efficacy in the acute treatment of migraine in 1,008 patients.¹⁹¹ Patients were randomized in a double-blind manner to placebo, eletriptan 40 mg or 80 mg, or sumatriptan 50 mg or 100 mg to treat up to 3 attacks. The sumatriptan doses were encapsulated in the study. The primary endpoint of the study was the 1-hour headache response, which was 12% for placebo, 24% for sumatriptan 50 mg, 27% for sumatriptan 100 mg, and 30 and 37% for eletriptan 40

and 80 mg, respectively. Two-hour response rates were 31% for placebo, 50% for sumatriptan 50 mg, 53% for sumatriptan 100 mg, 64% for eletriptan 40 mg, and 67% for eletriptan 80 mg. For the 2-hour response rate, all doses of eletriptan were superior to sumatriptan for headache response and complete pain relief ($p < 0.05$). All treatments were well tolerated.

eletriptan (Relpax) versus naratriptan (Amerge)

In a randomized, double-blind, placebo-controlled study, migraine patients ($n=548$) were randomized to treat a single migraine attack with eletriptan 40 mg, naratriptan 2.5 mg, or placebo.¹⁹² Headache response rates at 2 hours and 4 hours, respectively, were 56 and 80% for eletriptan, 42 and 67% for naratriptan ($p < 0.01$ for both time-points), and 31 and 44% for placebo ($p < 0.0001$ versus both active drugs at both time-points). Eletriptan showed a greater pain-free response at 2 hours (35 versus 18%; $p < 0.001$), as well as lower use of rescue medication (15 versus 27%; $p < 0.01$) and higher sustained headache response at 24 hours (38 versus 27%; $p < 0.05$) compared with naratriptan.

eletriptan (Relpax) versus zolmitriptan (Zomig)

In a multicenter, double-blind, double-dummy, parallel-group trial, 1,587 outpatients with migraine were randomized in a 3:3:3:1 ratio to eletriptan 80 mg, eletriptan 40 mg, zolmitriptan 2.5 mg, or placebo.¹⁹³ Of these, 1,312 treated a single migraine attack and were included in the intention-to-treat population. For the primary efficacy endpoint of headache response at 2 hours, rates were 74% for eletriptan 80 mg, 64% for eletriptan 40 mg, 60% for zolmitriptan ($p < 0.0001$ versus eletriptan 80 mg), and 22% on placebo ($p < 0.0001$ versus all active treatments). Eletriptan 40 mg had similar efficacy to zolmitriptan 2.5 mg and significantly ($p < 0.05$) lower recurrence rate and need for rescue medication past 24 hours. All treatments were well tolerated and, on patients' global ratings of treatment, both eletriptan doses scored significantly better than zolmitriptan.

naratriptan (Amerge) versus rizatriptan (Maxalt)

In a randomized, double-blind, placebo-controlled study, 522 patients treating a single migraine attack were given either rizatriptan 10 mg, naratriptan 2.5 mg, or placebo.¹⁹⁴ Rizatriptan provided earlier headache relief ($p < 0.001$), acting as early as 30 minutes following a dose. More patients were pain-free at 2 hours versus naratriptan (44.8 versus 20.7%; $p < 0.001$). Both treatments were effective compared to placebo.

naratriptan (Amerge) versus sumatriptan (Imitrex)

A randomized, double-blind, placebo-controlled trial compared naratriptan and sumatriptan for the acute treatment of migraine.¹⁹⁵ Patients ($n=643$) were randomized to naratriptan 1, 2.5, 5, 7.5, or 10 mg or sumatriptan 100 mg or placebo per attack. Efficacy was determined at 2 hours post-dose for headache relief. Naratriptan response (52% to 69%) and sumatriptan response (60%) were superior to placebo (31%, $p < 0.05$). Over the course of 24 hours, efficacy, as determined by sustained headache relief without need for rescue medication or recurrence, was reported more frequently with naratriptan and sumatriptan than placebo. Adverse effects were similar among naratriptan 1, 2.5, or 5 mg doses and placebo. Naratriptan 5, 7.5, and 10 mg doses and sumatriptan had a similar incidence of adverse effects.

A randomized, double-blind study evaluated headache recurrence between naratriptan 2.5 mg and sumatriptan 100 mg in 253 patients with known history of recurrent migraine headaches.¹⁹⁶

Recurrence was defined as recurrence of headache following a pain-free interval of at least 24 hours between attacks. No difference was observed in the incidence of recurrent headache pain during 4 to 24 hours after treatment for naratriptan (45%) and sumatriptan (57%; p =not significant [NS]). Pain relief after the second attack was achieved more frequently with sumatriptan (57%) than naratriptan (41%, $p=0.005$). Side effects were similar in both treatments with no difference in incidence following the second dose.

rizatriptan (Maxalt) versus sumatriptan (Imitrex)

Patients who had migraine with or without aura were randomized to receive 10, 20, or 40 mg doses of rizatriptan or sumatriptan 100 mg or placebo.¹⁹⁷ The trial was a double-blind outpatient trial enrolling 449 patients. The proportion of patients with headache relief at 2 hours was 18% for placebo, 46% for sumatriptan, 52% for rizatriptan 10 mg, 56% for rizatriptan 20 mg, and 67% for rizatriptan 40 mg. All differences with placebo were statistically significant ($p<0.001$). Rizatriptan 40 mg was superior to sumatriptan ($p=0.001$). The recurrence of headache within 24 hours was found to be equal across all treatment groups at approximately 40%. Adverse events occurred more frequently after rizatriptan 40 mg compared to other treatments. Rizatriptan doses of 20 and 40 mg exceed the current FDA-approved labeling.

Rizatriptan 5 and 10 mg and sumatriptan 25 and 50 mg were compared in a double-blind, placebo-controlled, crossover study for efficacy and safety in 2 migraine attacks.¹⁹⁸ Patients ($n=1,329$) were randomized to rizatriptan 5 mg/sumatriptan 25 mg; sumatriptan 25 mg/rizatriptan 5 mg; rizatriptan 10 mg/sumatriptan 50 mg; sumatriptan 50 mg/rizatriptan 10 mg; or placebo/placebo. At 2 hours, more patients had pain relief with rizatriptan 5 mg than sumatriptan 25 mg (68% versus 62%; $p<0.05$), and more patients were pain free (33% versus 28%, respectively; $p<0.05$). With the higher doses, rates of pain relief (72% versus 68%) and pain-free status (41% versus 37%) were similar between rizatriptan 10 mg and sumatriptan 50 mg. Safety was similar among all groups.

In a double-blind single migraine attack study, 1,268 patients were randomized to rizatriptan 5 or 10 mg, sumatriptan 100 mg, or placebo and evaluated after 2 hours for headache relief.¹⁹⁹ Headache relief at 1 hour with rizatriptan 10 mg (37%) was significantly higher than with sumatriptan (28%; $p=0.01$). At 2 hours, all groups had similar rates of headache relief (60% for rizatriptan 5 mg, 67% for rizatriptan 10 mg, and 63% for sumatriptan 100 mg) and were superior to placebo ($p\leq 0.001$). Significantly fewer adverse events were reported with rizatriptan 10 mg (33%) compared to sumatriptan 100 mg (41%; $p=0.014$).

rizatriptan (Maxalt) versus zolmitriptan (Zomig)

Rizatriptan 10 mg and zolmitriptan 2.5 mg were compared in a randomized, double-blind, placebo-controlled, single migraine attack study with 766 patients.²⁰⁰ Both drugs had a similar pain relief response at 2 hours (70.5% versus 66.8%), although pain-free response (43.2% versus 35.6%; $p=0.041$) and return to normal function (45.4% versus 37%; $p<0.05$) were greater with rizatriptan. Headache recurrence was similar between the groups. All therapies were well tolerated.

sumatriptan nasal powder (Onzetra Xsail) versus sumatriptan tablet (Imitrex)

The COMPASS trial was an active-comparator, double-dummy, cross-over, study that included 2 double-blind periods of up to 12 weeks each.²⁰¹ A total of 275 adults who experienced between 2 and 8 migraines per month in the past year were randomized to sumatriptan nasal powder 22 mg plus oral

placebo tablet or an identical placebo delivery system plus 100 mg oral sumatriptan tablet for the first period. Patients then switched treatment during the second period. Patients treated up to 5 qualifying migraines per period within 1 hour of onset. A significantly greater reduction in migraine pain intensity, as measured by the Headache Severity scores in the first 30 minutes post-dose (SPID-30), was reported with the nasal powder compared to the oral tablet ($p < 0.001$). Significantly greater rates of pain relief and pain freedom were reported with the nasal powder at each time point measured between 15 and 90 minutes. However, rates of pain relief and pain freedom were comparable from 2 to 48 hours post-dose for both formulations.

sumatriptan/naproxen (Treximet) versus sumatriptan (Imitrex)

Two randomized, double-blind, single-attack, parallel-group studies were conducted among 1,461 and 1,495 patients who were diagnosed as having migraine and received treatment for a moderate or severe migraine attack.²⁰² Patients were randomized to receive a sumatriptan/naproxen tablet, sumatriptan 85 mg, naproxen 500 mg, or placebo after onset of a migraine with moderate to severe pain. Primary outcome measures included the percentages of patients with headache relief 2 hours after dosing, absence of photophobia, absence of phonophobia, absence of nausea for the comparison between sumatriptan/naproxen and placebo, and the percentages of patients with sustained pain-free response for the comparison between sumatriptan/naproxen and each monotherapy. Sumatriptan/naproxen was more effective than placebo for headache relief at 2 hours after dosing (study 1: 65 versus 28%; $p < 0.001$ and study 2: 57 versus 29%; $p < 0.001$), absence of photophobia at 2 hours (58 versus 26%; 50 versus 32%; both $p < 0.001$), and absence of phonophobia at 2 hours (61 versus 38%; 56 versus 34%; both $p < 0.001$). The absence of nausea 2 hours after dosing was higher with sumatriptan/naproxen than placebo in study 1 (71 versus 65%; $p = 0.007$), but not in study 2 (65 versus 64%; $p = 0.71$). For 2- to 24-hour sustained pain-free response, sumatriptan/naproxen was superior (25 and 23% in studies 1 and 2, respectively; all $p < 0.01$) to sumatriptan (16, 14%), naproxen (10, 10%), and placebo (8, 7%). The incidence of adverse events was similar between sumatriptan/naproxen and sumatriptan.

zolmitriptan (Zomig) versus sumatriptan (Imitrex)

A total of 1,522 patients were randomized in a double-blind trial to receive zolmitriptan 2.5 mg or 5 mg or sumatriptan 50 mg for the treatment of up to 6 moderate to severe migraine attacks.²⁰³ The 2-hour headache response was 62.9, 65.7, and 66.6%, respectively. No significant differences were seen with the percentage of patients achieving headache response at 1 or 2 hours throughout the 6 attacks. All treatments were well tolerated.

Zolmitriptan and sumatriptan were compared for efficacy in the treatment of migraine headaches in 1,445 patients over 6 months.²⁰⁴ In the double-blind study, patients were randomized to zolmitriptan 2.5 or 5 mg, sumatriptan 25 or 50 mg, and were permitted to administer a second dose of study medication for recurrent headache at least 4 hours after the first dose. Headache response was determined at 2 hours after dosing and was 67.1% for zolmitriptan 2.5 mg, 64.8% for zolmitriptan 5 mg, 59.6% for sumatriptan 25 mg, and 63.8% for sumatriptan 50 mg. Statistically significant differences were observed at 2 hours between zolmitriptan 2.5 mg and 5 mg and sumatriptan 25 mg (odds ratio [OR], 1.47 and 1.54; both $p < 0.001$) and 50 mg doses (OR, 1.17; $p = 0.021$; and OR, 1.22; $p = 0.005$). Similar headache response rates at 2 hours were seen with zolmitriptan 5 mg and sumatriptan 50 mg. All therapies were well tolerated.

In a triptan-naïve patient population of 1,058, zolmitriptan 5 mg and sumatriptan 100 mg were compared in a multicenter, double-blind, placebo-controlled trial for efficacy in a single migraine attack.²⁰⁵ Patients were randomized and evaluated for headache response at 1 and 2 hours after dosing. Zolmitriptan and sumatriptan had similar rates of response at 1 and 2 hours; pain-free (complete) responses at 2 hours were 39% for zolmitriptan, 38% for sumatriptan, and 32% for placebo. Adverse effects were similar between the triptan groups.

META-ANALYSIS

Pharmaceutical companies and the principal investigators of company-independent trials were asked for raw patient data of all double-blind, randomized, controlled, clinical trials of oral triptans in migraine.²⁰⁶ There were 53 clinical trials (12 unpublished), involving 24,089 patients, meeting the criteria for inclusion. Mean results for sumatriptan 100 mg were 59% (95% CI, 57 to 60) for 2-hour headache response; 29% (95% CI, 27 to 30) for being pain-free at 2 hours; 20% (95% CI, 18 to 21) for sustained pain-free response; and 67% (95% CI, 63 to 70) for consistency of effect when administered for separate headaches. Placebo-subtracted adverse event rates were 13% (95% CI, 8 to 18) for patients with at least 1 adverse event, 6% (95% CI, 3 to 9) for at least 1 central nervous system adverse event, and 1.9% (95% CI, 1 to 2.7) for at least 1 chest adverse event. Compared with these data, rizatriptan 10 mg showed better efficacy and consistency, as well as similar tolerability, and almotriptan 12.5 mg showed similar efficacy at 2 hours and better results at other time points. Studies with other triptans resulted in no significant differences compared to sumatriptan. The results of the 22 trials that directly compared triptans show the same overall pattern. Frovatriptan and sumatriptan/naproxen were not available at the time of this analysis. Eletriptan 80 mg showed increased efficacy compared to sumatriptan, but it is not currently approved or available in the U.S.

A network meta-analysis of 88 studies including 44,222 patients was conducted to compare the efficacy and tolerability of NSAIDs and triptans for the acute treatment of migraine.²⁰⁷ For the 1 hour pain-relief measure, sumatriptan (3.10 odds ratio [OR], 95% credible interval [CrI], 1.90 to 5.00), zolmitriptan (3.10 OR, 95% CrI 1.80 to 6.20), rizatriptan (3.00 OR, 95% CrI 1.40 to 6.20), and eletriptan (4.90 OR, 95% CrI 1.70 to 14.0) are effective compared to placebo, but do not demonstrate statistical differences between active treatment groups. An analysis of the 2 hour pain-free measure shows eletriptan (10.0 OR, 95% CrI 5.20 to 21.0) and rizatriptan (7.90 OR, 95% CrI 5.30 to 12.0) are superior to sumatriptan (4.80 OR, 95% CrI 3.90 to 5.90), zolmitriptan (4.00 CR, 95% CrI 3.00 to 5.60), almotriptan (2.50 OR, 95% CrI 1.60 to 4.00), ibuprofen (3.40 OR, 95% CrI 1.90 to 6.10), and aspirin (2.90 OR, 95% CrI 1.60 to 5.30); although there was no statistical evidence to compare eletriptan and rizatriptan. Diclofenac-potassium (1.70 OR, 95% CrI 0.82 to 3.70) had the highest probability of requiring an additional medication to treat a migraine attack. The 11 treatments included in this network meta-analysis were ranked for each efficacy and tolerability measure using surface under curve ranking area (SUCRA). The ranking demonstrates that NSAIDs are well tolerated although triptans (particularly eletriptan and rizatriptan) are more efficacious for the 1 hour and 2 hour pain-relief measures. The study did not consider age, gender, or doses of the medications for each trial included in the network meta-analysis which may have affected the outcomes.

A Cochrane review of drugs for the acute treatment of migraine in children (< 12 years old) and adolescents (12 to 17 years old) found that triptans, as a class, were superior to placebo in children (risk ratio [RR], 1.67; 95% CI, 1.06 to 2.62; number needed to treat [NNT], 13; 3 randomized controlled trials [RCTs]; n=162) and adolescents (RR, 1.32; 95% CI, 1.19 to 1.47; NNT, 13; 21 RCTs; n=7,026).²⁰⁸

Sumatriptan/naproxen was also superior to placebo (RR, 3.25; 95% CI, 1.78 to 5.94; NNT, 6; 1 RCT; n=490). Triptans were reported as well tolerated, but studies did not report any serious adverse events. Notably, sumatriptan was the triptan evaluated in over half of the included trials; other triptans in the class included almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan/naproxen, and zolmitriptan.

SUMMARY

The US Headache Consortium, the American Academy of Family Physicians, and the American College of Physicians – American Society of Internal Medicine have recognized that the triptans are effective agents for the acute treatment of migraine. Non-steroidal anti-inflammatory drugs (NSAIDs), or combinations such as aspirin plus acetaminophen plus caffeine, are recommended as first-line therapy for those patients with mild to moderate migraine pain.

Migraine-specific agents, such as the triptans, should be used in patients whose migraine attacks do not respond to NSAIDs. Sumatriptan (Imitrex) is regarded as the standard by which the other agents in the triptan class are measured. By comparison, there is no other triptan that has been shown to be consistently more effective or safer; however, most triptans can be as effective as sumatriptan. If any, almotriptan and rizatriptan (Maxalt, Maxalt MLT), by virtue of meta-analysis, may be able to claim greater effectiveness. However, the triptans appear to be equally safe.

There may be advantages to certain products. Frovatriptan (Frova) has the longest half-life of the products. Theoretically, patients should not need to redose as frequently with this product; however, it may take longer for the product to begin to work. The other triptans have similar half-lives and durations of action, but naratriptan (Amerge) may have a slower onset of relief compared to the other triptans. In addition to approval in adults, almotriptan, sumatriptan/naproxen (Treximet), and zolmitriptan nasal spray (Zomig) are FDA-approved for use in patients 12 to 17 years old while rizatriptan is approved in patients 6 to 17 years old. In addition, non-oral routes of administration are available when nausea or vomiting present as significant components of migraine attacks. Rizatriptan is available as an oral tablet and a rapidly disintegrating oral tablet; sumatriptan is available as an oral tablet, an injection, and as two nasal spray formulations; and zolmitriptan is available as an oral tablet, rapidly disintegrating oral tablet, and nasal spray. Nasal irritation can occur, and unpleasant taste is common with nasal administration. Sumatriptan (Imitrex) and zolmitriptan (Zomig) nasal sprays often begin to produce migraine relief in 15 minutes, and the other sumatriptan nasal spray formulation, Tosymra, has demonstrated a faster absorption than the Imitrex nasal spray. Sumatriptan nasal powder (Onzetra Xsail), has been shown to have faster migraine relief compared to sumatriptan oral tablet in a comparative clinical trial, but it has not been compared to sumatriptan nasal spray (Imitrex) in a robust clinical trial. Subcutaneous administration of sumatriptan (Imitrex, Sumavel DosePro, and Zembrace SymTouch) can have an onset of pain relief as soon as 10 minutes following a dose. However, subcutaneous administration of sumatriptan may be associated with a higher incidence of adverse effects. Migranow kit simply combines sumatriptan tablets with a topical menthol/camphor gel.

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