Therapeutic Class Overview
Triptans

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of migraine include a unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by routine physical activity. Migraine without aura is also associated with at least 1 of the following: nausea, vomiting, or both and photophobia/phonophobia. Migraine with aura includes 1 or more of the following reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, or retinal. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (*Cutrer et al 2020, Snow et al 2002, IHS 2018[a], IHS, 2018[b]*).
- Migraine affects approximately 12% of the US general population and occurs more frequently in women than men (17% of women and 6% of men each year) (*Cutrer et al 2020, Lipton et al 2001*).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (*FDA Industry Guidance [migraine] 2018, Tfelt-Hansen et al 2012*).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (*Clinical Pharmacology 2021*). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Smith 2021*).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (*Smith 2021*).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan (with the exception of Zembrace SymTouch) is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (ODT) (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (*Drugs@FDA 2021*).
- According to Drugs@FDA, the marketing status of Alsuma and Sumavel DosePro is discontinued; therefore, these products have been removed from the therapeutic class overview (*Drugs@FDA 2021*).
- In October 2017, the FDA announced Teva's voluntary discontinuation of Zecuity (sumatriptan iontophoretic transdermal system) due to post-marketing reports of application site reactions, including severe redness, cracked skin, blistering/welts, and burns/scars associated with the product (*FDA Drug Shortages and Discontinuations 2017*). Therefore, this product has also been removed from the therapeutic class overview.
- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amerge (naratriptan hydrochloride tablet)	✔
Axert (almotriptan malate tablet)†	✔
Frova (frovatriptan succinate tablet)	✔
Imitrex (sumatriptan tablet, nasal spray, injection)	✔

Drug	Generic Availability
Imitrex Statdose (sumatriptan cartridges for injection)	✔
Maxalt (rizatriptan benzoate tablet)	✔
Maxalt MLT (rizatriptan benzoate ODT)	✔
Migranow* (sumatriptan tablet + camphor/menthol gel)	-
Onzetra Xsail (sumatriptan nasal powder)	-
Relpax (eletriptan hydrobromide tablet)	✔
Tosymra (sumatriptan nasal spray)	-
Treximet (sumatriptan/naproxen sodium tablet)	✔
Zembrace SymTouch (sumatriptan injection)	-
Zomig (zolmitriptan nasal spray, tablet)	✔ ‡
Zomig-ZMT (zolmitriptan ODT)	✔

*This product is not approved by the FDA.
†The brand name product has been discontinued; only generic availability.
‡ Generic zolmitriptan tablets are available. Zolmitriptan nasal spray is available as an authorized generic.

(Drugs@FDA 2021; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Amerge (naratriptan) tablet	Axert (almotriptan) tablet	Frova (frovatriptan) tablet	Imitrex (sumatriptan) tablets, nasal spray, injection	Imitrex Statdose (sumatriptan) cartridges (injection)	Maxalt (rizatriptan) tablet	Maxalt MLT (rizatriptan) ODT	Migranow (sumatriptan) tablet and (camphor/menthol) gel	Onzetra Xsail (sumatriptan) nasal powder	Relpax (eletriptan) tablet	Tosymra (sumatriptan) nasal spray	Treximet (sumatriptan/naproxen) tablet	Zembrace SymTouch (sumatriptan) injection	Zomig (zolmitriptan) tablet; nasal spray	Zomig ZMT (zolmitriptan) ODT
Acute treatment of migraine with or without aura in adults	✔	✔	✔	✔	✔	✔	✔	✔ ‖	✔	✔	✔	✔	✔	✔ ‡	✔
Acute treatment of cluster headache in adults				✔ *	✔										
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔								
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)		✔ §													
Acute treatment of migraine with or without aura (aged ≥ 12 years)												✔		✔ †‡	

Abbreviation: ODT = orally disintegrating tablet

Class Limitations of Use: No agents in this class are intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established
‖ Indication applies only to the sumatriptan component

(*Prescribing information: Amerge 2020; Axert 2017; Frova 2018; Imitrex injection 2020; Imitrex nasal spray 2017; Imitrex tablets 2020; Maxalt 2020; Maxalt MLT 2020; Migranow 2021; Onzetra Xsail 2019; Relpax 2020; Tosymra 2019; Treximet 2021; Zembrace SymTouch 2021; Zomig nasal spray 2019; Zomig tablets 2019; Zomig ZMT 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours, sustained pain-free response, reducing rescue medication use, and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (*Bird et al 2014, Brandes et al 2007, Cady et al 2015, Derry et al 2012 [a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Law et al 2016, Oldman et al 2002, Pascual et al 2007, Poolsup et al 2005, Zembrace SymTouch Prescribing Information 2021, Richer et al 2016*).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. Triptans have been evaluated in numerous meta-analyses and comparative trials, with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All triptans are effective at treating migraines and are well tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (*Derry et al 2012[a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Oldman et al 2002, Pascual et al 2007*):
  - Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-freedom and headache relief at 2 hours post-dose for oral agents (*Oldman et al 2002*); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (*Ferrari et al 2002, Pascual et al 2007*). Naratriptan 2.5 mg has lower efficacy rates of pain-freedom and headache relief at 2 hours (*Pascual et al 2007*) while eletriptan has a lower rate of recurrence (*Ferrari et al 2002*).
  - Subcutaneous sumatriptan is the most effective for acute migraine treatment but is associated with more adverse events (AEs) relative to the other triptan formulations (*Oldman et al 2002, Derry et al 2012[c]).*
  - Frovatriptan has the least number of head-to-head trials with active comparators. A pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group ($p < 0.001$) (*Cortelli et al 2011*).
  - Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (*Brandes et al 2007*).
  - Most triptans are well tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (*Ferrari et al 2002*).
- Recent evidence is summarized below:
  - Novel sumatriptan nasal formulations have been studied in placebo-controlled (PC) clinical trials. Onzetra Xsail was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines (ie, TARGET and COMPASS). The TARGET study (n = 230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs 45%, respectively; p = 0.002). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs 27%; p = 0.03) (Cady et al 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n = 275; 1531 migraines

assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores ($p < 0.001$). At 2 hours, the rates of pain relief (freedom) were comparable (*Tepper et al 2015*).

- A phase 2 trial of Tosymra in 107 patients with 2 to 8 migraines/month found improved response (freedom from headache pain at 2 hours post-dose) compared with placebo (43.8% vs 22.5%; $p = 0.044$). Tosymra was also significantly better than placebo at alleviating bothersome symptoms such as nausea, photophobia, and phonophobia 2 hours post-dose (70.7% vs 39.5%; $p = 0.004$) (*Lipton et al 2018*).
- Data to support the approval of Zembrace SymTouch were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (*Zembrace SymTouch Prescribing Information 2021, Imitrex Prescribing Information 2020*).
- In a randomized, DB, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (Zembrace SymTouch) and 6 mg subcutaneous sumatriptan (Sumavel DosePro – now discontinued) were compared in 20 patients with rapidly escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs 52.6%, respectively; $p = 0.87$). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the 6 mg dose (1 patient vs 4 patients) (*Cady et al 2017*).
- A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-freedom after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs sumatriptan 25 mg), rizatriptan 10 mg (vs sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence of AEs were found (*Derry et al 2014*).
- A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (*Bird et al 2014*).
- The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. This DB, 4-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours (29.7% vs 16.6%, respectively; $p < 0.001$). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% of patients) (*Winner et al 2016*).
- In pediatric patients, a Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing freedom from pain in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (*Richer et al 2016*).

CLINICAL GUIDELINES

- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (*AHS 2019*). The Society recommends the use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that non-oral routes are used when severe nausea or vomiting is present.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]).* For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (*Robbins et al 2016*).

- In 2019, the American Academy of Neurology and AHS published a guideline on the acute treatment of migraine in children and adolescents (*Oskoui et al 2019*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.

SAFETY SUMMARY

- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of a MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in those patients with a history of asthma, urticaria, rhinitis, nasal polyp syndrome, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.
- The following warnings and precautions are associated with medications in the class:
  - Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vasospasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides.
  - Almotriptan, rizatriptan, and zolmitriptan have reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures following administration. Sumatriptan/naproxen also has warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema that may worsen heart failure; hyperkalemia; renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); drug reaction with eosinophilia and systemic symptoms (DRESS); the potential to mask inflammation and fever; elevated liver enzymes; fetal toxicity (including premature closure of fetal ductus arteriosis and oligohydramnios/neonatal renal impairment); and hematologic toxicity (eg, anemia).
  - Naratriptan, frovatriptan, sumatriptan, sumatriptan/naproxen, eletriptan, and zolmitriptan nasal spray have a warning for hypersensitivity reactions, including anaphylaxis and angioedema. In addition, the needle shield of the prefilled syringe of injectable sumatriptan (Imitrex and Imitrex Statdose) contains a latex derivative that has the potential to cause allergic reactions in patients sensitive to latex.
  - Zolmitriptan ODT contains phenylalanine; the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with

atypical sensations, including numbness, tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - Generally, the most common AEs associated with 5-HT1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other cardiac events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR] = 1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR = 0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR = 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR = 2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund 2017*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amerge (naratriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 4 hours Maximum daily dose: 5 mg	Safety of treating >4 migraines in 1 month has not been established Mild or moderate renal or hepatic impairment: recommended starting dose is 1 mg not to exceed 2.5 mg in any 24-hour period Contraindicated for use in severe renal and hepatic impairment
Axert (almotriptan)	Tablets	Oral	Adults and adolescents (≥12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 25 mg	Safety of treating >4 migraines in 1 month has not been established In adults, 12.5 mg dose is more effective Hepatic impairment and severe renal impairment: recommended starting dose is 6.25 mg not to exceed 12.5 mg in any 24-hour period
Frova (frovatriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 7.5 mg	Safety of treating >4 migraines in 1 month has not been established

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Imitrex, Imitrex Statdose (sumatriptan)	Tablets, nasal spray, single dose vial, single dose prefilled cartridges for pen use	Oral, intranasal, SC	Tablets (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Intranasal (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 40 mg Maximum single dose: 20 mg SC injection (adults): Given as a single dose; may repeat administration in 1 hour Maximum daily dose: 12 mg Maximum single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine	Tablets and nasal spray: safety of treating >4 migraines in 1 month has not been established Contraindicated for use in severe hepatic impairment (all formulations) Mild or moderate hepatic impairment (tablets): maximum single dose should not exceed 50 mg Administer the needle only to the skin; IM or IV delivery should be avoided
Maxalt, Maxalt MLT (rizatriptan)	Tablets, ODT	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 30 mg Pediatric (≥6 years): Weight based dosing: 5 mg for <40 kg and 10 mg for ≥40 kg	Safety of treating >4 migraines in 1 month in adults and >1 dose within 24 hours in patients 6 to 17 years of age have not been established For ODT, administration with liquid is not necessary Dosage adjustments for patients on concurrent propranolol is required
Migranow (sumatriptan + camphor/ menthol)	Tablet (sumatriptan) + gel (4% camphor/10% menthol)	Oral + topical	Adults: Sumatriptan: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Camphor/menthol: Apply to affected area up to 3 or 4 times daily	Safety of treating >4 migraines in 1 month has not been established Gels should not be applied to wounds, damaged skin, mucous membranes, or eyes Hepatic impairment: maximum single dose of sumatriptan should in general not exceed 50 mg; contraindicated for use in severe hepatic impairment
Onzetra Xsail (sumatriptan)	Capsule in disposable nosepiece for use with breath-powered delivery device only	Intranasal	Adults: 2 nosepieces (1 nosepiece in each nostril) administered using the breath-powered delivery device; may repeat administration in 2 hours	Safety of treating >4 migraines in 1 month has not been established Breath-powered powder delivery requires a forceful blow through the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Maximum daily dose: 2 doses (44 mg/4 nosepieces) or 1 dose (22 mg/2 nosepieces) of Onzetra Xsail and 1 dose of another sumatriptan product, separated by at least 2 hours	mouthpiece to deliver the powder into each nostril Contraindicated for use in severe hepatic impairment
Relpax (eletriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 80 mg Maximum single dose: 40 mg	Safety of treating >3 migraines in 1 month has not been established
Tosymra (sumatriptan)	Nasal spray	Intranasal	Adults: Given as a single dose; may repeat after 1 hour Maximum daily dose: 30 mg	Administered as a single spray to 1 nostril May be administered 1 hour after another sumatriptan product
Treximet (sumatriptan/ naproxen)	Tablets	Oral	Adults and adolescents (≥12 years): Given as a single dose (85/500 mg for adults and 10/60 mg for adolescents) Maximum daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet in a 24-hour period for adolescents	May be administered with or without food; tablets should not be split, crushed, or chewed Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established Mild or moderate hepatic impairment: recommended dose is 1 tablet (10/60 mg) in a 24-hour period Contraindicated for use in severe hepatic impairment
Zembrace SymTouch (sumatriptan)	Single dose prefilled autoinjector	SC	Adults: Injected as a single dose; each dose should be separated by at least 1 hour Maximum daily dose: 12 mg Maximum single dose: 3 mg	The needle penetrates ¼ inch of skin; IM or IV delivery should be avoided Administer dose to the upper arm or thigh May be administered 1 hour after another sumatriptan product Contraindicated for use in severe hepatic impairment
Zomig, Zomig-ZMT (zolmitriptan)	Tablets, ODT, nasal spray	Oral; intranasal	Tablets (adults): Given as a single dose; may repeat administration in 2 hours	Safety of treating >3 migraines (oral) or >4 migraines (intranasal) in 1 month has not been established

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Nasal spray: (adults and adolescents (≥12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 10 mg Maximum single dose: 5 mg	For ODT, administration with liquid is not necessary Do not break ODT because they are not functionally scored. Moderate to severe hepatic impairment: recommended dose is 1.25 mg (one-half of one 2.5 mg tablet); limit the total daily dose in severe hepatic impairment to no more than 5 mg/day ODTs are not recommended in moderate or severe hepatic impairment as these tablets should not be broken in half Nasal spray is not recommended in moderate to severe hepatic impairment Dosage adjustments for patients on concurrent cimetidine is required

See the current prescribing information for full details

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Smith 2021, Clinical Pharmacology 2021*).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/NSAID (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet) and zolmitriptan (nasal spray, ODT, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (*Francis et al 2010*). Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan are available generically in at least 1 dosage form or strength (*Drugs@FDA 2021*).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of Zembrace SymTouch) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and pharmacodynamic data, subcutaneous and intranasal formulations generally have a

quicker onset of action and subcutaneous formulations generally have a lower NNT, but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.

- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (OR = 1.11; 95% CI, 0.84 to 1.43) and treatment-related AE (OR = 0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR = 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR = 2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund 2017*).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (AHS, 2019). They recommend the triptans or dihydroergotamine (DHE) for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that non-oral routes be used when severe nausea or vomiting is present. There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (*Francis et al 2010, Robbins et al 2016*). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (*Robbins et al 2016*).
- In 2019, the American Academy of Neurology and AHS published a guideline on the acute treatment of migraine in children and adolescents (*Oskoui et al 2019*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.
- All triptans are generally effective for the acute treatment of migraine attacks and are well tolerated with a similar safety profile. Although some triptans have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injectable treatments have been associated with the fastest onset of action; therefore, they are amenable for quick relief. However, injectable triptans are associated with more AEs compared to oral or nasal dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient need, response, preference, migraine severity, and tolerability.

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Publication date: July 1, 2021