Therapeutic Class Overview
Anti-migraine Agents (triptans)

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype and is 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 the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (Cutrer et al, 2017; Snow et al, 2002; IHS, 2018a; IHS, 2018b).
- The migraine 1-year prevalence rate in Americans is approximately 12% (17% of women and 6% of men) (Cutrer et al, 2017; 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, 2018). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2018).
- 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 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).
- 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 (Bajwa et al, 2018). Some treatment guidelines do not differentiate among various formulations (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the American Academy of Neurology [AAN] and the American Headache Society [AHS], 2013; Snow et al, 2002). Additional key therapies for the treatment of migraines include nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (DHE nasal spray or inhaler), and opioid medications; however, some medications are not recommended for regular use (Marmura et al, 2015; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the AAN and the AHS, 2013). For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (Robbins et al, 2016). In pediatric patients, the Child Neurological Society recommends ibuprofen, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (DRUGS@FDA, 2018). Branded products are outlined in Table 1.
- 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, 2018).
- 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 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	Manufacturer	FDA Approval Date	Generic Availability
AMERGE (naratriptan hydrochloride tablet)	various	02/10/1998	✔
AXERT (almotriptan malate tablet)	various	05/07/2001	✔
FROVA (frovatriptan succinate tablet)	various	11/08/2001	✔
IMITREX (sumatriptan tablet, nasal spray, injection)	various	12/28/1992	✔
IMITREX STATDOSE (sumatriptan cartridges for injection)	various	12/23/1996	✔
MAXALT (rizatriptan benzoate tablet)	various	06/29/1998	✔
MAXALT MLT (rizatriptan benzoate orally disintegrating tablet)	various	06/29/1998	✔
ONZETRA XSAIL (sumatriptan nasal powder)	Merck & Co., Inc.	01/27/2016	-
RELPAX (eletriptan hydrobromide tablet)	Pfizer	12/26/2002	✔
TREXIMET (sumatriptan/naproxen sodium tablet)	GlaxoSmithKline	04/15/2008	✔
ZEMBRACE SYMTOUCH (sumatriptan injection)	Nupathe Inc.	01/28/2016	-
ZOMIG (zolmitriptan nasal spray, tablet)	various	09/30/2003	✔ (tablets only)
ZOMIG-ZMT (zolmitriptan orally disintegrating tablet)	various	02/13/2001	✔

(DRUGS@FDA, 2018; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	AMERGE (naratriptan tablet)	AXERT (almotriptan tablet)	FROVA (frovatriptan tablet)	IMITREX (sumatriptan tablets, nasal spray, injection)	IMITREX STATDOSE (sumatriptan cartridges for injection)	MAXALT (rizatriptan tablet)	MAXALT MLT (rizatriptan ODT)	ONZETRA XSAIL (sumatriptan nasal powder)	RELPAX (eletriptan tablet)	ZEMBRACE SYMTOUCH (sumatriptan injection)	ZOMIG (zolmitriptan nasal spray, tablet)	ZOMIG ZMT (zolmitriptan ODT)	TREXIMET (sumatriptan/naproxen tablet)
Acute treatment of migraine with or without aura	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔ ‡	✔	✔
Acute treatment of cluster headache				✔ *	✔								
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)											✔ †‡		✔

Abbrv: ODT = orally disintegrating tablet
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
Class Limitations of Use: All agents in class are not 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:
‡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.

(Prescribing information: AMERGE, 2016; AXERT, 2017; FROVA, 2013; IMITREX injection, 2017; IMITREX nasal spray, 2017; IMITREX tablets, 2017; MAXALT, 2015; MAXALT MLT, 2015; ONZETRA XSAIL, 2016; RELPAX, 2013; TREXIMET, 2016; ZEMBRACE SYMTOUCH, 2017; ZOMIG nasal spray, 2016; ZOMIG tablets, 2017; ZOMIG ZMT, 2017)

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 and 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; Prescribing information: IMITREX, 2015; ZEMBRACE SYMTOUCH, 2017; 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. 5-HT_1 receptor agonists 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 5-HT_1 receptor agonists 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):
  - o Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-free 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-free and headache relief at 2 hours (Pascual et al, 2007) while eletriptan has a lower rate of recurrence (Ferrari et al, 2002).
  - o Subcutaneous sumatriptan is the most effective for migraine treatment but is associated with more adverse events (AEs) relative to the other 5-HT_1 receptor agonist formulations (Oldman et al, 2002; Derry et al, 2012[c]).
  - o Frovatriptan has the least number of head-to-head trials with active comparators. A recent 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).
  - o 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).
  - o Most 5-HT_1 receptor agonists 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:
  - o The newest intranasal sumatriptan formulation, ONZETRA XSAIL, was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines through the TARGET and COMPASS studies. 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; 1,531 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).
  - o 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 (Prescribing Information: ZEMBRACE SYMTOUCH, 2017; IMITREX, 2015).
  - o In a randomized, double-blind, 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 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-free 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 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. The 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 of administration (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% more of patients) (Winner et al, 2016).
  - In pediatric patients, 1 Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing pain freedom in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be with higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (Richer et al, 2016).

SAFETY SUMMARY

- The manufacturer of sumatriptan iontophoretic TDS has received post-marketing reports of application site reactions described as burns and scars in patients treated with sumatriptan iontophoretic TDS. Distribution of sumatriptan iontophoretic TDS has been voluntarily suspended. Patients are recommended to discontinue sumatriptan iontophoretic TDS and discuss alternative treatment options with their physicians.
- 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-HT_1 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 an 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 asthma, rhinitis, and in those patients with a history of asthma, urticaria, 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 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 vaso-spasm-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 had reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures reported 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 may worsen heart failure or cause hyperkalemia and renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); the potential to mask inflammation and fever; and elevated liver enzymes have been reported with use.
  - Zolmitriptan ODTs contain phenylalanine, in which 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 than the others. 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-HT_1 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-HT_1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other 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	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Oral agents			
AMERGE (naratriptan)	Tablet: 1 mg 2.5 mg	Adult: 1 mg or 2.5 mg orally as a single dose; may repeat administration in 4 hours. Max daily dose: 5 mg.	Safety of treating > 4 migraines in 1 month has not been established.
AXERT (almotriptan)	Tablet: 6.25 mg 12.5 mg	Adult and adolescent (≥12 years): 6.25 mg or 12.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose for adults: 25 mg.	Safety of treating >4 migraines in 1 month has not been established. In adults, 12.5 mg dose is more effective.
FROVA (frovatriptan)	Tablet: 2.5 mg	Adult: 2.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 7.5 mg.	Safety of treating >4 migraines in 1 month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
IMITREX (sumatriptan)	Tablet: 25 mg 50 mg 100 mg	Adult: 25, 50, or 100 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 200 mg.	Safety of treating >4 migraines in 1 month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose.
MAXALT, MAXALT MLT (rizatriptan)	Orally disintegrating tablet; Tablet: 5 mg 10 mg	Adult: 5 mg or 10 mg orally as a single dose. Max daily dose: 30 mg. Pediatric (≥6 years): Weight based dosing of 5 mg for <40 kg and 10 mg for ≥40 kg. May repeat administration in 2 hours in adults and 24 hours in pediatric patients. Dose adjustments are needed for patients taking propranolol concomitantly.	Safety of treating >4 migraines/month in adults or children, and >1 dose within 24 hours in patients 6 to 12 years of age have not been established.
RELPAX (eletriptan)	Tablet: 20 mg 40 mg	Adult: 20 or 40 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 80 mg. Max single dose: 40 mg.	Safety of treating >3 migraines in 1 month has not been established.
TREXIMET (sumatriptan/ naproxen)	Tablet: 10/60 mg 85/500 mg	Adult and adolescent (≥12 years): 1 tablet (85/500 mg for adults and 10/60 mg for adolescents) orally as a single dose. Max 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.	Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Orally disintegrating tablet; Tablet: 2.5 mg 5 mg	Adult: starting dose is 1.25 or 2.5 mg dose; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >3 migraines in 1 month has not been established.
Intranasal agents			
IMITREX nasal spray (sumatriptan)	Nasal spray: 5 or 20 mg/actuator unit-of-use inhaler	Adult: 5, 10, or 20 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 40 mg. Max single dose: 20 mg.	Safety of treating >4 migraines in 1 month has not been established.
ONZETRA XSAIL (sumatriptan)	Nasal powder: 2 breath-powered delivery systems containing 11 mg sumatriptan per each nosepiece	Adult: 22 mg (2 nosepieces) administered using the breath-powered delivery device; may repeat administration in 2 hours. Max daily dose: 2 doses (44 mg/4 nosepieces).	Safety of treating >4 migraines in 1 month has not been established. Breath-powered powder delivery requiring a forceful blow into each nostril.
ZOMIG (zolmitriptan)	Nasal spray: 2.5 or 5 mg/spray single-use nasal spray units	Adult and adolescent (≥12 years): 2.5 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >4 migraines in 1 month has not been established.
Subcutaneous agents			
IMITREX (sumatriptan)	Subcutaneous injection: 6 mg single dose vial	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg,	Administer the needle only to the skin; intramuscular (IM) or intravascular (IV)

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	delivery should be avoided.
IMITREX STATDOSE (sumatriptan)	Subcutaneous injection: 4 and 6 mg single dose, prefilled cartridges for pen use	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided.
ZEMBRACE SYMTOUCH (sumatriptan)	Subcutaneous injection: 3 mg single dose, prefilled autoinjector	Adult: 3 mg injected subcutaneously; each dose should be separated by at least 1 hour. May administer up to 4 times per day. Max daily dose: 12 mg. Max single dose: 3 mg.	Administer where 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 at least 1 hour following a dose of another sumatriptan agent.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
AXERT (almotriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	For CrCL ≤30 mL/minute, an initial dose of 6.25 mg and a max dose of 12.5 mg/day are recommended.	Dosage adjustment required for moderate to severe impairment, reduce dose to 6.25 mg and a max dose of 12.5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
RELPAX (eletriptan)	No overall difference in safety or efficacy between elderly and younger patients. BP was increased to a greater extent in elderly patients. Additionally, a statistically	Safety and efficacy have not been established.	No significant change in clearance for patients with mild, moderate, or severe impairment; although, BP elevations were observed in this population. No	Use in severe impairment is not recommended.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Drug would not be expected to cause any adverse effects in breastfed infants,

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	significant increased half-life (from 4.4 hours to 5.7 hours) was observed between elderly and younger patients. No dose adjustments are recommended.		dosage adjustment required.		especially if the infant is >2 months; use with caution.
FROVA (frovatriptan)	Mean blood concentrations were 1.5 to 2 times higher in elderly patients versus younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No dosage adjustment is required.	An estimated 2-fold increase in AUC is predicted with severe impairment; use with caution. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk. However, because of the long half-life, a shorter-acting drug may be preferred, especially while nursing a newborn or preterm infant; use with caution.
AMERGE (naratriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (CrCL ≤15 mL/min) is contraindicated.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (Child-Pugh C) is contraindicated.	†Unclassified Several studies have suggested women with migraine may be at increased risk of preeclampsia. Post-marketing reports of naratriptan included mainly first trimester exposures. The incidence of major birth defects with naratriptan was similar to the incidence of the general US population (2.2% vs. 2.2 to 2.9%, respectively). Use with caution. Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
MAXALT, MAXALT MLT (rizatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <6 years of age.	No dosage adjustment is required.	Drug plasma concentrations are 30% greater with moderate impairment. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, ZEMBRACE SYMTOUCH (sumatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	Not studied.	The maximum single oral dose should not exceed 50 mg. Use of IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, and ZEMBRACE SYMTOUCH in severe impairment is contraindicated.	Pregnancy Category C* (ONZENTRA XSAIL, ZEMBRACE SYMTOUCH) †Unclassified (IMITREX, IMITREX STATDOSE) Overall, data from a pregnancy exposure registry have not detected an increased frequency of birth defects or a consistent pattern of birth defects associated with sumatriptan exposure during pregnancy. Several studies have suggested women with migraine may be at increased risk of preeclampsia. A registry study reported a 4.2% occurrence of major birth defects during first-trimester exposure and during any trimester of exposure which is numerically higher than the 2.2% to 2.9% rate of major birth defects among deliveries to women with migraine. ALL FORMULATIONS: Excreted in breast milk after subcutaneous administration. Unknown excretion after oral administration. Withhold breastfeeding for 12 hours after oral, nasal, or subcutaneous administration to minimize infant exposure.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
TREXIMET (sumatriptan/ naproxen)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	No renal dosage adjustment required for mild to moderate impairment. Not recommended for severe impairment (CrCL ≤30 mL/min). Renal effects of the drug may hasten progression of renal dysfunction in pre-existing renal disease.	Administer 1 10/60 mg tablet in a 24 hour period for mild to moderate impairment. Use in severe impairment is contraindicated.	Pregnancy Category C during the first 2 trimesters; Pregnancy Category X during the third trimester* Both agents are excreted in breast milk. Limited information indicates that levels are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant; use with caution.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established for the nasal spray in children <12 years of age and <18 years of age for oral formulations.	Clearance was reduced by 25% in patients with severe impairment (CrCL ≤25 mL/min); no significant change in clearance was observed in moderate impairment (CrCL 26 to 50 mL/min). No dosage adjustment required.	Dosage adjustment required for moderate to severe impairment, reduce dose to 1.25 mg and a max dose of 5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Abbrv: AAP = American Academy of Pediatrics; AUC = area under the curve; BP = blood pressure; CrCL = creatinine clearance; CV = cardiovascular; ODT = orally disintegrating tablet

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

(American Academy of Pediatrics, 2001; LactMed, 2018)

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 (Bajwa et al, 2018; Clinical Pharmacology, 2018).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/nonsteroidal anti-inflammatory combination product (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, orally disintegrating tablet, 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, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen and zolmitriptan are available generically in at least 1 dosage form or strength (DRUGS@FDA, 2018).
- 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 –dynamic 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 than the others. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of placebo-controlled 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).
- 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.
- According to the AAN, American College of Physicians-American Society of Internal Medicine, and U.S. Headache Consortium, 5-HT_1 receptor agonists are clinically interchangeable for the treatment of migraines. These guidelines do not provide a recommendation for the use of 1 agent over another. In addition, non-oral formulations provide relief for patients unable to swallow due to symptoms of nausea and vomiting (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 (guideline reaffirmed in 2015); Erratum in Subcommittee of the AAN and the AHS, 2013; Snow et al, 2002). According to the 2015 AHS evidence assessment, triptans (regardless of formulation) and DHE (nasal spray or inhaler) have been established to be effective treatments for acute migraines in adults. Reaffirming the AAN migraine guidelines, the recommendation remains that clinicians should consider medication efficacy and potential AEs when prescribing acute medications

for migraine. Opioid medications are probably effective; however, they are not recommended for regular use (Marmura et al, 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 pediatric patients, older guidelines published by the Child Neurological Society recommend ibuprofen as first-line therapy for the treatment of migraines, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.

- All 5-HT_1 receptor agonists are generally effective for the acute treatment of migraine attacks and are well-tolerated with a similar safety profile. Although some 5-HT_1 receptor agonists 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, the clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injection treatments have been associated with the fastest onset of action; therefore, are amenable to quick relief. However, injectable triptans are associated with more AE compared to oral or topical dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient needs, response, and preference, migraine severity, and tolerability.

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