Therapeutic Class Overview
5-HT1 Receptor Agonists

Therapeutic Class

- **Overview/Summary:** Migraine is a common disabling primary headache disorder that can present with or without aura. The International Headache Society describes migraine without aura as a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or accompany the headache.[1] Migraine without aura is further described as a recurrent headache disorder manifesting in attacks that can last four to 72 hours. Typical characteristics of these headaches are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura is also a recurrent headache disorder; however, it manifests in attacks of reversible focal neurological symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes.[1] The serotonin (5-HT) 1 receptor agonists, commonly referred to as triptans, work in the management of migraine via the release of vasoactive peptides, promotion of vasoconstriction and blockade of pain pathways in the brainstem.[2] Triptans are Food and Drug Administration (FDA)-approved for the acute treatment of migraine with or without aura.[3-12] There is a lack of consistent head-to-head data demonstrating "superiority" of any triptan, making it difficult to recommend the use of one over another.[2] Currently there are seven single-entity triptans available (Axert® [almotriptan], Relpax® [eletriptan], Frova® [frovatriptan], Amerge® [naratriptan], Maxalt® and Maxalt-MLT® [rizatriptan], Imitrex® [sumatriptan] and Zomig® and Zomig ZMT® [zolmitriptan]) and one combination product (Treximet® [sumatriptan/naproxen]). Sumatriptan/naproxen is a fixed-dose combination product containing a triptan and a nonsteroidal anti-inflammatory drug. The combination targets the multiple mechanisms of migraine pathology. Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7] The triptans are available in several different dosage formulations, including orally disintegrating tablets, nasal sprays, subcutaneous injections and tablets. All triptans are currently available as an oral tablet. Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.[13]

Table 1. Current Medications Available in the Class[3-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Almotriptan (Axert®)	Acute treatment of migraine attacks in adults with a history of migraine with or without aura and acute treatment of migraine headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more	Tablet: 6.25 mg 12.5 mg	-
Eletriptan (Relpax®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 20 mg 40 mg	-
Frovatriptan (Frova®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 2.5 mg	-
Naratriptan (Amerge®*)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 1 mg 2.5 mg	✔
Rizatriptan (Maxalt®*, Maxalt-MLT®*)	Acute treatment of migraine with or without aura in adults and in	Orally disintegrating	✔

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	pediatric patients six to 17 years of age	tablet: 5 mg 10 mg Tablet: 5 mg 10 mg	
Sumatriptan (Alsuma®, Imitrex®*, Sumavel DosePro®)	Acute treatment of cluster headache episodes†, acute treatment of migraine attacks with or without aura in adults	Nasal spray: 5 mg 20 mg Subcutaneous injection: 4 mg/0.5 mL 6 mg/0.5 mL Tablet: 25 mg 50 mg 100 mg	✔
Zolmitriptan (Zomig®, Zomig-ZMT®)	Acute treatment of migraine attacks with or without aura in adults	Nasal spray: 5 mg Orally disintegrating tablet: 2.5 mg 5 mg Tablet: 2.5 mg 5 mg	-
Combination Products			
Sumatriptan/naproxen (Treximet®)	Acute treatment of migraine attacks with or without aura in adults	Tablet: 85/500 mg	-

*Generic available in at least one dosage form or strength.
† Subcutaneous injection only.

Evidence-based Medicine

- In general, clinical trial data consistently demonstrates the "superiority" of the triptans over placebo in achieving headache pain relief, freedom from pain at two hours, sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia.[14-53]
- Clinical trial data also suggest the available triptans, when administered orally, range in comparative efficacy. Specifically, in a large meta-analysis, consisting of 53 controlled trials and over 24,000 patients, results demonstrated that while all triptans were effective and well tolerated, eletriptan (80 mg) and rizatriptan (10 mg) were "superior" to sumatriptan (100 mg) in terms of achievement of headache response at two hours, pain-free response at two hours and sustained pain-free response. Almotriptan (12.5 mg) demonstrated "superiority" over sumatriptan for pain-free response at two hours and sustained pain-free response. Of note, lower doses of eletriptan and rizatriptan in this analysis did not achieve the same results.[15]

- While there appears to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of one over another, suggesting that individual variations in the response to different triptans exist. [54-66]
- Trials comparing different formulations of triptans measured patient preference as the primary endpoint.[60, 65-67]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The triptans are recommended for initial treatment of an acute migraine attack of moderate to severe severity, especially when "nonspecific" therapies have failed. [68-71]
  - "Nonspecific" therapies, such as nonsteroidal anti-inflammatory drugs are recommended for initial treatment of acute migraine attacks of mild to moderate severity. [68-71]
  - A non-oral route of administration is recommended for patients whose migraines present early with nausea or vomiting. Nausea should be treated with an antiemetic. [68-71]
  - The subcutaneous sumatriptan injection and zolmitriptan nasal spray are recognized as potential treatment options for the acute management of cluster headaches. [68-71]
- Other Key Facts:
  - Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7]
  - The subcutaneous sumatriptan injection is also Food and Drug Administration-approved for the acute treatment of cluster headache episodes.[8]
  - The subcutaneous sumatriptan injection has the fastest onset of action, but there is no evidence to suggest that different oral triptan formulations have a faster onset of action than the others.[71]
  - Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.[13]

References

1. International Headache Society (IHS). The international classification of headache disorders 2nd edition [monograph on the Internet]. Oxford (UK): IHS. 2004 [cited 2013 Apr 3]. Available from: http://ihs-classification.org/en/0_downloads/.
2. Bajwa ZH, Sabahat AS. Acute treatment of migraine in adults. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Apr 3]. Available from: http://www.utdol.com/utd/index.do.
3. Axert® [package insert]. Titusveille (NJ): Janssen Pharmaceuticals, Inc.; 2011 Sept.
4. Replax® [package insert]. New York (NY): Roerig; 2012 Jan.
5. Frova® [package insert]. Malvern (PA): Endo Pharmaceuticals Inc.; 2012 Dec.
6. Amerge® [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Mar.
7. Maxalt®, Maxalt-MLT® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Jan.
8. Imitrex® injection [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
9. Imitrex® spray [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
10. Imitrex® tablets [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
11. Zomig®, Zomig-ZMT® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2012 Sept.
12. Treximet® [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2011 Apr.
13. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2013 Apr 3]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
14. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. Acta Neurol Scand. 1993;88(1):63-9.
15. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalagia. 2002;22:633-58.
16. Dahlof CG, Tfelt-Hansen P, Massiou H, Fazekas A. Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. Neurology. 2001;57(10):1811-7.
17. Dahlof C, Pascual J, Dodick DW, Dowson AJ. Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. Cephalagia. 2006;26:400-8.
18. Garcia-Ramos G, MacGregor EA, Hilliard B, Bordini CA, Leston J, Hettiarachchi J. Comparative efficacy of eletriptan vs naratriptan in the acute treatment of migraine. Cephalalgia. 2003;23:869-76.
19. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg vs sumatriptan 100 mg. Headache. 2003;43:214-22.
20. Goadsby PJ, Ferrari MD, Olesen J, Stovner LJ, Senard JM, Jackson JC, et al. Eletriptan in acute migraine: a double blind, placebo-controlled comparison to sumatriptan. Neurology. 2000;54(1):156-61.
21. Mandema JW, Cox E, Alderman J. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain-results of a model-based meta-analysis that accounts for encapsulation. Cephalalgia. 2005;25:715-25.

22. Steiner TJ, Diener HC, MacGregor EA, Schoenen J, Muirhead N, Sikes CR. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. Cephalalgia. 2003;23:942-52.
23. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol. 2004;11:671-7.
24. Farkkila M, Olesen J, Daholf C, Stovner LJ, Bruggen JP, Rasmussen S, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to sumatriptan. Cephalagia. 2003;23:463-71.
25. Sheftell F, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. Headache. 2003;43:202-13.
26. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot®) in the treatment of migraine: A multicentre, randomized, double-blind, placebo-controlled comparison. Eur Neurol. 2002;47:99-107.
27. Ryan R, Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. Headache. 2002;(42 Suppl 2):S84-92.
28. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology. 2004;63:261-9.
29. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomized controlled trials. Pharmacoepidemiol Drug Saf. 2004;13(2):73-82.
30. Bomhof M, Paz J, Legg N, Allen C, Vandermael K, Patel K; Rizatriptan-Naratriptan Study Group. Comparison of rizatriptan 10 mg vs naratriptan 2.5 in migraine. Euro Neurol. 1999;42:173-9.
31. Kolodny A, Polis A, Battisti WP, Johnson-Pratt L, Skobieranda F. Comparison of rizatriptan 5 and 10 mg tablets and sumatriptan 25 and 50 mg tablets. Cephalagia. 2004;24:540-6.
32. Lipton RB, Pascual J, Goadsby PJ, Massiou H, McCarroll KA, Vandormael K, et al. Effect of rizatriptan and other triptans on the nausea symptom of migraine: a post hoc analysis. Headache. 2001;41(8):754-63.
33. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. Headache. 2004;44:669-73.
34. Cady RK, Martin VT, Geraud G, Rodgers A, Zhang Y, Ho AP, et al. Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response. Headache. 2009 May;49(5):687-96.
35. Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia. 2001;21:129-36.
36. Oldman AD, Smith LA, McQuay HJ, Moore RA, Derry S. Rizatriptan for acute migraine. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.:CD003221. DOI:10.1002/14651858.CD003221.pub2.
37. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD008615.
38. Cutler N, Mushet GR, Davis R, Clements B, Whitcher L. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. Neurology.1995;45(Suppl 7):S5-9.
39. Winner P, Landy S, Richardson M, Ames M. Early intervention in migraine with sumatriptan tablets 50 vs 100 mg: a pooled analysis of data from six clinical trials. Clin Ther. 2005;27:1785-94.
40. Cady RK, Sheftell F, Lipton RB, Quinn S, Jones M, Putnam G, et al. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. Clin Ther. 2000;22:1035-48.
41. Djupesland PG, Docekal P. Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: a randomized, placebo-controlled study. Cephalagia. 2010;30(8):933-42.
42. Salonen R, Ashford E, Dahlöf C, Dawson R, Gilhus NE, Luben V, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol. 1994;241:463-9.
43. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA. 1991;265(21):2831-5.
44. No authors listed. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Sumatriptan Auto-Injector Study Group. Eur Neurol. 1991;31:323-31.
45. Silberstein S, Mannix L, Goldstein J, Couch J, Byrd SC, Ames MH, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. Neurology. 2008;71:114-21.
46. Lipton RB, Dodick DW, Adelman JU, Kaniecki RG, Lener SE, White JD, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. Cephalagia. 2009;29:826-36.
47. Mathew NT, Landy S, Stark S, Tietjen GE, Derosier FJ, White J. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. Headache. 2009;49:971-82.
48. Brandes J, Kudrow D, Stark S, O'Carroll C, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007 April;297:1443-54.
49. Landy S, DeRossett S, Rapoport A, Rothrock J, Ames MH, McDonald SA, et al. Two double-blind, multicenter, randomized, placebo-controlled, single-dose studies of sumatriptan/naproxen sodium in the acute treatment of migraine: function, productivity, and satisfaction outcomes. MedGenMed. 2007 Jun;9(2):53.
50. Geraud G, Olsen J, Pfaffenrath V, Tfelt-Hansen P, Zupping R, Diener HC, Sweet R. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. Cephalagia. 2000;20:30-8.
51. Dowson AJ, Almqvist P. Part III: The convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. Curr Med Res Opin. 2005;21(Suppl 3):S13-7.
52. Diener HC, Gendolla A, Gerbert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. Headache. 2005;45:874-82.
53. Dowson AJ, Charlesworth BR, Prudy A, Becker WJ, Boes-Hansen S, Farkkila M. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. CNS Drugs. 2003;17:839-51.
54. Adelman JU, Lipton RB, Ferrari MD, Diener HC, McCarrol KA, Vandormael K, et al. Comparison of rizatriptan and other triptans on stringent measures of efficacy. Neurology. 2001;57:1377-83.

55. Colman SS, Brod MI, Krishnamurthy A, Rowland CR, Jirgens KJ, Gomez-Mancilla B. Treatment satisfaction, functional status, and health related quality of life of migrating patients treated with almotriptan or sumatriptan. Clin Ther. 2001;23(1):127-45.
56. Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, et al. Oral almotriptan vs oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. Arch Neurol. 2001;58(6):944-50.
57. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. Cephalagia. 2002;22(6):453-61.
58. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto G, Bussone G. Efficacy and tolerability of almotriptan vs zolmitriptan for the acute treatment of menstrual migraine. Neurol Sci. 2006;27:S193-7.
59. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg vs subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. Eur J Neurol. 2005;25:108-17.
60. Sandrini G, Farkkila M, Burgess G, Forster E, Haughie S. Eletriptan vs sumatriptan a double-blind, placebo-controlled, multiple migraine attack study. Neurol. 2002;59:1210-7.
61. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan vs almotriptan for the acute treatment of migraine. J Headache Pain. 2011;12:361-8.
62. Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, et al. Frovatriptan vs zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci. 2010;31(Suppl1):S51-4.
63. Gobel H, Winter P, Boswell D, Crisp A, Becker W, Hauge T, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. Clin Ther. 2000 Aug;22(8):981-9.
64. Ng-Mak DS, Hu XH, Bigal M. Migraine treatment with rizatriptan and almotriptan: a crossover study. Headache. 2009;49:655-62.
65. Láinez MJA, Evers S, Kinge E, Allais G, Allen C, Rao NA, et al. Preference for rizatriptan 10-mg wafer vs eletriptan 40-mg tablet for acute treatment of migraine. Cephalalgia. 2006;26:246-56.
66. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. Headache. 2001 Sept;41(8):745-53.
67. Gershovich OE, Billups SJ, Delate T, Hoffman CK, Carroll N. Assessment of clinical, service, and cost outcomes of a conversion program of sumatriptan to rizatriptan ODT in primary care patients with migraine headaches. J Manag Care Pharm. 2006 Apr;12:246-53.
68. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62.
69. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63:2215-24.
70. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002 Nov 19;137(10):840-9.
71. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.

Therapeutic Class Review
5-HT1 Receptor Agonists

Overview/Summary

Migraine is a common disabling primary headache disorder that can be divided into two major subtypes: migraine without aura and migraine with aura. The International Headache Society describes migraine without aura as a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or accompany the headache.[1] Migraine without aura is further described as a recurrent headache disorder manifesting in attacks that can last four to 72 hours. Typical characteristics of these headaches are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia. Migraine with aura is also a recurrent headache disorder; however, it manifests in attacks of reversible focal neurological symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes. The subsequent headache, with features similar to those associated with migraine without aura, usually develops after aura symptoms. The International Headache Society describes cluster headaches as severe attacks that are strictly unilateral in pain, which is orbital, supraorbital, temporal or any combination of these sites. Attacks last for 15 to 180 minutes and can occur from once every other day to eight times a day. Cluster headaches are also associated with one or more of the following symptoms, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis or eyelid oedema.[1]

The serotonin (5-HT) 1 receptor agonists, commonly referred to as triptans, work in the management of migraine via the release of vasoactive peptides, promotion of vasoconstriction 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.[2] Triptans are Food and Drug Administration (FDA)-approved for the acute treatment of migraine with or without aura.[3-12] Of the available agents, the subcutaneous sumatriptan injection is also FDA-approved for the acute treatment of cluster headache episodes.[8] Almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7] In general, the evidence demonstrating the triptans to be an effective option for acute treatment of migraine is well established. However, there is a lack of consistent head-to-head data demonstrating “superiority” of any triptan, making it difficult to recommend the use of one over another.[2] Treatment guidelines do not generally distinguish among triptans. The triptans are recommended for initial treatment of an acute migraine attack of moderate to severe severity, especially when “nonspecific” therapies have failed. “Nonspecific” therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended for initial treatment of acute migraine attacks of mild to moderate severity.[13-16] In addition, the subcutaneous sumatriptan injection and zolmitriptan nasal spray are recognized as potential treatment options for the acute management of cluster headaches.[17]

Currently there are seven single-entity triptans available (Axert® [almotriptan], Relpax® [eletriptan], Frova® [frovatriptan], Amerge® [naratriptan], Maxalt® and Maxalt-MLT® [rizatriptan], Imitrex® [sumatriptan] and Zomig® and Zomig ZMT® [zolmitriptan]) and one combination product (Treximet® [sumatriptan/naproxen]). Sumatriptan/naproxen is a fixed-dose combination product containing a triptan and a NSAID. The combination is designed to target the multiple mechanisms of migraine pathology. The triptans are available in several different dosage formulations, including orally disintegrating tablets, nasal sprays, subcutaneous injections and tablets. All triptans are currently available as an oral tablet. Sumatriptan (nasal spray, 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 the others.[16] Naratriptan, rizatriptan and sumatriptan are currently available generically in various formulations.[18]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Almotriptan (Axert®)	5-HT1 receptor agonists	-
Eletriptan (Relpax®)	05-HT1 receptor agonists	-
Frovatriptan (Frova®)	5-HT1 receptor agonists	-
Naratriptan (Amerge®*)	5-HT1 receptor agonists	✔
Rizatriptan (Maxalt®*, Maxalt-MLT®*)	5-HT1 receptor agonists	✔
Sumatriptan (Alsuma®, Imitrex®*, Sumavel DosePro®)	5-HT1 receptor agonists	✔
Zolmitriptan (Zomig®, Zomig-ZMT®)	5-HT1 receptor agonists	-
Combination Products		
Sumatriptan/naproxen (Treximet®)	5-HT1 receptor agonists/ nonsteroidal anti-inflammatory drugs	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[3-12]

Indication	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/Naproxen
Acute treatment of cluster headache episodes						✔ *		
Acute treatment of migraine attacks in adults with a history of migraine with or without aura	✔							
Acute treatment of migraine attacks with or without aura in adults		✔	✔	✔		✔	✔	✔
Acute treatment of migraine headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more	✔							
Acute treatment of migraine with or without aura in adults and in pediatric patients six to 17 years of age					✔			

*Subcutaneous injection only.

Pharmacokinetics

Table 3. Pharmacokinetics[18]

Generic Name	Bioavailability (%)	Elimination (%)	Active Metabolites	Serum Half-Life (hours)	Onset (hours)	Duration (hours)
Single-Entity Agents						
Almotriptan	70	Feces (13); renal (75)	None	3 to 4	1 to 2	Not reported
Eletriptan	50	Renal (9)	N-deoxidation	4 to 5	1	18
Frovatriptan	24 to 30	Feces (62); renal (10 to 32)	None	25	2	Not reported
Naratriptan	70	Renal (50)	None	5 to 6	1	24
Rizatriptan	40 to 50	Feces (12); renal (82)	N-monodes-methyl-rizatriptan	2 to 3	0.5	14 to 16
Sumatriptan	24 to 25 (IN)	Feces (38); renal (57)	None	2	1 (IN)	Not reported (IN)
	14 to 15 (PO)				1 to 2 (PO)	3 (PO)
	97 (SC)				0.2 to 1.0 (SC)	Not reported (SC)
Zolmitriptan	102 (IN)*	Feces (20 to 30); renal (60)	N-desmethyl zolmitriptan	2.5 to 3.0	1	Not reported
	39 to 48 (PO)					
Combination Products						
Sumatriptan/ naproxen	14 to 15/95	Feces (40/not reported); renal (57/95)	None	2/19	Not reported	Not reported

IN=intranasal, PO=oral, SC=subcutaneous
*Relative to oral formulation.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the serotonin (5HT) 1 receptor agonists, or triptans, for the acute treatment of migraine are outlined in Table 4.[19-96] In general, clinical trial data consistently demonstrates the "superiority" of the triptans over placebo in achieving headache pain relief and freedom from pain at two hours, and sustained pain-free response; reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia.[20,21,32-34,37-44,49,50,52,54,58-60,62-66,71-77,85-93] Clinical trial data also suggests the available triptans, when administered orally, range in comparative efficacy. Specifically, in a large meta-analysis, consisting of 53 controlled trials and over 24,000 patients, results demonstrated that while all triptans were effective and well tolerated, eletriptan (80 mg) and rizatriptan (10 mg) were "superior" to sumatriptan (100 mg) in terms of achievement of headache response at two hours, pain-free response at two hours and sustained pain-free response. Almotriptan (12.5 mg) demonstrated "superiority" over sumatriptan for pain-free response at two hours and sustained pain-free response. Of note, lower doses of eletriptan and rizatriptan in this analysis did not achieve the same results.[21] While there appears to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of one over another, suggesting that individual variations in the response to different triptans exist.[21-26,35,36,45,47,53,56,57,69] Furthermore, guidelines do not generally distinguish among the available triptans.[13-16] Trials comparing different formulations of triptans measured patient preference as the primary endpoint.[36,57,69,70]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Cluster Headaches				
Gobel et al[19] Sumatriptan 6 mg SC	MC, OL Patients 18 to 65 years of age with a diagnosis of cluster headache or episodic cluster headache	N=52 1 year	Primary: Freedom from pain within 15 minutes in >90% of attacks Secondary: Tolerability	Primary: Freedom from pain within 15 minutes in >90% of attacks was reported by 42% of patients (*P* value not reported). Secondary: Adverse events were reported by 62% of patients (*P* value not reported).
Ekbom et al[20] Sumatriptan 6 mg SC vs sumatriptan 12 mg SC vs placebo	DB, MC, PC, RCT, XO Patients 18 to 65 years of age with a diagnosis of cluster headache or episodic cluster headache	N=134 Single migraine attack	Primary: Headache improvement to mild or no pain at 10 and 15 minutes Secondary: Not reported	Primary: At 10 minutes, headache relief was reported by 25, 49 and 63% of patients receiving placebo, sumatriptan 6 mg and sumatriptan 12 mg (*P* values not reported). At 15 minutes, headache relief was reported by 35, 75 and 80% of patients receiving placebo, sumatriptan 6 mg and sumatriptan 12 mg, respectively (*P*<0.001 for all compared to placebo). There were no differences between sumatriptan 6 and 12 mg (*P* value not reported). Secondary: Not reported
Migraines (With or Without Aura)				
Ferrari et al[21] Almotriptan 12.5 mg vs eletriptan 20 mg vs eletriptan 40 mg vs	MA (53 DB, RCTs) Patients 18 to 65 years of age receiving treatment with an oral triptan at a recommended clinical dose for moderate or severe migraine attacks within	N=24,089 Duration varied	Primary: Headache response rates at two hours, pain-free rates at two hours, sustained pain-free response Secondary: Adverse events	Primary: Headache response rates at two hours (mean percent) for sumatriptan 100 mg were 59.0 (95% CI, 7.3 to 60.8). Triptans with better efficacy than sumatriptan 100 mg were rizatriptan 10 mg (mean percent, 68.6; 95% CI, 66.9 to 70.4) and eletriptan 80 mg (mean percent, 65.8; 95% CI, 63.6 to 68.3). Triptans with similar efficacy to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 61.2; 95% CI, 57.6 to 64.8), eletriptan 40 mg (mean percent, 60.2; 95% CI, 58.0 to 62.4), zolmitriptan 2.5 mg (mean percent, 63.5; 95% CI, 60.8 to 66.2), zolmitriptan 5 mg (mean percent, 62.8; 95% CI, 60.0 to 65.6) and rizatriptan 5 mg (mean percent, 62.4; 95% CI, 60.2 to 64.5).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
eletriptan 80 mg vs frovatriptan 2.5 mg vs naratriptan 2.5 mg vs rizatriptan 5 mg vs rizatriptan 10 mg vs sumatriptan 25 mg vs sumatriptan 50 mg vs sumatriptan 100 mg vs zolmitriptan 2.5 mg vs	eight hours of onset			Triptans with lower efficacy compared to sumatriptan 100 mg were sumatriptan 25 mg (mean percent, 56.0; 95% CI, 53.1 to 58.9), naratriptan 2.5 mg (mean percent, 48.6; 95% CI, 45.7 to 51.4), eletriptan 20 mg (mean percent, 48.9; 95% CI, 44.5 to 53.3) and frovatriptan 2.5 mg (mean percent, 41.5; 95% CI, 39.3 to 43.8). Pain-free results at two hours (mean percent) for sumatriptan 100 mg was 28.9 (95% CI, 27.2 to 30.5). Triptans with higher rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 61.2; 95% CI, not reported), eletriptan 80 mg (mean percent, 33.0; 95% CI, 30.5 to 35.4) and rizatriptan 10 mg (mean percent, 40.1; 95% CI, 38.3 to 42.0). Triptans with lower rates compared to sumatriptan 100 mg were sumatriptan 25 mg (mean percent, 23.4; 95% CI, 21.0 to 25.9), naratriptan 2.5 mg (mean percent, 22.4; 95% CI, 20.0 to 24.7) and eletriptan 20 mg (mean percent, 16.4; 95% CI, 13.2 to 19.7). All other triptans did not significantly differ from sumatriptan 100 mg. Sustained pain-free results (mean percent) for sumatriptan 100 mg were 20.0 (95% CI, 18.2 to 21.3). Triptans with higher rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean percent, 25.9; 95% CI, 22.7 to 29.1), rizatriptan 10 mg (mean percent, 25.3; 95% CI, 23.7 to 26.9) and eletriptan 80 mg (mean percent, 25.0; 95% CI, 22.8 to 27.2). Triptans with lower rates compared to sumatriptan 100 mg were eletriptan 20 mg (mean percent, 10.6; 95% CI, 7.7 to 13.5), sumatriptan 25 mg (mean percent, 16.7; 95% CI, 14.5 to 18.9) and naratriptan 2.5 mg (mean percent, 15.9; 95% CI, 13.4 to 18.5). No differences were found with other triptan doses.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
zolmitriptan 5 mg vs placebo				Secondary: Placebo subtracted adverse events (mean) for sumatriptan 100 mg were 13.2 (95% CI, 8.6 to 17.8). Triptans with lower rates compared to sumatriptan 100 mg were almotriptan 12.5 mg (mean, 1.8; 95% CI, -2.5 to 6.2) and naratriptan 2.5 mg (mean, 2.4; 95% CI, -2.2 to 7.0). Central nervous system placebo subtracted adverse events (mean) for sumatriptan 100 mg was 6.3 (95% CI, 3.2 to 9.5). Triptans with higher central nervous system adverse event rates than sumatriptan 100 mg was eletriptan 80 mg (mean, 14.6; 95% CI, 10.2 to 19.0). Rates for all other triptans and doses largely overlap. Triptans with lower central nervous system adverse event rates compared to sumatriptan 100 mg was almotriptan 12.5 mg (mean, -1.5; 95% CI%, -3.9 to 1.0). Rates for all other triptans and doses largely overlap.
Adelman et al[22] Rizatriptan 10 mg vs naratriptan 2.5 mg vs zolmitriptan 2.5 mg vs sumatriptan 25 mg vs	MA (5 DB, PC, RCTs) Outpatients with at least a six month history of migraine with or without aura	N=4,064 24 hours	Primary: Pain-free response at two hours, symptom-free response at two hours, 24-hour sustained pain-free response Secondary: Adverse events	Primary: Pain-free rates at two hours were significantly higher with rizatriptan compared to all other triptans. The proportions of patients who were pain-free ranged from 38 to 45% with rizatriptan 10 mg and 21 to 36% with all other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; *P*=0.019, rizatriptan vs sumatriptan 50 mg; *P*=0.009, rizatriptan vs sumatriptan 25 mg; *P*<0.001, rizatriptan vs naratriptan 2.5 mg; *P*<0.001 and rizatriptan vs zolmitriptan 2.5 mg; *P*=0.041. Symptom-free rates at two hours were significantly higher with rizatriptan compared to all other triptans. The proportions of patients with freedom from pain and associated symptoms ranged from 30 to 33% with rizatriptan and 11 to 28% with other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; *P*=0.002, rizatriptan vs sumatriptan 50 mg; *P*=0.003, rizatriptan vs sumatriptan 25 mg; *P*<0.001, rizatriptan vs naratriptan 2.5 mg; *P*<0.001 and rizatriptan vs zolmitriptan 2.5 mg; *P*=0.042. Sustained pain-free response rates were significantly higher with rizatriptan

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 50 mg vs sumatriptan 100 mg				compared to all other triptans. The significance of these differences are noted as: rizatriptan vs sumatriptan 100 mg; *P*=0.112, rizatriptan vs sumatriptan 50 mg; *P*=0.015, rizatriptan vs sumatriptan 25 mg; *P*=0.005, rizatriptan vs naratriptan 2.5 mg; *P*=0.004 and rizatriptan vs zolmitriptan 2.5 mg; *P*=0.013. Secondary: Incidences of drug related adverse events were as follows: rizatriptan 10 mg vs sumatriptan 100 mg; 33 vs 41% (*P*=0.014), rizatriptan 10 mg vs sumatriptan 50 mg; 37 vs 35% (*P*=0.671), rizatriptan 10 mg vs sumatriptan 25 mg; 37 vs 31% (*P*=0.043), rizatriptan 10 mg vs naratriptan 2.5 mg; 27 vs 19% (*P*=0.079) and rizatriptan 10 mg vs zolmitriptan 2.5 mg; 25 vs 28% (*P*=0.410).
Colman et al[23] Almotriptan 12.5 mg vs sumatriptan 50 mg	DB, RCT Patients 18 to 71 years of age who had not been treated previously with a triptan, with a history of migraine with or without aura for at least six months	N=1,173 48 hours	Primary: Change in treatment satisfaction measure, functional status measure, MqoLQ values from baseline to 48 hours Secondary: Not reported	Primary: There were no significant differences between the two treatments in terms of satisfaction with pain relief (mean score, 50.85 vs 52.10; *P*=0.67). Patients receiving either treatment improved by about 44 points on the 100-point functional status scale after 24 hours. Patients receiving both treatments reported improvement in functional status after treatment, from marginally functional at onset of migraine (mean scores, 42.54 vs 42.50, respectively) to about 90% of normal (mean scores, 86.49 vs 86.99, respectively) at 24 hours. No difference was found between the two treatments in a comparison of MqoLQ at 24 hours after treatment (*P* value not reported). Patients receiving almotriptan were significantly more satisfied and experienced fewer adverse events compared to patients receiving sumatriptan (*P*=0.016). Secondary: Not reported
Spierings et al[24] Almotriptan 12.5 mg vs sumatriptan 50 mg	DB, MC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=1,255 24 hours	Primary: Headache relief and pain-free status at two hours Secondary:	Primary: Headache relief at two hours was observed in 58.0 and 57.3% of patients receiving almotriptan and sumatriptan, with no difference between the two treatments (*P* value not reported). Pain-free response rates at two hours were observed in 17.9 and 24.6% of patients, respectively (*P*=0.005). Secondary:

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			Migraine relief, improvement of migraine-associated symptoms, incidence of migraine recurrence at 24 hours after dosing and use of rescue medication	There was no difference between the treatments with regard to relief from migraine-associated symptoms of nausea, vomiting, photophobia and phonophobia (*P* values not reported). Rescue medications were taken by 36.7 and 33.2% of patients receiving almotriptan and sumatriptan, respectively (*P* value not reported). Of the 343 responders receiving almotriptan, 27.4% experienced a migraine recurrence within 24 hours, compared to 24.0% of the 333 responders receiving sumatriptan. The difference was not significant (*P* value not reported).
Dowson et al[25] Almotriptan 12.5 and 25 mg vs sumatriptan 100 mg vs placebo All medications were administered during a migraine attack. A second dose was allowed if headache relapsed in two to 24 hours after first dose. Escape medication was allowed if pain	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=668 Single migraine attack	Primary: Pain relief at two hours Secondary: Pain relief at one hour, pain-free status at one and two hours, migraine recurrence within 24 hours and rescue medication use	Primary: The proportion of patients achieving pain relief at two hours was higher with almotriptan (12.5 mg, 56.8%; 25 mg, 56.5%) and sumatriptan (63.7%) compared to placebo (42.2%; *P* values not reported). Both doses of almotriptan were equivalent to sumatriptan with the 90% CI inside the range of the equivalence region (*P* value not reported). Secondary: Pain relief at one hour was not different between the three treatments (*P* values not reported). Recurrence within 24 hours for patients with moderate pain at baseline was reported as follows: almotriptan 12.5 mg, 22.7%; almotriptan 25 mg, 14.9%; sumatriptan 100 mg, 22.4% and placebo, 16.7% (*P* values not reported). Corresponding rates at 24 hours for patients with severe pain at baseline were: 8.8, 16.2, 28.9 and 27.3% (*P* values not reported). The use of escape medication was reported as follows: almotriptan 12.5 mg, 38.6%; almotriptan 25 mg, 38.2%; sumatriptan 100 mg, 32.4% and placebo, 55.5% (*P* values not reported).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
persisted beyond two hours.				
Allais et al[26] Almotriptan 12.5 mg vs zolmitriptan 2.5 mg	DB, MC, PC, RETRO, RCT Women with a history of migraine for more than one year and two to six migraine attacks in each of the two months preceding the trial	N=255 24 hours	Primary: Pain relief at one-half, one, one and one-half and two hours; pain-free at one-half, one, one and one-half and two hours; sustained pain-free at two hours with no recurrence and no rescue medication; recurrence within 24 hours of treatment; level of functional impairment before intake and after one-half, one, one and one-half and two hours Secondary: Tolerability	Primary: In the ITT analysis, almotriptan did not differ from zolmitriptan for any of the outcomes evaluated. Two hours after dosing, 67.9 and 68.6% of the women receiving almotriptan and zolmitriptan, respectively, had obtained pain relief (*P*=0.900). Evolution of pain from “moderate to severe” to “mild to no pain” was also similar between treatments at one-half hour post dose (14.9 vs 11.9%; *P*=0.477). A pain-free state at two hours was reported by 44.9 and 41.2% of women receiving almotriptan and zolmitriptan, respectively (*P*=0.554). Twenty-four hours after dosing 56.6 and 64.7% of patients, respectively, were pain-free (*P*=0.187). Recurrences was reported in 32.8 and 34.7% of patients respectively (*P*=0.833). Use of rescue medication within two to 24 hours was reported by 21.8 and 25.4% of patients, respectively (*P*=0.499). A sustained pain-free response was reported by 29.3 and 27.1% of patients receiving almotriptan and zolmitriptan, respectively (*P*=0.698). Secondary: Adverse events occurring within 24 hours were reported in 19.8 and 23.1% of patients; with 13.2 and 17.6% (*P*=0.328), respectively, being considered triptan-related.
Berenson et al[27] Almotriptan 12.5 mg	OL Patients 12 to 17 years of age with	N=447 1 year	Primary: Safety Secondary:	Primary: Overall, 282 patients (67.1%) reported one or more adverse events for one or more headaches during the trial. Thirty two patients (7.6%) had an adverse event that was judged to be related to almotriptan and 44% of patients had at least one

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
	at least a one year history of migraine with or without aura, an average of one to 14 migraines per month with <15 total headache days per month for at least six months prior to trial enrollment, receiving one or fewer prophylactic medication and had ≥24 hours of freedom from headache between migraine attacks		Patient-rated intensity of the migraine-associated symptoms of phonophobia, photophobia and nausea; use of rescue medication or a second dose of study medication	adverse event that was considered to be moderate or marked in intensity. Eight patients (1.9%) had a serious adverse event and 10 patients (2.4%) discontinued treatment because of an adverse event. No deaths were reported during the trial and all serious adverse events resolved. The most commonly reported adverse events (≥5% incidence) were: nasopharyngitis, sinusitis, upper respiratory tract infection, pharyngitis streptococcal, nausea, vomiting, pharyngolaryngeal pain and nasal congestion. Secondary: Photophobia was common at baseline (76.6%) and after treatment photophobia was present in 39.1 and 11.6% of all migraines at two and 24 hours after treatment. Phonophobia was common at baseline (71.8%) and after treatment it was present in 35.4 and 10.0% of all migraines two and 24 hours after treatment. Nausea was common at baseline (40.5%) and after treatment it was present in 22.2 and 6.7% of all migraines two and 24 hours after treatment. Overall, rescue medication was taken by 334 patients (79.5%) for one or more migraines during the trial. Rescue medication was used for 681 migraines (8.5%) within two hours of first dose of almotriptan and for 1,999 migraines (24.8%) within 24 hours of the first dose of almotriptan. A second dose of almotriptan was taken by 306 patients (72.9%) for one or more migraines during the trial, with 441 (5.5%) and 1,676 patients (20.8%) treated with a second dose within two and 24 hours of the first dose.
Cabarrocas et al[28] Almotriptan 12.5 mg	OL Patients 18 to 65 years of age with migraine with or without aura	N=747 1 year	Primary: Headache response rates at one and two hours Secondary: Safety	Primary: Headache response rates at one and two hours were 43 and 73%, respectively (*P* value not reported). Secondary: The most common adverse events were back pain, bronchitis and flu-like symptoms (*P* value not reported).
Lanteri-Minet et al[28] START Almotriptan 12.5 mg	OL, OS, PRO Patients 18 to 65 years of age with	N=501 3 migraine attacks	Primary: Proportion of patients who were pain-free	Primary: Early intervention resulted in a significantly greater proportion of patients achieving freedom of pain at two hours for the first migraine attack (61.90 vs 35.37%; *P*<0.001).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Patients administered almotriptan either within one hour of pain onset when pain was still mild (early intervention) or beyond one hour and/or until pain progressed to moderate/severe (delayed intervention).	a diagnosis of migraine with or without aura, at least a one year history of migraine which progressed from mild to at least moderate intensity with a frequency of two to six attacks per month during the previous three months		at two hours Secondary: Proportion of patients pain-free at two hours across all attacks, proportion of patients achieving sustained pain-free status with or without adverse events, relapse at 24 hours, use of rescue medication, evolution of migraine symptoms, duration of pain, functional disability and tolerability	Secondary: Early intervention resulted in a significantly greater proportion of patients achieving freedom of pain at two hours for all three migraine attacks (65.22 vs 37.64%; *P*<0.001). Across all attacks, early intervention resulted in a significantly greater proportion of patients achieving sustained pain-free status (59 vs 33%; *P*<0.001). Similar results were observed for sustained pain-free status with no adverse events (55 vs 31; *P*<0.001). A significantly smaller proportion of patients who received early treatment required rescue medication (15 vs 27%; *P*=0.003). Early intervention was associated with a significantly shorter period of migraine and functional disability (*P*<0.001 for both). There was no difference between early or delayed intervention with regard to relapse in 24 hours was observed (*P* value not reported). Early intervention was associated with significantly fewer migraine-associated symptoms after two hours (nausea, 7.5 vs 19.2%; *P*<0.001, vomiting, 1.5 vs 3.9%; *P*=0.218, photophobia, 10.5 vs 24.7%; *P*<0.001, phonophobia, 10.5 vs 23.5%; *P*<0.001). A total of 65 treatment-emergent adverse events were reported during the trial, none of which were serious or lead to treatment discontinuation. Only two were considered possibly related to study medication (dizziness and tremor). There was no difference in the incidence of adverse events between early and delayed intervention (*P*=0.202).
Pascual et al[29] Almotriptan 6.25 mg vs	DB, OL Patients 18 to 65 years of age with at least a one year history of	N=762 1 year	Primary: Incidence of treatment-emergent adverse events	Primary: During the trial, 391 patients (51.3%) experienced at least one adverse event. Patients reported at least one adverse event in 11.0% of attacks treated. The incidence of adverse events decreased during the trial; 30.7% of patients had at least one adverse event during the first three months of the trial compared to only 21.5% of patients during the last three months.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
almotriptan 12.5 mg	migraine, with or without aura; all patients experienced one to six migraine attacks per month with ≥24 hours of freedom between attacks		Secondary: Percent of attacks resolved (to mild or no pain) by two hours after dose (attacks of moderate/ severe baseline intensity only)	The majority (88.6%) of adverse events were of mild to moderate intensity. Only 28.8% of adverse events were considered to be possibly, probably or definitely related to the study drug. Of these drug-related events, those which occurred in at least one percent of patients were vomiting (2.1%), somnolence (1.7%), dizziness (1.6%), fatigue (1.4%) and nausea (1.4%; *P* values not reported). Secondary: Pain relief at two hours after the initial dose was achieved in 84.2% of moderate/severe attacks. Patients were pain-free at two hours after dose in 58.2% of all attacks (*P* values not reported).
Diener et al[30] Almotriptan 12.5 mg vs placebo All patients were poor responders to sumatriptan 50 mg.	DB, MC, PC, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for at least one year and had experienced unsatisfactory responses to sumatriptan on at least two occasions	N=328 Single migraine attack	Primary: Relief from headache at two hours Secondary: Pain-free efficacy at two hours, use of rescue medication within 24 hours	Primary: A significantly greater proportion of patients receiving almotriptan achieved pain relief at two hours compared to patients receiving placebo (47.5 vs 23.2%; *P*<0.01). Secondary: A significantly greater proportion of patients receiving almotriptan achieved pain-free status at two hours compared to patients receiving placebo (33.3 vs 14.1%; *P*<0.005). Rescue medications were required by significantly fewer patients receiving almotriptan compared to patients receiving placebo (26.6 vs 46.9%; *P*<0.005).
Dahlof et al[31] Almotriptan 2, 6.25, 12.5 and 25 mg vs placebo	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one	N=742 Single migraine attack	Primary: Change in headache pain intensity at two hours without rescue medication Secondary:	Primary: Almotriptan demonstrated a dose-dependent increase in the proportion of patients with improvement in headache pain intensity (58.5 and 66.5% improvement for the 12.5 and 25 mg doses, respectively, compared to 32.5% for placebo; *P*<0.001). Almotriptan 2 mg was equivalent to placebo (*P* value not reported). Secondary: With regard to freedom from pain, almotriptan produced a significant dose-dependent increase over placebo at one, one and a half and two hours (*P*<0.0001

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
All medications were administered during a moderate to severe migraine attack. A second dose was allowed if pain severity increased within two to 24 hours. Escape medication was allowed if pain did not decrease after two hours.	year and migraines occurring up to six times per month		Freedom from pain, relief from migraine-associated symptoms	for all). Almotriptan 12.5 mg produced significant improvement compared to placebo at half an hour (*P*<0.0485). Almotriptan demonstrated a significant dose-dependent improvement in pain-free state at two hours both with 12.5 and 25 mg compared to placebo (*P*<0.001). A significantly better response was observed for patients with baseline moderate headache than patients with severe headache (*P* value not reported). A dose-dependent decrease in the incidence of migraine-associated symptoms was noted for almotriptan. The incidence of migraine recurrence was not different among the treatment groups, ranging from 25.2 to 28.7% (*P* value not reported).
Dahlof et al[33] Almotriptan 2 mg vs almotriptan 5 mg vs almotriptan 6.25 mg vs almotriptan 12.5 mg vs almotriptan 25 mg vs	MA (4 DB, PC, RCT) Patients 18 to 65 years of age who had at least a six month history of migraine and experienced one to six migraine attacks per month	N=2,294 Single migraine attack	Primary: Efficacy, speed of onset and tolerability of almotriptan in the acute treatment of migraine; proportion of patients achieving sustained pain-free with no adverse events Secondary: Not reported	Primary: As early as 30 minutes after dosing, almotriptan 12.5 mg was significantly more effective than placebo for pain relief (14.9 vs 8.2%; *P*<0.05) and freedom from pain (2.5 vs 0.7%; *P*<0.05). At two hours, pain relief rates were 56.0, 63.7 and 66.0% for almotriptan 6.25, 12.5 and 25 mg, respectively, compared to 35.0% for placebo; two hour pain-free rates were 26.7, 36.4 and 43.4% compared to 13.9% for placebo (*P* values not reported). All almotriptan dosages were significantly more effective compared to placebo in eliminating migraine-associated symptoms (*P*<0.05) and in achieving sustained pain relief up to 24 hours (*P*<0.05). The incidences of adverse events for almotriptan 6.25 and 12.5 mg were not different from that of placebo. Secondary: Not reported

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
almotriptan 100 mg vs almotriptan 150 mg vs placebo				
Garcia-Ramos et al[33] Eletriptan 40 mg vs naratriptan 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 80 years of age with migraine with or without aura reporting a minimum of one acute migraine attack every six weeks	N=548 Single migraine attack	Primary: Headache response at two hours Secondary: Headache response at one and four hours; pain-free response at one, two and four hours; presence or absence of associated symptoms at the same time points; functional status; headache recurrence and time to headache recurrence; use	Primary: A significantly greater proportion of patients receiving eletriptan achieved headache response at two hours compared to patients receiving naratriptan (56 vs 42%; *P*<0.01). Both active treatments were significantly better than placebo (*P*<0.0001 and *P*<0.05). Secondary: A significantly greater proportion of patients receiving eletriptan achieved headache response at one and four hours compared to patients receiving naratriptan (34 vs 25%; *P*<0.05, 80 vs 67%; *P*<0.01) and patients receiving placebo (21%; *P*<0.01, 44%; *P*<0.0001). A significantly greater proportion of patients receiving eletriptan achieved a pain-free response at two and four hours compared to patients receiving naratriptan (35 vs 18%; *P*<0.001 and 56 vs 41%; *P*<0.01) and patients receiving placebo (19%; *P*<0.001 and 24%; *P*<0.0001). At one hour, freedom from pain was significantly greater with eletriptan (12%) compared to naratriptan (6%; *P*<0.05). Freedom from pain with naratriptan was significantly greater compared to placebo at four hours (*P*<0.01) but not at two hours (*P* value not reported). Absence of nausea at two hours was not significantly different among the treatments (73 vs 68 vs 66%; *P*=0.09 vs naratriptan; *P*=0.07 vs placebo). Eletriptan resulted in significantly better functional improvement at two hours compared to naratriptan (60 vs 52%; *P*=0.014) and placebo (44%; *P*<0.001). No difference between naratriptan and placebo was noted (*P* value not reported).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			of rescue medication, time to use of rescue medication; sustained headache; sustained pain-free response; global evaluation of medication and acceptability of study medication	Among patients who achieved a two hour headache response, headache recurrence rates were consistently low with eletriptan (29%), naratriptan (26%) and placebo (28%), with no differences among the three (*P* values not reported). The proportion of patients taking a second dose of study medication for headache recurrence was lower for eletriptan and naratriptan (19 and 18%, respectively) compared to placebo (26%; *P* value not reported). Significantly less rescue medication was used with eletriptan compared to naratriptan (15 vs 27%; *P*<0.01). A significantly greater proportion of patients receiving eletriptan reported a sustained headache response (38%) compared to patients receiving naratriptan (27%; *P*<0.05) and patients receiving placebo (19%; *P*<0.01). No difference between naratriptan and placebo was noted (*P* value not reported). A significantly greater proportion of patients receiving eletriptan reported a sustained pain-free response (22%) compared to patients receiving naratriptan (11%; *P*<0.05) and patients receiving placebo (12%; *P*<0.05). Patient ratings of treatment acceptability were significantly higher for eletriptan compared to naratriptan (68 vs 50%; *P*<0.001) and placebo (31%; *P*<0.0001). Naratriptan was "superior" to placebo (*P*<0.05). The proportion of patients reporting treatment to be 'good to excellent' was significantly greater with eletriptan compared to naratriptan (70 vs 53%; *P*<0.001) and placebo (33%; *P*<0.0001). Naratriptan was "superior" to placebo (*P*<0.001).
Schoenen et al[34] Eletriptan 80 mg vs sumatriptan 6 mg SC	OL, RCT, XO Patients 18 to 65 years of age with migraine with or without aura and suffering at least one acute attack every six weeks	N=311 3 migraine attacks	Primary: Patient preference Secondary: Change from pretreatment baseline in headache	Primary: Fifty one percent of patients preferred or greatly preferred eletriptan, while 43% of patients preferred sumatriptan SC (*P* value not reported). When permitted to choose between eletriptan and sumatriptan SC for subsequent treatment, 78% of patients who had preferred eletriptan took eletriptan during the extension phase for all three of their attacks, while only 37% of patients who preferred sumatriptan SC took sumatriptan SC for all of their extension phase attacks (*P*<0.05). Secondary:

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			intensity; change from pretreatment baseline in a five-point patient-rated Global Impression of efficacy scale; the presence or absence of nausea, vomiting, photophobia and phonophobia; change in functional impairment scale; headache recurrence (and time to headache recurrence) between two and 24 hours; time to use of rescue medication; sustained relief and acceptability of study medication	Secondary efficacy measures showed comparable efficacy for each study medication, except for faster headache response and pain-free rates in favor of sumatriptan SC, and a significantly lower recurrence rate with eletriptan (25 vs 40%; *P*<0.05).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Sandrini et al[35] Eletriptan 40 mg vs eletriptan 80 mg vs sumatriptan 50 mg vs sumatriptan 100 mg	DB, DD, MC, PC, PG, RCT Patients >18 years of age who were expected to have at least one attack of migraine with or without aura every six weeks	N=1,008 3 migraine attacks	Primary: Headache response at one and two hours Secondary: Headache response rates, functional improvement and patient acceptability	Primary: Headache response rates were 12% at one hour and 31% at two hours for placebo; 24 and 50% for sumatriptan 50 mg; 27 and 53% for sumatriptan 100 mg; 30 and 64% for eletriptan 40 mg and 37 and 67% for eletriptan 80 mg. Significantly more patients receiving eletriptan 80 mg achieved a one hour headache response compared to patients receiving sumatriptan 50 mg (P<0.05). All doses of eletriptan were more efficacious than sumatriptan at two hours for headache response and complete pain relief (P<0.05). Secondary: Significantly more patients receiving eletriptan 80 mg achieved headache response in all attacks compared to sumatriptan (P values not reported). Eletriptan 40 mg was more efficacious than sumatriptan in functional improvement (P<0.005 for both). The higher efficacy of both eletriptan doses was associated with higher rates of patient acceptability than sumatriptan 50 mg (P<0.05).
Mathew et al[36] Eletriptan 40 mg vs sumatriptan 100 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=2,113 24 hours	Primary: Headache response at two hours Secondary: Headache response at one hour, pain-free rates, absence of associated symptoms, functional response at one and two hours and sustained headache response	Primary: Headache response at two hours was significantly greater for eletriptan compared to sumatriptan (67 vs 59%; P<0.001) and placebo (26%; P<0.0001). Secondary: Eletriptan consistently demonstrated significantly greater efficacy compared to sumatriptan across all secondary outcomes, including headache response at one hour, freedom from pain at two hours, absence of nausea, photophobia and phonophobia, functional improvement, use of rescue medication, treatment acceptability and sustained headache response (P<0.05 for all).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Goadsby et al[37] Eletriptan 20 mg vs eletriptan 40 mg vs eletriptan 80 mg vs sumatriptan 100 mg vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with migraine with or without aura	N=692 Single migraine attack	Primary: Proportion of responders (any patient who within two hours after ingesting study drug, reported improvement in headache intensity to mild or pain-free levels from a pretreatment level of moderate or severe) Secondary: Not reported	Primary: The proportions of patients who responded were 24 (30/126), 55 (63/115), 54 (70/129), 65 (76/117) and 77% (91/118) for placebo, sumatriptan, eletriptan 20 mg, eletriptan 40 mg and eletriptan 80 mg, respectively. There was a significant difference compared to placebo for all doses of eletriptan (*P*<0.001). There was a significant difference between sumatriptan 100 mg and eletriptan 80 mg (*P*<0.001). Freedom from headache at two hours was significantly better with eletriptan 80 (37%) and 40 mg (29%) compared to placebo (6%; *P*<0.001). Eletriptan 80 mg was "superior" to sumatriptan (23%; *P*<0.05). Secondary: Not reported
Mandema et al[38] Eletriptan 20 mg vs eletriptan 40 mg vs eletriptan 80 mg vs sumatriptan 25 mg	MA (DB, PC, RCTs) Adult patients receiving treatment of moderate or severe migraine within eight hours of onset, with no re-medication or rescue before two hours	N=11,400 Duration not specified	Primary: Pain relief at four hours and proportion of patients that became pain-free Secondary: Not reported	Primary: A significant difference for eletriptan 40 mg for pain relief compared to sumatriptan 100 mg at any point in time up to four hours after treatment was observed (*P* value not reported). The benefit of eletriptan 40 mg is greatest around one and half to two hours after treatment. There was an absolute difference at two hours of 9.1% (7.4 to 11.5%) more patients achieving pain relief and 7.3% (5.8 to 8.6%) more patient achieving pain-free when compared to sumatriptan 100 mg (*P* values not reported). An absolute benefit of more than five percent of patients is maintained from 45 minutes up to four hours after treatment for pain relief and from one and half hours up to four hours for pain-free response (*P* values not reported). Eletriptan 20 mg was more efficacious than sumatriptan 50 mg and similar to sumatriptan 100 mg for pain relief, while it was similar to sumatriptan 50 mg for pain-free response (*P* values not reported).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs sumatriptan 50 mg vs sumatriptan 100 mg vs sumatriptan 200 mg vs sumatriptan 300 mg vs placebo				The benefit of eletriptan 20 mg when compared to sumatriptan 50 mg is greatest around one and a half to two hours after treatment with an absolute difference at two hours of 5.0% (2.9 to 8.1%) more patients achieving pain relief (*P* value not reported). An absolute benefit of more than three percent of patients was maintained from one hour up to three hours after treatment. No difference was observed between eletriptan 20 mg and sumatriptan 50 mg for the fraction of patients that became pain-free (*P* value not reported). No significant effect of encapsulation of sumatriptan was found on the time course of response up to four hours after treatment when compared to commercial sumatriptan (*P* value not reported). Secondary: Not reported
Steiner et al[39] Eletriptan 40 mg vs eletriptan 80 mg vs zolmitriptan 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with migraine with or without aura	N=1,312 Single migraine attack	Primary: Headache response within two hours Secondary: Headache response rates at one hour; pain-free rates at one and two hours, absence of associated symptoms at one-half, one, one and a half and two hours,	Primary: Significantly more patients receiving eletriptan 80 mg (74%) achieved a headache response within two hours compared to patients receiving zolmitriptan (60%; *P*<0.0001) and patients receiving placebo (22%; *P*<0.0001). Eletriptan 40 mg was "superior" to placebo (64 vs 28%; *P* value not reported). Eletriptan 80 mg was "superior" to eletriptan 40 mg at two hours (*P*<0.01). Secondary: A significantly greater proportion of patients receiving eletriptan 80 mg (40%) achieved a headache response at one hour compared to patients receiving zolmitriptan (25%; *P*<0.0001) and patients receiving placebo (5%; *P*<0.0001). Pain-free rates with eletriptan 80 mg were significantly higher at two (44%) and one hours (12%) compared to zolmitriptan (26%; *P*<0.0001 and 6%; *P*<0.01) and placebo (6%; *P*<0.0001 and <1%; *P*<0.01). Eletriptan 40 mg was "superior" compared to placebo (32%; *P*<0.0001, 6%; *P*<0.05). Eletriptan 80 mg was "superior" to eletriptan 40 mg at two hours (*P*<0.01). Eletriptan 80 mg was

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			functional recovery at one and two hours, headache recurrence rate, use of rescue medication, sustained headache response, patient's global evaluation of study medication at 24 hours on a seven-point Likert scale and acceptability of study medication	significantly better (*P*<0.01) than eletriptan 40 mg in pain-free rates at two hours. In patients with severe or moderate functional impairment at baseline, all active treatments were superior to placebo at bringing improvement (*P*<0.0001 for all). Response rates at one and two hours were significantly higher with eletriptan 80 mg (68 and 34%) compared to zolmitriptan (56%; *P*<0.05, 24%; *P*<0.05). There was no difference between eletriptan 40 mg (61 and 24%) and zolmitriptan (*P* values not reported). In patients achieving headache response by two hours, headache recurrence rates were numerically lower with eletriptan 80 mg (33%; *P*=0.271) and significantly lower with eletriptan 40 mg (29%; *P*<0.05) compared to zolmitriptan (38%). Both doses of eletriptan had significantly lower recurrence rates than placebo (52%; *P*<0.05). Rescue medication was used significantly less with eletriptan 80 mg (14%) compared to zolmitriptan (26%; *P*<0.0001) and placebo (58%; *P*<0.0001). Similar results were observed with eletriptan 40 mg (20%; *P*<0.05 vs zolmitriptan; *P*<0.0001 vs placebo). Significantly greater proportions of patients receiving eletriptan 80 (47%; *P*<0.001) and 40 mg (44%; *P*<0.01) achieved sustained headache response compared to patients receiving zolmitriptan (35%). Eletriptan 80 (*P*<0.0001) and 40 mg (*P*<0.0001), as well as zolmitriptan (*P*<0.0001), were “superior” to placebo (11%). Sustained pain-free rates were higher with eletriptan 80 mg (29%) compared to zolmitriptan (17%; *P*<0.001). Eletriptan 80 (*P*<0.0001) and 40 mg (22%; *P*<0.0001), as well as zolmitriptan (*P*<0.01), were “superior” to placebo (5%). Patients’ ratings of treatment acceptability (‘would use again') showed significant preference for eletriptan 80 (61%; *P*<0.05) and 40 mg (64%; *P*<0.01) compared to zolmitriptan (53%). All active treatments were “superior” to placebo (19%; *P*<0.0001). On the seven-point global rating of study medication, analysis was of the percentage of patients in each group recording either “excellent” or “good”.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				Eletriptan 80 (66%) and 40 mg (64%) were rated significantly higher than zolmitriptan (55%; *P*<0.01). All active treatments were "superior" to placebo (17%; *P*<0.0001).
Olesen et al[40] Eletriptan 80 mg vs placebo	DB, PC, RCT Patients ≥18 years of age with migraine with aura every four weeks	N=123 24 hours	Primary: Proportion of patients not developing a migraine headache of moderate or severe intensity within six hours of dosing Secondary: Time to headache development, duration of aura symptoms, use of second dose, response to the second dose, use of rescue medication, treatment acceptability, time to rescue medication	Primary: Treatment with eletriptan during the aura phase was not effective in preventing the onset of moderate to severe headache post aura. There was no difference in the proportions of patients developing a headache on eletriptan and placebo (61 vs 46%; *P* value not reported). Secondary: Eletriptan did not increase the duration of the aura phase compared to placebo (0.7 vs 0.8 hour), nor was it associated with a significant delay in the median time to headache onset (1.3 vs 1.0 hour; *P* values not reported). A second dose of eletriptan was permitted for patients in both the eletriptan and placebo groups who developed a moderate to severe headache. Response rates to the 40 mg dose of eletriptan were similar (*P* value not reported). Additional rescue medication was taken by 28 and 17% of patients receiving eletriptan and placebo, respectively (*P* value not reported). The proportion of patients rating study medication as acceptable was comparable for both treatments (76 vs 72%; *P* value not reported). There was no difference between treatments on any efficacy measure.
Farkkila et al[41] Eletriptan 40 mg vs eletriptan 80 mg	DB, MC, PC, RCT Patients ≥18 years of age with migraine with or without aura	N=446 3 migraine attacks	Primary: Two hour headache response rates Secondary: Onset of action,	Primary: Two hour headache response, based on first dose, first attack data, was 59, 70 and 30% with eletriptan 40 mg, eletriptan 80 mg and placebo (*P*<0.0001 for both doses of eletriptan vs placebo; *P*<0.05 for eletriptan 80 vs 40 mg). Secondary: Onset of action was rapid, with one hour headache response rates significantly

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			freedom from pain at two hours, incidence of nausea, vomiting and headache recurrence and consistency of response	higher with eletriptan 40 and 80 mg compared to placebo (40 and 48 vs 15%; *P*<0.0005 for both). Both eletriptan 40 and 80 mg were significantly better than placebo, based on first dose, first attack data, for freedom from pain at two hours (35 and 42 vs 7%; *P*<0.0001). Both eletriptan 40 and 80 mg demonstrated significant consistency of response, with headache relief rates at two hours on at least two of three attacks of 66 and 72%, respectively, compared to 15% with placebo (*P*<0.001).
Sheftell et al[42] Eletriptan 20 mg vs eletriptan 40 mg vs eletriptan 80 mg vs placebo	DB, MC, PC, PG, RCT Patients >18 years of age with a history of at least one typical attack of migraine with or without aura every six weeks	N=1,334 3 migraine attacks	Primary: Headache response at two hours for the first attack Secondary: Incidence of associated symptom relief, pain-free, sustained pain-free and consistency of response	Primary: Eletriptan 20, 40 and 80 mg achieved significantly (*P*<0.001) better headache response rates compared to placebo at two (47, 62 and 59 vs 22%) and four hours (64, 76 and 79 vs 25%). Secondary: Two hour pain-free response rates for eletriptan 20, 40 and 80 mg were 14, 27 and 27%, respectively, compared to 4% with placebo (*P*<0.001). Sustained pain-free response rates for eletriptan 20, 40 and 80 mg were 10, 20 and 18%, respectively, compared to 3% with placebo (*P*<0.001). Eletriptan had a higher consistency of intra patient response compared to placebo in two of three and three of three attacks (68 to 82% and 32 to 60% vs 16 and 8%, respectively; *P* value not reported). All eletriptan doses yielded significant functional improvement at two hours (*P*<0.001).
Diener et al[43] Eletriptan 40 mg vs eletriptan 80 mg	DB, MC, PC, PG, RCT Patients 18 to 65 years of age, with a history of migraine with or without	N=733 24 hours	Primary: Headache response (improvement from severe or moderate to mild or no pain) at two hours	Primary: The proportion of patients reporting headache response at two hours was significantly greater with eletriptan compared to ergotamine tartrate/caffeine (54 and 68 vs 33%; *P*<0.001). Secondary: Eletriptan headache response rates at one hour were significantly greater compared to ergotamine tartrate/caffeine and placebo headache response rates

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs ergotamine tartrate/caffeine 2/200 mg* vs placebo	aura for at least one year; frequency of migraine attacks at least every six weeks but not more than six per month		Secondary: Headache response at one hour; pain-free rates at one and two hours, functional hour impairment, functional response, presence of migraine-associated symptoms or absence of nausea, vomiting, photophobia and phonophobia	(29 and 39 vs 29 vs 13%; *P*<0.002 for each comparison). The proportion of patients reporting no pain at two hours was significantly greater with eletriptan compared to ergotamine tartrate/caffeine (28 and 38 vs 10 vs 5%; *P*<0.001 for each comparison). Both doses of eletriptan were significantly more effective than ergotamine tartrate/caffeine in reducing nausea (*P*<0.0001), photophobia (80 mg; *P*<0.0001, 40 mg; *P*<0.002), phonophobia (80 mg; *P*<0.0001, 40 mg; *P*<0.003) and functional impairment (*P*≤0.001) at two hours.
Bartolini et al[44] Frovatriptan 2.5 mg vs almotriptan 12.5 mg	DB, MC, RCT, XO Patients 18 to 65 years of age with a history of migraine with or without aura and six or fewer migraine attacks in the preceding six months	N=133 One to three migraine attacks	Primary: Between treatment comparison of the direction and average strength of preference Secondary: Pain-free and pain relief at two and four hours and recurrent and	Primary: There was no difference in average preference scores between the two treatments (3.1±1.3 vs 3.4±1.3; *P* value not significant). Sixty three percent of patients expressed a clear preference for a triptan, with 29 and 34% preferring frovatriptan and almotriptan, respectively (*P* value not significant). The most common reasons for preferring one triptan were the rapid action (54.4 vs 55.0%), prevention of aggravation (13.5 vs 2.5%) and reduction of severity (13.5 vs 15.0%; *P* values not significant). Secondary: At two hours, rates of pain-free (30 vs 32%) and pain relief episodes (54 vs 56%) were not significantly different between the two treatments (*P* value not significant).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			sustained pain-free episodes within 48 hours	There was no difference in the rate of sustained pain-free episodes between the two treatments (*P* value not significant). Recurrent episodes within 48 hours occurred significantly less with frovatriptan compared to almotriptan (*P*<0.05).
Bartolini et al[45] Frovatriptan 2.5 mg vs almotriptan 12.5 mg	DB, MC, RCT, XO Women suffering from menstrual-related migraine for at least six months	N=114 Six months or six migraine attacks	Primary: Proportion of pain-relief episodes and pain-free episodes at two, four and 24 hours and proportion of patients with migraine recurrence within 24 or 48 hours	Primary: The proportions of pain-relief episodes were similar between patients treated with frovatriptan and almotriptan, respectively, at two hours (36 vs 41%; *P*=NS), four hours (53 vs 50%; *P*=NS) and 24 hours (62 vs 67%; *P*=NS). The proportions of pain-free episodes were not significantly different between the frovatriptan and almotriptan groups, respectively, at two (19 vs 29%; *P*=NS), four (47 vs 54%; *P*=NS) and 24 hours (60 vs 67%; *P*=NS). The rate of migraine recurrence after 24 hours was significantly lower during frovatriptan treatment compared to almotriptan treatment (8 vs 21%; *P*<0.05). Similarly, there was a significantly lower incidence of recurrences at 48 hours with frovatriptan compared to almotriptan (9 vs 24%; *P*<0.05).
Tullo et al[46] Frovatriptan 2.5 mg vs zolmitriptan 2.5 mg	DB, MC, RCT, XO Patients 18 to 65 years of age with current history of migraine with or without aura and at least one migraine attack per month for six months prior to enrollment	N=107 6 months	Primary: Patient preference Secondary: Pain-free response at two hours, recurrence, sustained pain-free episodes within 48 hours, pain relief episodes at two hours	Primary: There was no difference between the two treatments in terms of patient preference (34 vs 43%; *P* value not significant). Secondary: There was no difference between the two treatments for rates of pain-free response at two hours (26 vs 31%; *P* value not significant). There was no difference between the two treatments for rates of recurrent episodes (21 vs 24%), sustained pain-free episodes (18 vs 22%) and pain relief episodes at two hours (57 vs 58%; *P* values not significant).
Cady et al[47] Frovatriptan 2.5 mg early use (dose one,	DB, MC, PC, XO Patients with a history of	N=165 2 migraine attacks	Primary: The incidence of no headache at two hours	Primary: Twenty eight and 20% of early frovatriptan- and placebo-treated patients, respectively, were headache-free at two hours (*P*=0.04).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
frovatriptan; dose two, placebo) vs frovatriptan 2.5 mg late use (dose one, placebo; dose two, frovatriptan)	migraine for more than one year and two to eight migraines in the previous two months		Secondary: Comparison of early vs later use of frovatriptan	Secondary: Fifty percent of early users were pain-free at three hours. Early use of frovatriptan prevented mild migraine headaches from progressing to moderate or severe headaches (*P* value not reported). Migraine recurrence was low, (four to six percent), regardless of treatment (*P* value not reported). During the 24 hours following the first dose, 64% of patients experienced nothing worse than mild functional impairment when frovatriptan was used early compared to 48% of patients when placebo was used early (*P*<0.001).
Ryan et al[48] Frovatriptan 2.5 mg vs placebo	MA (3 DB, PC, PG, RCTs) Patients with migraine	N=2,676 24 hours (up to three migraine attacks)	Primary: Headache response at two hours Secondary: Time to headache recurrence and headache recurrence	Primary: In all three trials, headache response two hours after frovatriptan was significantly greater compared to headache response two hours after placebo (*P*≤0.001), with approximately a twofold measure of effect over placebo for headache response at two and four hours. Secondary: Time to headache response occurred within one and half hours in a substantial proportion of patients. The incidence of 24-hour headache recurrence with frovatriptan was low (10 to 25%).
Silberstein et al[49] Frovatriptan 2.5 mg once daily vs frovatriptan 2.5 mg twice daily vs	DB, MC, PC, XO Women >18 years of age with a history of migraine for more than one year and three to four attacks (perimenstrual period)	N=443 Three perimenstrual periods	Primary: Efficacy Secondary: Not reported	Primary: The incidence of menstrual migraine was 67% (n=468) with placebo compared to 52 (n=484; *P*<0.0001) and 41% (n=483; *P*<0.0001) with frovatriptan once and twice daily, respectively. Significant reductions in headache severity were observed in frovatriptan-treated patients (*P*<0.0001). Frovatriptan twice daily was more efficacious than once daily (*P*<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Gobel et al[50] Frovatriptan 2.5 mg Patients were instructed to choose the time of self administration and if migraine symptoms recurred, a second dose was permitted two to 24 hours later.	OL, OS, PRO Patients 18 to 65 years of age with an established diagnosis of migraine with or without aura, age at migraine onset <50 years, at least one migraine attack per month and <10 days of non-migraine headache per month for the three months prior to study	N=2160 Patients were allowed to treat up to three migraine attacks during the study period; the third attack treated was evaluated	Primary: Headache response, defined as the length of time (in minutes) between medication consumption and the onset of headache relief Secondary: Time taken to achieve complete headache relief, incidence of headache recurrence within 24 hours, the number of frovatriptan tablets required to treat each attack and the use of rescue medication	Primary: Patients were divided into two groups: those that dosed frovatriptan with low symptom severity scores based on the MIS (severity one to five) and those that dosed with more severe symptoms based on the MIS (severity six to 10). Time to onset of efficacy was faster in the group with low symptom severity at dosing compared to those with more severe symptoms (42.06±32.33 vs 49.25±34.92 minutes; *P*=0.0023). Secondary: Patients with lower symptom severity scores at time of dose had an earlier time to pain-free response compared to those with more severe symptoms at dosing (79.33±65.33 vs 96.05±100.85 minutes; *P*=0.0109). A similar proportion of patients with lower symptom severity scores experienced headache recurrence compared to those with more severe symptoms at the time of dose (224±29 [86.82%±11.24] vs 1053±176 [83.57%±13.97]; *P*=0.2711). Patients with lower symptom severity also required a similar number of frovatriptan tablets to treat each attack when compared to those patients that were dosed with a higher symptom severity score (1.17±0.42 vs 1.24±0.56 tablets; *P*=0.0575). Fewer patients that dosed frovatriptan with lower symptom severity scores required escape medication when compared to those patients in the group that dosed with higher symptom severity scores (10 [3.88%] vs 173 [13.73%]; *P*<0.0001).
Stark et al[51] Naratriptan 2.5 mg vs sumatriptan 50 mg	DB, PC, PG, RCT Self-described poor sumatriptan responders with a history of	N=347 2 migraine attacks	Primary: Conversion from moderate or severe pain to mild or no pain at four hours for attack	Primary: Naratriptan was significantly more efficacious compared to placebo for the relief of headache pain at four hours (*P*<0.001). Secondary: Naratriptan was more efficacious than placebo at two hours for relief of headache (*P*=0.005).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	migraine for more than one year		two Secondary: Headache relief at two hours, freedom from pain at two hours	There was no difference between naratriptan and placebo for freedom from pain at two hours (*P*>0.05).
Gobel et al[52] Naratriptan 2.5 mg vs sumatriptan 100 mg	DB, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=253 Single migraine attack	Primary: Headache recurrence and proportion of patients with 24-hour maintenance of headache relief Secondary: Proportion of patients experiencing headache relief, proportion of patients using rescue medication during the 24 hours after dosing and proportion of patients that took a second dose of study drug	Primary: The incidence of headache recurrence was numerically lower with naratriptan compared to sumatriptan (45 vs 57%; *P* value not reported). Twenty-four hour maintenance of headache relief was reported by 39 and 34% of patients receiving naratriptan and sumatriptan respectively (OR, 1.26; 95% CI, 0.86 to 1.85; *P* value not significant). Secondary: The proportions of patients experiencing headache relief were 76 and 84% with naratriptan and sumatriptan respectively (*P* value not significant). The proportions of patients who received rescue medications for inadequate relief up to 24 hours after dosing did not differ between the two treatments (21 vs 16%; OR, 1.47; 95% CI, 0.94 to 2.30; *P* value not reported). The proportions of patients that took a second dose of study drug was significantly less with naratriptan (40 vs 57%; OR, 0.51; 95% CI, 0.37 to 0.71; *P*<0.001).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Ashcroft et al[53] Naratriptan 2.5 mg vs naratriptan 1 mg vs rizatriptan 10 mg vs sumatriptan 100 mg vs placebo	MA Patients with moderate or severe migraine attacks	N=449 Single migraine attack	Primary: Response rate ratios for pain-free response Secondary: Adverse events	Primary: Pooled RRs compared to placebo for pain-free response at two and four hours for naratriptan 2.5 mg were 2.52 (95% CI, 1.78 to 3.57) and 2.58 (95% CI, 1.99 to 3.35), respectively. Naratriptan 2.5 mg was more effective than naratriptan 1 mg; the corresponding RRs for pain-free response at two and four hours were 1.54 (95% CI, 1.28 to 1.86) and 1.35 (95% CI, 1.20 to 1.51), respectively. Naratriptan 2.5 mg was less effective in pain-free response than rizatriptan 10 mg (RR, 0.68; 95% CI, 0.55 to 0.85) or sumatriptan 100 mg at four hours (RR, 0.79; 95% CI, 0.67 to 0.93). Secondary: Significantly fewer patients experienced adverse events with naratriptan 2.5 mg compared to rizatriptan 10 mg (RR, 0.73; 95% CI, 0.56 to 0.97) or sumatriptan 100 mg (RR, 0.68; 95% CI, 0.55 to 0.86).
Klassen et al[54] Naratriptan 0.1, 0.25, 1 and 2.5 mg vs placebo	DB, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura at least one year	N=613 Single migraine attack	Primary: Proportion of patients who experienced headache relief at four hours Secondary: Proportion of patients with meaningful relief, proportions of patients with headache relief at eight, 12 and 24 hours,	Primary: Headache relief at four hours was reported in 60% of patients receiving naratriptan 2.5 mg compared to 50, 35, 32 and 34% of patients receiving naratriptan 1, 0.25, 0.1 mg and placebo, respectively (P<0.05 naratriptan 2.5 and 1 mg vs placebo, 1 vs 0.1 mg and 2.5 vs 0.1 and 0.25 mg). Secondary: Meaningful relief of headache at four hours occurred in 59% of patients receiving naratriptan 2.5 mg compared to 56, 38, 33 and 36% of patients receiving naratriptan 1, 0.25 and 0.1 mg and placebo (P≤0.006 vs 0.1 and 0.25 mg and placebo). The proportions of patients achieving headache relief at eight, 12 and 24 hours were significantly greater with naratriptan 2.5 mg compared to the lower doses of naratriptan (P<0.05) and placebo (P<0.001). Rescue medication was used significantly less with naratriptan 2.5 mg compared

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			proportion of patients taking rescue medication within 24 hours and proportion of patients experiencing headache recurrence within 24 hours	to the lower doses of naratriptan (*P*≤0.025 and 0.25 mg, *P*≤0.034 vs 0.1 mg) and placebo (*P*≤0.022). The proportions of patients reporting headache recurrence were not different among the treatments (39, 38, 39, 28 and 38%; *P* values not reported).
Ng-Mak et al[55] Rizatriptan 10 mg vs almotriptan 12.5 mg	MC, OL, XO Patients ≥18 years of age with migraine and a recent history of at least one migraine per month	N=146 Two migraine attacks	Primary: Mean and median times to onset of pain relief and pain-freedom Secondary: Patient satisfaction	Primary: The mean time to pain relief was numerically shorter with rizatriptan compared to almotriptan (69.7 vs 178.8 minutes; mean difference, 109 minutes; 95% CI, -6.8 to 224.8; *P*=0.065). The median time to pain relief was significantly shorter with rizatriptan (45 vs 60 minutes; *P*=0.002). The mean time to pain-freedom was numerically shorter with rizatriptan compared to almotriptan (247.2 vs 247.0 minutes; mean difference, 179.8 minutes; 95% CI, -21.8 to 381.4; *P*=0.079). The median time to pain-freedom was significantly shorter with rizatriptan (100 vs 135 minutes; *P*=0.004). Significantly more patients receiving rizatriptan achieved onset of pain relief within two hours compared to patients receiving almotriptan (88.6 vs 73.4%; *P*=0.007). More patients receiving rizatriptan achieved onset of pain-freedom within two hours compared to patients receiving almotriptan (55.7 vs 45.6%; *P*=0.10). Secondary: More patients indicated they were very satisfied when treating a migraine with rizatriptan (29.9 vs 16.7%). Less patients indicated they were dissatisfied (13.2 vs 23.1%) or very dissatisfied (9.2 vs 7.7%) when treating a migraine attack with rizatriptan. Of the 39 patients who responded to the diary question regarding medication preference, 48.7 and 23.1% expressed preference for rizatriptan and almotriptan, while 28.2% expressed no preference.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Lainez et al[56] Rizatriptan 10 mg wafer vs eletriptan 40 mg tablet	MC, OL, XO Patients 18 to 65 years of age with a history of migraine with or without aura for at least six months	N=372 Single migraine attack	Primary: Patient preference Secondary: Not reported	Primary: Significantly more patients preferred rizatriptan (61.1%; 95% CI, 55.7 to 66.3) compared to eletriptan (38.9%; 95% CI, 33.7 to 44.3; *P*≤0.001). The most common reason given for preference of either treatment was speed of headache relief. At two hours, 80 and 69% of patients reported that rizatriptan and eletriptan, respectively, were convenient or very convenient to take (mean convenience score, 1.99 vs 2.31, respectively; *P*≤0.001). Secondary: Not reported
Bomhof et al[57] Rizatriptan 10 mg vs naratriptan 2.5 mg vs placebo	DB, DD, MC, PC, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for more than six months and experiencing up to eight attacks per month	N=552 Single migraine attack	Primary: Time to headache relief within two hours Secondary: Headache relief and pain-free up to two hours, associated symptoms, functional disability, satisfaction with medication at two hours, need for additional medication from two to 24 hours, 24-hour quality of life and safety	Primary: Rizatriptan was significantly more effective than naratriptan for time to headache relief within two hours (HR, 1.62; 95% CI, 1.26 to 2.09; *P*<0.001). Secondary: Headache relief at two hours was 68.7 and 48.4% with rizatriptan and naratriptan, respectively (*P*<0.001). In patients with migraine associated symptoms at baseline, rizatriptan gave earlier relief than naratriptan from nausea (HR, 1.53; 95% CI, 1.11 to 2.11; *P*=0.009), photophobia (HR, 1.57; 95% CI, 1.13 to 2.19; *P*=0.007) and phonophobia within two hours (HR, 1.61; 95% CI, 1.15 to 2.27; *P*=0.006), respectively. Rizatriptan was significantly better than naratriptan with regard to time to no functional disability (HR, 1.96; 95% CI, 1.36 to 2.82; *P*<0.001). Patients receiving rizatriptan were more satisfied with their medication compared to patients receiving naratriptan at two hours (means scores, 3.55 vs 4.21; *P*<0.001). Fewer patients receiving rizatriptan and naratriptan needed additional medications compared to patients receiving placebo (*P*<0.001); however, there was no difference between the two active treatments (*P*=0.068). Rizatriptan and naratriptan were significantly better than placebo on all five quality of life domains (*P*<0.01).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				The overall incidence of any clinical adverse event was significantly higher with rizatriptan compared to naratriptan and placebo (*P*<0.05).
Kolodny et al[58] Rizatriptan 5 mg vs rizatriptan 10 mg vs sumatriptan 25 mg vs sumatriptan 50 mg vs placebo	DB, PC, RCT Patients >18 years of age with a history of migraine with or without aura for at least six months	N=1,447 5 days (2 migraine attacks)	Primary: Time to pain relief within two hours Secondary: Presence of associated symptoms at two hours and pain relief at two hours	Primary: The primary efficacy variable, expressed as the HR of rizatriptan 10 mg vs sumatriptan 50 mg, was 1.10 (95% CI, 0.96 to 1.26; *P*=0.161). Rizatriptan 5 mg was significantly (*P*=0.007) more efficacious than sumatriptan 25 mg; the HR of rizatriptan 5 mg vs sumatriptan 25 mg was 1.22 (95% CI, 1.06 to 1.41). Secondary: Rizatriptan 10 mg-treated patients had significantly less nausea compared to sumatriptan 50 mg-treated patients (*P*=0.004). For all other secondary measures at two hours, rizatriptan 10 mg was not different than sumatriptan 50 mg (*P* values not reported).
Lipton et al[59] Rizatriptan 10 mg vs sumatriptan 100 mg vs sumatriptan 50 mg vs	MA (5 trials) Patients >18 years of age with history of migraine with or without aura	N=4,097 Single migraine attack	Primary: Relief of nausea in those who had it at baseline, emergence of nausea in those who were free of it at baseline Secondary: Not reported	Primary: Approximately 60% of patients in each treatment group had nausea at baseline. Significantly more patients treated with rizatriptan 10 mg were free of nausea at two hours compared to patients treated with sumatriptan 100 mg (66 vs 58%; *P*=0.043), sumatriptan 50 mg (68 vs 57%; *P*=0.010), sumatriptan 25 mg (68 vs 59%; *P*=0.017) and naratriptan 2.5 mg (59 vs 45%; *P*=0.014). Averaging over the four post treatment time points in the first two hours, significantly more patients receiving rizatriptan 10 mg were free of nausea compared to patients treated with sumatriptan 100 mg (*P*=0.004), sumatriptan 50 mg (*P*=0.001) and naratriptan 2.5 mg (*P*=0.015). No differences in nausea relief were seen between rizatriptan 10 mg and zolmitriptan 2.5 mg, either at two hours (65 vs 61%; *P*=0.210) or over the first two

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 25 mg vs naratriptan 2.5 mg vs zolmitriptan 2.5 mg vs placebo				hours (*P*=0.781). Rates of treatment-emergent nausea at two hours ranged from 11 to 18% with placebo, from 5 to 13% with rizatriptan 10 mg and from 10 to 20% with other comparator triptans (*P* values not reported). Secondary: Not reported
Seeburger et al[60] Rizatriptan 10 mg ODT vs placebo Two migraine attacks were to be treated with rizatriptan and one with placebo, order of treatment was randomized and DB.	DB, MC, PC, XO Patients were ≥18 years of age with a history of migraine for more than one year, with or without aura, a minimum of two moderate-to-severe migraine attacks per month during the three months prior to randomization while taking a stable dose of topiramate for migraine prophylaxis (minimum dose	N=108 Patients treated up to three migraine attacks	Primary: Proportion of treated attacks resulting in pain relief at two hours postdose Secondary: Proportion of treated attacks resulting in: sustained pain relief from two to 24 hours postdose, pain-freedom two hours postdose, “normal” ratings of functional disability at two hours postdose, and satisfaction with treatment	Primary: Significantly more rizatriptan-treated attacks resulted in pain relief at two hours post dose compared to placebo-treated attacks (55 vs 17%; OR, 5.80; 95% CI, 3.13 to 10.76; *P*<0.001). Secondary: Treatment with rizatriptan resulted in a greater proportion of attacks resulting in sustained pain relief from two to 24 hours postdose compared to treatment with placebo (33 vs 11%; *P*<0.001). Treatment with rizatriptan also resulted in a greater proportion of attacks resulting in pain-freedom two hours postdose compared to treatment with placebo (6 vs 36%; *P*<0.01), a greater proportion of “normal” ratings of functional disability at two hours postdose vs placebo (42 vs 13%; *P*<0.001), and a greater proportion of satisfaction with treatment at 24 hours postdose vs placebo (61 vs 34%; *P*<0.001).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
	of 50 mg)		at 24 hours postdose	
Mathew et al[61] Rizatriptan 10 mg vs placebo	DB, PC, RCT Patients 20 to 64 years of age with migraine and a history of headache progressing to moderate or severe pain when no intervention was used	N=112 Three migraine attacks	Primary: Proportion of migraine attacks in which treatment produced a pain-free response at two hours Secondary: Pain-free response at one hour, percentage of migraine attacks in which treatment provided a sustained pain-free response lasting between two and 24 hours	Primary: Pain-free response at two hours occurred in 151 of 216 attacks (70%) with rizatriptan and 24 of 109 attacks (22%) with placebo (*P*<0.01). Secondary: Pain-free response at one hour occurred in more attacks treated with rizatriptan compared to placebo (45 vs 8%; *P*<0.01). When the attacks were categorized by headache severity at the time of treatment, the pain-free response at two hours was higher for mild attacks than for moderate or severe attacks (*P*<0.01). Sustained pain-free response rates were significantly higher with rizatriptan compared to placebo (60 vs 17%; *P*<0.001).
Cady et al[62] Rizatriptan 10 mg ODT vs placebo Patients within each treatment group were	DB, MC, PC, PG, RCT Patients ≥18 years of age with a history of migraine with or without aura for at least one year and a history of	N=207 Single migraine attack	Primary: Proportion of patients free of pain at two hours and determination of whether treatment effects were consistent	Primary: Significantly more patients reported pain-freedom at two hours with rizatriptan compared to placebo (66 vs 26%; OR, 5.20; 95% CI, 2.75 to 9.80; *P*<0.001). The proportion reporting sustained pain-freedom between two and 24 hours was also significantly greater with rizatriptan (52 vs 18%; OR, 5.40; 95% CI, 2.71 to 10.79; *P*<0.001). A nonsignificant greater proportion of patients receiving rizatriptan plus migraine education reported pain-freedom at two hours compared to those receiving rizatriptan alone (72 vs 61%; *P*=0.430). Similar results were observed with patients

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
also randomized to receive migraine education or to receive no migraine education.	one to four migraine attacks per month with attacks that were typically mild at onset and recognizable as migraine		across migraine education vs no migraine education with respect to pain-freedom at two hours Secondary: Use of rescue medication, elimination of photophobia, phonophobia, nausea and functional disability at two hours	receiving placebo with or without migraine education (28 vs 28%; *P* value not reported). Secondary: Significantly more patients reported no rescue medication use up to 24 hours with rizatriptan (71.7 vs 34.4%; *P*<0.001). Rizatriptan had significantly fewer patients reporting photophobia (*P*=0.002) and functional disability (*P*=0.001) at two hours. No difference in the incidence of phonophobia (*P*=0.110) and nausea (*P*=0.090) occurred.
Ferrari et al[63] Rizatriptan 5 mg vs rizatriptan 10 mg vs placebo	MA (DB, RCTs) Outpatients with a history of migraine for at least six months	N=4,816 Single migraine attack	Primary: Pain relief, associated migraine symptoms and functional disability and headache recurrence Secondary: Not reported	Primary: At two hours, rizatriptan 10 mg was significantly more effective than placebo for pain relief (71 vs 38%; *P*<0.001), and for elimination of pain, nausea, photophobia, phonophobia and functional disability (*P* values not reported). The benefit was maintained over 24 hours; 37% of patients had sustained pain relief compared to 18% with placebo (*P*<0.001). Rizatriptan 10 mg was more effective than 5 mg, with a significant difference at two hours on all measures except for elimination of nausea (*P* values not reported). The benefit was maintained over 24 hours; 38% of patients had sustained pain relief vs 32% of patients with 5 mg (*P*=0.001). Secondary: Not reported
Oldman et al[64] Rizatriptan 5 mg	MA Patients >18 years of age with	N=2,626 Single migraine	Primary: Headache response at two hours,	Primary: Headache response at two hours was reported as follows: rizatriptan 5 mg: relative benefit, 1.8 (1.6 to 2.0); NNT, 3.9 (3.3 to 4.7); n=1,646 and rizatriptan 10 mg: relative benefit, 2.2 (2.0 to 2.4); NNT, 2.7 (2.4 to 2.9); n=2,770.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs rizatriptan 10 mg vs placebo	moderate or severe migraine with or without aura	attack	headache response at one hour, pain-free response at two hours and sustained relief over 24 hours Secondary: Not reported	Headache response at one hour was reported as follows: rizatriptan 5 mg: relative benefit, 1.6 (1.4 to 1.9); NNT, 7.2 (5.4 to 10); n=1,646 and rizatriptan 10 mg: relative benefit, 1.9 (1.6 to 2.1); NNT, 4.9 (4.2 to 6.0); n=2,770. Pain-free response at two hours was reported as follows: rizatriptan 5 mg: relative benefit, 3.4 (2.6 to 4.4); NNT, 4.7 (4.0 to 5.7); n=1,646 and rizatriptan 10 mg: relative benefit, 4.8 (3.8 to 5.9); NNT, 3.1 (2.9 to 3.4); n=2,770. Sustained-relief over 24 hours was reported as follows: rizatriptan 5 mg: relative benefit, 1.5 (1.3 to 1.8); NNT, 8.3 (6.0 to 14); n=1,450 and rizatriptan 10 mg: relative benefit, 1.7 (1.5 to 2.0); NNT, 5.6 (4.5 to 7.4); n=1,677. Secondary: Not reported
Derry et al[65] Sumatriptan vs placebo vs active control Results from the pooled analysis of PC trials and results of pooled analyses (including within-class, head-to-head trials not represented elsewhere in Table 4) have been reported.	MA (61 studies) Patients were at least 18 years of age with migraine	N=37,250 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief during the 24 hours postdose, pain intensity and pain relief	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 50 mg, the NNTs were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. The NNTs for sustained pain-free and sustained headache relief during the 24 hours postdose were 9.5 and 6.0, respectively. For sumatriptan 100 mg compared to placebo the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2 for pain-free at two hours, headache relief at one hour, headache relief at two hours, sustained pain-free, and sustained headache relief during the 24 hours post dose, respectively. Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. It was found that treating early, while pain was still mild, resulted in significantly better NNTs for pain-free at two hours and sustained pain-free during 24 hours when compared to treating established attacks with moderate or severe pain intensity. Relief of associated symptoms (including nausea, photophobia, and phonophobia) was greater and the use of rescue medication was lower with sumatriptan, compared to placebo. Adverse events were mostly transient and mild; however, they occurred with greater frequency with sumatriptan compared to placebo.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with particular adverse events during the 24 hours postdose, withdrawals due to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and/or presence at two hours)	Primary: *Sumatriptan 25 mg vs rizatriptan 5 mg* The proportion of participants pain-free at two hours with sumatriptan 25 mg was 28% (310/1117; range, 27to 28%) compared to 33% with rizatriptan 5 mg (363/1093; range, 33 to 33%). The relative benefit of sumatriptan compared to rizatriptan was 0.84 (0.74 to 0.95; analysis, 2.1); the NNT was 18 (11 to 62) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range, 33 to 34%) compared to 27% with rizatriptan 5 mg (404/1093; range, 36 to 38%). The relative benefit of sumatriptan compared to rizatriptan was 0.91 (0.81 to 1.00; analysis, 2.2); the NNT was 29 (14 to 170) in favor of rizatriptan. The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range, 12 to 58%) compared to 67% with rizatriptan 5 mg (731/1093; range, 66 to 68%). The relative benefit of sumatriptan compared to rizatriptan was 0.90 (0.84 to 0.95; analysis, 2.3); the NNT was 14 (9.1 to 34.0) in favor of rizatriptan. *Sumatriptan 25 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 25 mg was 28% (310/1117; range, 27 to 28%) compared to 39% with rizatriptan 10 mg (440/1114; range, 38 to 41%). The relative benefit of sumatriptan compared to rizatriptan was 0.70 (0.62 to 0.79; analysis, 3.1); the NNT was 8.5 (6.4 to 13.0) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range, 33 to 34%) compared to 41% with rizatriptan 10 mg (456/1114; range, 40 to 42%). The relative benefit of sumatriptan compared to rizatriptan was 0.82 (0.74 to 0.91; analysis, 3.2); the NNT was 14 (8.8 to 30.0) in favor of rizatriptan. The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range, 12 to 58%) compared to 70% with rizatriptan 10 mg (780/1114; range, 68 to 72%). The relative benefit of sumatriptan compared to rizatriptan was 0.86 (0.80 to 0.91; analysis, 3.3); the NNT was 9.9 (7.1 to 16.0) in favor of rizatriptan. *Sumatriptan 50 mg vs rizatriptan 5 mg* The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range, 34 to 37%) compared to 33% with rizatriptan 5 mg (363/1093; range, 33 to 33%). The relative benefit of sumatriptan compared to rizatriptan was 1.1 (0.95 to 1.20; analysis, 8.1); there was no significant difference

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				between treatments. The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range, 35 to 39%) compared to 37% with rizatriptan 5 mg (404/1093; range, 36 to 38%). The relative benefit of sumatriptan compared to rizatriptan was 0.99 (0.89 to 1.10; analysis, 8.2); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 65% (949/1469; range, 62 to 67%) compared to 66% with rizatriptan 5 mg (951/1442; range, 63 to 68%). *Sumatriptan 50 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range, 34 to 37%) compared to 39% with rizatriptan 10 mg (440/1114; range, 38 to 41%). The relative benefit of sumatriptan compared to rizatriptan was 0.89 (0.80 to 1.00; analysis, 9.1); there was no significant difference between treatments. The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range, 35 to 39%) compared to 41% with rizatriptan 10 mg (456/1114; range, 40 to 42%). The relative benefit of sumatriptan compared to rizatriptan was 0.9 (0.81 to 1.00; analysis, 9.2); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 64% (710/1113; range, 62 to 66%) compared to 70% with rizatriptan 10 mg (780/1114; range, 68 to 72%). The relative benefit of sumatriptan compared to rizatriptan was 0.91 (0.86 to 0.97; analysis, 9.3); the NNT was 16 (9.9 to 43.0) in favor of rizatriptan. *Sumatriptan 50 mg vs zolmitriptan 2.5 mg* The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range, 35 to 44%) compared to 40% with zolmitriptan 2.5 mg (318/795; range, 35 to 43%). The relative benefit of sumatriptan compared to zolmitriptan was 1(0.90 to 1.10; analysis, 6.1); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range, 59 to 71%) compared to 66% with zolmitriptan 2.5 mg (523/795; range, 65 to 67%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.95 to 1.1; analysis, 6.2); there was no significant difference between treatments.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				Sumatriptan 50 mg vs zolmitriptan 5 mg The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range 35 to 44%) compared to 39% with zolmitriptan 5 mg (320/819; range, 37 to 40%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.90 to 1.2; analysis, 7.1); there was no significant difference between treatments. The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range, 59 to 71%). The proportion of participants with headache relief at two hours with zolmitriptan 5 mg was 66% (537/819; range, 65 to 66%). The relative benefit of sumatriptan compared to zolmitriptan was 1 (0.95 to 1.10; analysis, 7.2); there was no significant difference between treatments. *Sumatriptan 100 mg vs rizatriptan 10 mg* The proportion of participants pain-free at two hours with sumatriptan 100 mg was 31% (143/460; range, 22 to 33%) compared to 37% with rizatriptan 10 mg (178/476; range, 26 to 40%). The relative benefit of sumatriptan compared to rizatriptan was 0.82 (0.69 to 0.98; analysis, 15.1); the NNT was 16 (8.1 to 410.0) in favor of rizatriptan. The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 26% (120/460; range, 24 to 27%) compared to 34% with rizatriptan 10 mg (163/476; range, 25 to 36%). The relative benefit of sumatriptan compared to rizatriptan was 0.76 (0.62 to 0.92; analysis, 15.2); the NNT was 12 (7.1 to 43.0) in favor of rizatriptan. *Sumatriptan 100 mg vs almotriptan 12.5 mg* The proportion of participants pain-free at two hours with sumatriptan 100 mg was 33% (129/387; range, 33 to 34%) compared to 28% with almotriptan 12.5 mg (102/367; range, 28 to 28%). The relative benefit of sumatriptan compared to almotriptan was 1.2 (0.97 to 1.50; analysis, 16.1); there was no significant difference between treatments. The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 100 mg was 29% (111/387; range, 28 to 29%) compared to 30% with almotriptan 12.5 mg (110/367; range, 25 to 35%). The relative benefit of sumatriptan compared to almotriptan was 0.96 (0.77 to 1.20; analysis, 16.2); there was no significant difference between treatments. Secondary: *Sumatriptan 25 mg vs rizatriptan 5 mg*

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range, 23 to 25%) compared to 25% with rizatriptan 5 mg (213/845; range, 23 to 30%). The relative benefit of sumatriptan compared to rizatriptan was 0.96 (0.82 to 1.10; analysis, 2.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range, 39 to 46%) compared to 41% with rizatriptan 5 mg (238/582; range, 38 to 44%). The relative harm of sumatriptan compared to rizatriptan was 1 (0.91 to 1.20; analysis, 2.5); there was no significant difference between the two treatments. *Sumatriptan 25 mg vs rizatriptan 10 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range, 23 to 25%) compared to 20% with rizatriptan 10 mg (175/863; range, 19 to 23%). The relative benefit of sumatriptan compared to rizatriptan was 1.2 (1.0 to 1.4; analysis, 3.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range, 39 to 46%) compared to 46% with rizatriptan 10 mg (276/599; range, 45 to 47%). The relative harm of sumatriptan compared to rizatriptan was 0.92 (0.81 to 1.10; analysis, 3.5); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs rizatriptan 5 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range, 19 to 21%) compared to 25% with rizatriptan 5 mg (213/845; range, 23 to 30%). The relative benefit of sumatriptan compared to rizatriptan was 0.78 (0.65 to 0.93; analysis, 8.4); the NNT was 18 (10 to 62). The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range, 46 to 49%) compared to 41% with rizatriptan 5 mg (238/582; range, 38 to 44%). The relative harm of sumatriptan compared to rizatriptan was 1.2 (1.0 to 1.3; analysis, 8.5); there was no significant difference

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				between the two treatments. *Sumatriptan 50 mg vs rizatriptan 10 mg* Two studies provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity. The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range, 19 to 21%) compared to 20% with rizatriptan 10 mg (175/863; range, 19 to 23%). The relative benefit of sumatriptan compared to rizatriptan was 0.97 (0.80 to 1.20; analysis, 9.4); there was no significant difference between treatments. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range, 46 to 49%) compared to 46% with rizatriptan 10 mg (276/599; range, 45 to 47%). The relative harm of sumatriptan compared to rizatriptan was 1 (0.92 to 1.20; analysis, 9.5); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs zolmitriptan 2.5 mg* Two studies in participants with moderate or severe baseline pain intensity provided data. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range, 29 to 34%) compared to 32% with zolmitriptan 2.5 mg (283/878; range, 28 to 35%). The relative harm of sumatriptan compared to zolmitriptan was 1 (0.88 to 1.20; analysis, 6.3); there was no significant difference between the two treatments. *Sumatriptan 50 mg vs zolmitriptan 5 mg* Two studies in participants with moderate or severe baseline pain intensity provided data. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range, 29 to 34%) compared to 36% with zolmitriptan 5 mg (322/897; range, 33 to 38%). The relative harm of sumatriptan compared to zolmitriptan was 0.91 (0.80 to 1.00; analysis, 7.3); there was no significant difference between the two treatments. *Sumatriptan 100 mg vs rizatriptan 10 mg* Two studies in participants with moderate or severe baseline pain intensity provided data regarding adverse events within 24 hours. The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 52% (217/421; range, 45 to 52%) compared to 47% with rizatriptan 10 mg

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				(203/435; range, 47 to 48%).
Derry et al[66] Sumatriptan SC vs placebo vs active control Results from the pooled analysis of PC trials and results of within-class, head-to-head trials (not represented elsewhere in Table 4) have been reported.	MA (32 studies) Study rating: Not applicable Patients were at least 18 years of age with migraine	N=9,365 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief during the 24 hours postdose, pain intensity and pain relief Secondary: Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with particular adverse events during the 24 hours postdose, withdrawals due	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 6 mg compared to placebo the NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively. The NNT for sustained pain-free vs placebo was 6.1. Results for sumatriptan 4 and 8 mg were similar to that seen with 6 mg, with 6 mg demonstrating significantly better results than 4 mg for pain-free at one hour, and 8 mg demonstrating significantly better results than 6 mg for headache relief at one hour. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was administered after an inadequate response to the first. Relief of headache-associated symptoms (nausea, photophobia, and phonophobia) was greater and use of rescue medication was lower with sumatriptan, compared to placebo. Adverse events were mostly transient and mild, and were more common with sumatriptan than placebo. Primary: *Sumatriptan 6 mg SC vs naratriptan* The proportion of participants pain-free at two hours after treating with sumatriptan was 55%, compared to 30, 44, 60, 79, and 88% of participants treating with SC naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with headache relief at one hour after treating with sumatriptan was 87%, compared to 60, 64, 81, 85, and 76% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with headache relief at two hours after treating with sumatriptan was 89%, compared to 65, 75, 83, 94, and 91% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. *Sumatriptan 6 mg SC vs dihydroergotamine SC* The proportion of participants with headache relief at one hour after treating with sumatriptan was 78%, compared to 57% of participants treating with dihydroergotamine. The proportion of participants with headache relief at one hour after treating with sumatriptan was 85%, compared to 73% of participants treating with dihydroergotamine.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and/or presence at two hours)	Secondary: *Sumatriptan 6 mg SC vs naratriptan* The proportion of participants requiring rescue medication within 24 hours of treating with sumatriptan was 4%, compared to 35, 22, 12, 6, and 3% of participants treating with naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. The proportion of participants with relief of nausea at two hours after treating with sumatriptan was 90%, compared to 74, 92, 91, 96, and 96% of participants treating with SC naratriptan 0.5, 1, 2.5, 5, and 10 mg, respectively. No adverse event withdrawals were reported from any of the treatment arms. *Sumatriptan 6 mg SC vs dihydroergotamine SC* Neither treatment group reported any serious adverse events. The incidence of adverse event-related withdrawal was 0% (0/158) for sumatriptan and 1.3% (2/152) for SC dihydroergotamine.
Derry et al[67] Sumatriptan IN vs placebo vs active control Results from the pooled analysis of PC trials have been reported.	MA (12 studies) Patients were ≥18 years of age with migraine	N=4,755 Duration varied	Primary: Pain-free at two hours without the use of rescue medication, reduction in headache pain at one and two hours, sustained pain-free during the 24 hours postdose, sustained headache relief during the 24 hours postdose, pain intensity and pain relief Secondary:	Primary and Secondary: *Sumatriptan vs placebo* Sumatriptan surpassed placebo for all efficacy outcomes evaluated. For sumatriptan 10 mg, the NNTs compared to placebo were 7.3, 7.4, and 5.5 for pain-free at two hours, and headache relief at one and two hours, respectively. For sumatriptan 20 mg compared to placebo, the NNTs were 4.7, 4.9, and 3.5 for pain-free at two hours, and headache relief at one and two hours, respectively. Sumatriptan 20 mg was significantly better than sumatriptan 10 mg for pain-free at two hours, and headache relief at one and two hours, respectively. Relief of headache-associated symptoms (nausea, photophobia, and phonophobia) was greater and use of rescue medication was lower with sumatriptan, compared to placebo. Adverse events were mostly transient and mild and occurred more frequently with sumatriptan than placebo.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			Use of rescue medication, participants with any adverse events during the 24 hours postdose, participants with particular adverse events during the 24 hours postdose, withdrawals due to adverse events, headache-associated symptoms (relief and/or presence at two hours), functional disability (relief and presence at two hours)	
Loder et al[68] Sumatriptan 50 mg vs rizatriptan 10 mg ODT Patients treated first migraine with ODT and second with	MC, OL, RCT, XO Patients ≥18 years of age	N=524 Two migraine attacks	Primary: Patient preference Secondary: Head pain severity, functional disability and headache recurrence	Primary: Significantly more patients preferred rizatriptan compared to sumatriptan (57 vs 43%; *P*=0.009). No preference was expressed by 2.6% of patients. Secondary: A significantly greater proportion of patients reported pain relief with rizatriptan compared to sumatriptan at 45 and 60 minutes (38 vs 29% and 58 vs 49%, respectively; *P*<0.01 for both). A significantly greater proportion of patients receiving rizatriptan reported a pain-free status at 60 and 120 minutes (23 vs 17%; *P*<0.05 and 60 vs 52%; *P*<0.01,

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan.				respectively). Significantly more patients receiving rizatriptan reported normal function at 60 and 120 minutes (36 vs 27%; *P*=0.004 and 70 vs 64%; *P*=0.029). The overall rate of headache recurrence was similar with both treatments.
Gershovich et al[69] Sumatriptan vs rizatriptan ODT	RETRO Patients ≥18 years of age	N=457 (n=315 randomly sampled for a satisfaction questionnaire) 180 day medication conversion period (plus an 180 day follow up period)	Primary: Successful conversion rate, medication preference Secondary: Not reported	Primary: The total number of successful conversions from sumatriptan to rizatriptan (214/457; 47%) correlated to the number of successful conversions among the questionnaire group (173/315 [55%] returned the questionnaire; 82/173 [47%] had successful conversion; *P*=0.969). Among the patients that were successfully converted to rizatriptan and responded to the questionnaire, 68.0% preferred the rizatriptan compared to sumatriptan; whereas 8.5% of patients who failed conversion rated rizatriptan as their preferred medication (*P*<0.001). Successfully converted patients reported faster and more complete headache relief with rizatriptan (51.9 and 45.0% of the time, respectively; *P*<0.001). Failed conversion respondents reported that sumatriptan yielded faster and more complete headache relief 78.3 and 75.9% of the time, respectively (*P*<0.001). Secondary: Not reported
Cutler et al[70] Sumatriptan 25, 50 and 100 mg vs placebo	DB, PC, PG, RCT Adult patients with history of migraine with or without aura	N=259 Single migraine attack	Primary: Headache relief at two hours Secondary: Headache relief at four hours	Primary: By two hours, 50 to 56% of the patients who received sumatriptan (any dosage) experienced relief compared to 26% of the patients who received placebo (*P*<0.05). Secondary: By four hours, 68 to 71% of patients receiving sumatriptan experienced relief compared to 38% of the patients who received placebo (*P*<0.05).
Winner et al[71] Sumatriptan 50 and 100 mg	MA (6 DB, PC, RCTs) Patients 18 to 65	N=2,297 Single migraine	Primary: Proportion of patients pain-free at two	Primary: Freedom from pain at two hours was reported by significantly more patients receiving either dose of sumatriptan compared to patients receiving placebo, and by significantly more patients receiving sumatriptan 100 mg compared to patients

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years of age with a history of migraine with or without aura for at least one year	attack	hours Secondary: Migraine-free at two hours, worsening pain at two hours and sustained pain-free results from two to 24 hours	receiving sumatriptan 50 mg (50 mg, 49%; 100 mg, 58% and placebo, 24%; *P*<0.001, for both sumatriptan doses vs placebo and sumatriptan 100 mg vs 50 mg). Secondary: The proportions of patients who were migraine-free at two hours was 42, 47 and 20% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (*P*<0.05 for both sumatriptan doses vs placebo). The proportions of patients reporting worsening of pain at two hours was 26, 21 and 46% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (*P*<0.05 for both sumatriptan doses vs placebo). Sustained pain-free results from two through 24 hours were 30, 35 and 12% with sumatriptan 50 mg, sumatriptan 100 mg and placebo (*P*<0.05 for both sumatriptan doses vs placebo).
McCrory et al[72] Sumatriptan 25, 50 and 100 mg vs placebo	MA (16 PC, RCTs) Adult patients with history of migraine with or without aura	N=16,200 Single migraine attack	Primary: Pain-free response at two hours, headache relief/ headache intensity, functional disability, headache recurrence, adverse events Secondary: Not reported	Primary: Sumatriptan 100 (14 trials), 50 (five trials) and 25 mg (three trials) provided significantly better pain-free responses (100 and 25 mg only), headache relief and relief of disability at two hours compared to placebo (*P* values not reported). The NNT for pain-free response at two hours was 5.1 (3.9 to 7.1; n=2,221) and 7.5 (2.7 to 142.0; n=131) for sumatriptan 100 and 25 mg; there was no difference between sumatriptan 50 mg and placebo for this outcome (n=127). For headache relief at two hours, the NNT was 3.4 (3.0 to 4.0), 3.2 (2.4 to 5.1) and 3.4 (2.3 to 6.6) for sumatriptan 100 (n=2,940), 50 (n=420) and 25 mg (n=226), respectively. Adverse events were more common with sumatriptan 100 mg compared to placebo (RR, 0.14 [0.09 to 0.20]; NNH, 7.1 [5.0 to 11.1]; n=3172). The RR for sumatriptan 50 and 25 mg compared to placebo were not significant. Secondary: Not reported

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Cady et al[73] Sumatriptan 25, 50 and 100 mg vs ergotamine tartrate/caffeine 2/200 mg* vs aspirin 900 mg plus metoclopramide 10 mg vs placebo	MA (DB, PC, RCTs) Patients with at least one headache which was treated early when pain was mild	N=92 (118 migraine attacks) Single migraine attack	Primary: Pain-free response at two and four hours Secondary: Use of a second dose of medication, clinical disability, migraine-associated symptoms, meaningful pain relief, time to meaningful relief, sustained pain-free response, proportion of attacks in which pain had worsened two and four hours after dosing; all compared in headaches treated during mild vs moderate to severe pain	Primary: Pain-free responses were significantly higher two hours after dosing with sumatriptan 50 (51%) or 100 mg (67%; *P*<0.05) compared to placebo (28%), and were significantly higher with early treatment of mild pain compared to moderate to severe pain at two hours (sumatriptan 50 mg, 51 vs 31%; *P*<0.05, sumatriptan 100 mg, 67 vs 36%; *P*<0.05) and four hours (sumatriptan 50 mg, 75 vs 56% and sumatriptan 100 mg, 90 vs 61%; *P*<0.05). Secondary: Early intervention also resulted in less re-dosing with mild pain compared to moderate to severe pain (sumatriptan 50 mg, 21 vs 32% and sumatriptan 100 mg, 20 vs 29%; *P* values not reported). More attacks treated early with sumatriptan 50 or 100 mg were associated with normal function at four hours compared to placebo (70 and 93 vs 46%, respectively; *P* value not reported). Sustained pain-free response rates two to 24 hours after mild pain with sumatriptan 50 or 100 mg were higher (34 and 53%, respectively) compared to treatment of moderate to severe pain (19 and 24%, respectively; *P* values not reported). Early treatment with sumatriptan 100 mg produced significantly higher pain-free rates at two hours compared to ergotamine/caffeine (69 vs 34%, respectively) or aspirin plus metoclopramide (73 vs 25%, respectively; *P*<0.001 for both).
Djupesland et al[74] Sumatriptan 10 or 20 mg IN	DB, MC, PC, PG, RCT Patients 18 to 65	N=117 Single migraine	Primary: Proportion of patients free of pain at two	Primary: A significantly greater proportion of patients were pain-free at two hours with sumatriptan compared to placebo (54 and 57 vs 25%; *P*<0.05 for both).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years of age with a developing or established attack of migraine with or without aura of moderate to severe intensity and no improvement in the attack at the time of assessment, migraine present for at least one year, age of diagnosis <50 years and up to six migraine attacks per month for the past six months	attack	hours, proportion of patients with pain relief at one and two hours, proportion of patients achieving sustained freedom from pain Secondary: Safety	A significantly greater proportion of patients receiving sumatriptan experienced pain relief at two (84 and 80 vs 44%; *P*<0.001 and *P*<0.01) and one hours (73 and 74 vs 38%; *P*<0.01 for both). A significantly greater proportion of patients achieved a sustained pain-free response with sumatriptan compared to placebo (*P*<0.05 for both). Secondary: Adverse events were rare, with a metallic taste being the most commonly reported (10 to 13% with sumatriptan).
Salonen et al[75] Sumatriptan 1, 5, 10, 20 and 40 mg IN vs placebo Study medication taken as a single dose in the first trial and as a divided dose in the second trial.	2 DB, MC, PC, PG Adult patients with history of migraine with or without aura	N=245 (Trial 1) N=210 (Trial 2) Single migraine attack	Primary: Headache relief at two hours Secondary: Not reported	Primary: In both trials, headache severity had significantly improved by 120 minutes with sumatriptan 10 to 40 mg compared to placebo (*P*<0.05). The greatest efficacy rates were obtained with sumatriptan 20 mg. With sumatriptan 20 mg, 78 and 74% of patients experienced headache relief in trial one and two, respectively, compared to 35 and 42% of patients, respectively, with placebo. Sumatriptan 10, 20 and 40 mg were significantly more effective than placebo (*P*<0.01, *P*<0.001, *P*<0.05, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Cady et al[76] Sumatriptan 6 mg SC vs placebo	PC, RCT Adult patients with history of migraine with or without aura	N=1,104 Duration not specified	Primary: Headache response at one hour Secondary: Complete relief of headache, clinical disability and reduction in other migraine symptoms	Primary: Sumatriptan produced a response (mild pain or no pain) in 70% of patients compared to 22% with placebo (*P*<0.001). Secondary: Sumatriptan was significantly more effective than placebo in totally eliminating migraine headache by 60 minutes (49 vs 9%; *P*<0.001). Clinical disability improved significantly more with sumatriptan treatment compared to treatment with placebo (76 vs 34%; *P*<0.001). Sumatriptan was effective in reducing other symptoms such as nausea, vomiting and photophobia.
No authors listed, SC Sumatriptan International Study Group[77] Sumatriptan 6 and 8 mg SC vs placebo	DB, PC, PG, RCT Adult patients with history of migraine with or without aura	N=639 Duration not specified	Primary: Severity of headache at 60 and 120 minutes Secondary: Not reported	Primary: After 60 minutes, the severity of headache pain declined in 72% of 422 patients receiving sumatriptan 6 mg, 79% of 109 patients receiving sumatriptan 8 mg and 25% of 105 patients receiving placebo (three patients were not evaluable; *P* values not reported). Compared to placebo, 47 and 54% more patients receiving sumatriptan 6 and 8 mg had less severe headaches (*P*<0.001). After 120 minutes, 86 to 92% of 511 patients receiving sumatriptan felt headache severity improve compared to 37% of 104 patients receiving placebo (*P*<0.001). Secondary: Not reported
Cady et al[78] Sumatriptan 6 mg SC Patients were instructed to treat up to four migraine attacks of moderate to severe intensity.	MC, OL, PRO Patients 18 to 65 years of age with at least a one-year history of migraine with or without aura, with an average	N=246 Patients were instructed to treat up to four migraine attacks and were followed until three to	Primary: Change in score from baseline to end of treatment for the Overall Satisfaction item on the PPMQ-R	Primary: The Overall Satisfaction domain score of the PPMQ-R increased from baseline to the end of treatment (65.7±19.8 vs 73.7±29.1; *P*=0.0007). Other satisfaction endpoints evaluated: The Efficacy domain score of the PPMQ-R increased from baseline to the end of treatment (62.2±17.6 vs 76.2±23.7; *P*<0.0001). Improvements were also seen on the Functionality domain score of the PPMQ-R (59.0±22.3 vs 73.8±25.3; *P*<0.0001). The Ease of Use domain score declined from baseline to the end of

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
	of two to six migraine episodes monthly, current triptan users, and a baseline score from satisfied to very dissatisfied on the Overall Satisfaction domain of the PPMQ-R	five days after the fourth treated attack or for 60 days, whichever came sooner	Secondary: Not reported	treatment (82.6±15.3 vs 67.8±27.6; *P*<0.0001). The total PPMQ-R score increased (63.9±16.5 vs 74.6±22.4; *P*<0.0001). The percentage of patients confident or very confident in treating repeated migraine attacks increased from 41.0% (95% CI, 35.4 to 46.9) to 64.6% (95% CI, 58.9 to 70.1) at the end of treatment. At the end of treatment, 35.1% of patients stated they preferred sumatriptan SC (Sumavel®) to treat their next migraine attack. Secondary: Not reported
Rothrock et al[79] Sumatriptan 6 mg SC Patients were instructed to treat up to four migraine attacks of moderate to severe intensity.	MC, OL, PRO Study rating: Not applicable Patients 18 to 65 years of age with a history of migraine for at least one year with or without aura, with an average of two to six migraine episodes monthly, current triptan users, a baseline score from satisfied to very dissatisfied on the Overall Satisfaction domain of the	N=90 Patients were instructed to treat up to four migraine attacks and were followed until three to five days after the fourth treated attack or for 60 days, whichever came sooner	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported Across all of the treated attacks evaluated, the rates of attacks associated with pain relief were 30.7, 66.4, 80.1, 81.6, and 77.6% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively. The rates for attacks associated with pain-free response were 0.7, 14.8, 35, 48, and 65.7% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively. Sustained 24-hour pain relief and sustained 24-hour pain-free response was observed in 61.0 and 26.4% of attacks, respectively. The percentage of attacks requiring a second dose was 26%. Across attacks, PPMQ-R scores improved from baseline through the end of the treatment period for the Efficacy (52.5±17.8 vs 74.8±23.4; *P*<0.0001) and Functionality subscales (46.2±22.3 vs 71.3±25.2; *P*<0.0001). There was no decrease in the Tolerability subscale (80.6±14.7 vs 83.5±17.7; *P*=0.12). Scores declined for the Ease of Use subscale (79.6±16.0 vs 69.7±25.6; *P*=0.0007). The total PPMQ-R score and the PPMQ-R Overall Satisfaction score also increased over baseline (54.2±16.3 vs 73.3±22.1; *P*<0.0001 and 55.1±23.2 vs 74.6±27.7; *P*<0.0001, respectively). The percentage of patients satisfied or very satisfied increased from baseline to the end of treatment on the following global satisfaction domains: Overall Satisfaction (16.7 vs 62.2%; *P* value not reported), Satisfaction with Medication Effectiveness

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	PPMQ-R, and a baseline Migraine-ACT scores ≤2 (reflecting the need for a chance in acute migraine therapy)			(17.8 vs 63.4%; *P* value not reported), and Satisfaction with Side Effects (35.5 vs 67.8%; *P* value not reported). The percentage of patients confident or very confident in treating repeated migraine attacks increased from 22.2% (90% CI, 15.2 to 30.6) at baseline to 57.8% (90% CI, 48.6 to 66.6) at the end of treatment.
Boureau et al (abstract)[80] Sumatriptan 20 mg IN vs dihydroergotamine 1 mg IN	DB, DD, MC, RCT, XO Patients with migraine	N=368 Two migraine attacks	Primary: Pain relief at one hour Secondary: Nausea relief at one hour and safety	Primary: Significantly more patients receiving sumatriptan achieved pain relief at one hour compared to patients receiving dihydroergotamine (53 vs 41%; *P*<0.001). Secondary: Significantly more patients receiving sumatriptan achieved nausea relief at one hour compared to patients treated with dihydroergotamine (64 vs 49%; *P*=0.006). Both treatments were well tolerated as 10% of patients receiving either treatment reported one or more adverse events. The most frequently reported adverse event with sumatriptan was bad or bitter taste (5%). Nasal cavity/sinuses (4%) and nausea and/or vomiting (3%) were reported most commonly with dihydroergotamine.
Touchon et al[81] Sumatriptan 6 mg SC vs dihydroergotamine 1 mg IN	DB, DD, MC, RCT, XO Patients 18 to 65 years of age with migraine with or without aura for at least one year and up to six migraine attacks per month	N=266 Two migraine attacks	Primary: Two hour headache relief Secondary: Sustained relief, use of rescue medication, recurrence, migraine symptoms and clinical disability	Primary: Significantly more patients receiving sumatriptan achieved headache relief at two hours compared to patients receiving dihydroergotamine (*P*<0.001). Secondary: Significantly more patients receiving sumatriptan achieved sustained relief up to 24 hours compared to patients treated with dihydroergotamine (54 vs 39%; *P*<0.001). Rescue medication was required in significantly fewer attacks treated with sumatriptan compared to dihydroergotamine (28 vs 42%; *P*<0.001). More patients reported recurrence after sumatriptan compared to patients receiving dihydroergotamine (31 vs 17%; *P* value not reported).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
				At all time points from 30 minutes after dosing, significantly fewer patients receiving sumatriptan reported nausea (*P*<0.001). Results for photophobia and phonophobia were similar to those observed for nausea, with a rapid improvement in sumatriptan-treated patients and significant differences compared to dihydroergotamine-treated patients from 15 minutes post dosing (*P*<0.001). A rapid reduction in clinical disability (from grade three or two to grade one or zero) was observed with sumatriptan. The reduction was significantly less in patients receiving dihydroergotamine at all time points from 15 minutes (*P*<0.001). After one hour, 38% of patients receiving sumatriptan were able to perform their work or daily activities normally compared to 16% of patients receiving dihydroergotamine (*P*<0.001). Meaningful relief was achieved by more patients treated with sumatriptan (76 vs 46%; *P*<0.001).
Smith et al[82] Sumatriptan/naproxen 85/500 mg Administered at the onset of a moderate to severe migraine attack.	MC, OL Patients 18 to 35 years of age with first migraine attack before 50 years of age, with an average of two to eight moderate to severe attacks per month in six months prior to trial onset	N=600 12 months	Primary: Pain severity, change from baseline in PPMQ scores and change from baseline in MSQ scores Secondary: Not reported	Primary: A total of 81% of all attacks were reported pain-free at two hours post dose. At three months, the percentage of “satisfied” or “very satisfied” patients increased on all eight PPMQ items. At 12 months, PPMQ results remained high (*P* values not reported). Mean MSQ scores increased by 13 to 15 points at three months. Three and 12 month MSQ scores were significantly improved from baseline (*P*<0.001). Secondary: Not reported
Winner et al[83] Sumatriptan/naproxen 85/500 mg Administered at the	MC, OL Patients 18 to 35 years of age with first migraine attack before 50	N=562 12 months	Primary: Clinical adverse events and clinical chemical analysis	Primary: For overall safety data, 66% of patients reported at least one treatment emergent adverse event. A total of 41/565 patients withdrew from the trial due to an adverse event, 36 of which were not serious. Overall, 14 patients had one or more serious adverse

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
onset of a moderate to severe migraine attack.	years of age, with an average of two to eight moderate to severe attacks per month in six months prior to trial onset		Secondary: Not reported	event; none were fatal or life-threatening. All were judged unrelated to treatment except one case of acute coronary syndrome. Clinical chemical analyses observed at 12 months were reported as follows: range of 0.3 to 1.7 decrease in hemoglobin levels, zero patients; minimal increases in ALT levels; nine patients (none greater than two times the upper limit of normal); minimal increases in serum creatinine levels, nine patients (none exceeded 1.2 times the upper limit of normal) and minimal increases in BUN; seven patients (the highest being 30 mg/dL [1.3 times the upper limit of normal]). Secondary: Not reported
Landy et al[84] Sumatriptan/naproxen 85/500 mg Used to treat up to four migraine attacks over 12 weeks, administered within 30 minutes of the onset of pain while the pain was still mild.	OL, PRO Patients 18 to 65 years of age with a minimum of a one-year history of migraine with a positive screening for cutaneous allodynia; patients were required to have two to six migraines per month in the three months prior to screening	N=40 Patients could dose up to four migraine attacks over 12 weeks with a repeat dose after two hours was permitted for rescue	Primary: Percent of migraines with sustained pain-free response from two through 24 hours post dose and patients' overall satisfaction with sumatriptan/ naproxen from the PPMQ-R Secondary: Percentage of migraines pain-free at two hours, overall efficacy and overall adverse events from the PPMQ-R	Primary: Patients reported 78 (49%) migraines as sustained pain-free at 24 hours. Of the 40 included patients, 42.5% were satisfied for overall satisfaction. Secondary: Patients reported 94 (59%) migraines as pain-free at two hours. Of the 40 patients, 40% and 50% were satisfied for overall efficacy and overall adverse events, respectively.

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
Silberstein et al[85] Sumatriptan/naproxen 85/500 mg vs placebo All medications were administered at the onset of a migraine attack while pain was mild and not more than one hour after onset.	2 DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura of six months and an average of two to six attacks per month in three months prior to trial onset	N=658 (Trial 1) N=647 (Trial 2) Single migraine attack	Primary: Pain-free response at two hours Secondary: Pain-free responses at one-half, one and four hours; sustained pain-free response; migraine-free response at two and four hours; use of rescue medication within 24 hours postdose; nausea, photophobia and phonophobia rates at two and four hours; neck pain/discomfort and sinus pain/pressure at two and four hours	Primary: In Trial 1, sumatriptan/naproxen was significantly more effective than placebo at relieving pain at two hours (52 vs 17%; *P*<0.001). The corresponding rates in Trial 2 were 51 and 15%, respectively (*P*<0.001). Secondary: In Trial 1, combination therapy was significantly more effective at relieving pain after one-half (5 vs 2%; *P*=0.016), one (20 vs 7%; *P*<0.001) and four (70 vs 25%; *P*<0.001) hours. The corresponding rates in Trial 2 were 6 and 2% (*P*=0.021), 24 vs 7% (*P*<0.001) and 67 vs 25% (*P*<0.001), respectively. In Trial 1, combination therapy was significantly more effective at achieving a sustained pain-free response (45 vs 12%; *P*<0.001). The corresponding rate in Trial 2 was 40 vs 14% (*P*<0.001), respectively. In Trial 1, combination therapy was significantly more effective at achieving a migraine-free response at two and four hours (45 vs 15%; *P* value not reported and 63 vs 24%; *P*<0.05). The corresponding rates in Trial 2 were 46 vs 14% (*P* value not reported) and 64 vs 25% (*P*<0.05). In Trial 1, combination therapy was significantly more effective in reducing the use of rescue medications within 24 hours post dose (20 vs 47%; *P*<0.001). The corresponding rate in Trial 2 was 16 vs 45% (*P*<0.001). In Trial 1, combination therapy was significantly more effective in reducing two and four hour nausea (*P*=0.018), photophobia (*P*<0.001) and phonophobia (*P*<0.001) Results were similar in Trial 2 (*P*<0.001 for all measures). In Trial 1, combination was significantly more effective at relieving two and four hour neck pain/discomfort and sinus pain/pressure (*P*<0.001 for all measures). Results were similar in Trial 2 (*P*<0.001 for all measures).
Lipton et al[86] Sumatriptan/naproxen 85/500 mg	2 DB, PC, RCT, XO Patients 18 to 65 years of age,	N=4,145 Four migraine attacks	Primary: Pain-free response at two hours and 24-hour sustained	Primary: Across attacks in both trials, pain-free response at two hours was reported in significantly more attacks treated with combination therapy compared to attacks treated with placebo (Trial 1: 52 vs 25%; difference, 28%; 95% CI, 21 to 36; *P*<0.001, Trial 2: 50 vs 20%; difference, 30%; 95% CI, 24 to 36; *P*<0.001). Similar

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	history of migraine with or without aura for at least six months, an average of two to six migraine episodes monthly during the three months preceding enrollment, typically experienced moderate to severe headache pain preceded by an identifiable mild pain phase		pain-free response Secondary: Migraine-free response at two and four hours	results were observed for each individual attack (*P*<0.001 for all). Across attacks in both trials, sustained pain-free response from two to 24 hours was reported in significantly more attacks treated with combination therapy compared to attacks treated with placebo (Trial 1: 37 vs 17%; difference, 20%; 95% CI, 15 to 27; *P*<0.001, Trial 2: 34 vs 12%; difference, 22%; 95% CI, 18 to 27; *P*<0.001). Similar results were observed for each individual attack (*P*<0.05 for all). Secondary: Across attacks in both trials, migraine-free response after two and four hours was reported in significantly more attacks treated with combination therapy (*P*<0.001 for both).
Mathew et al[87] Sumatriptan/naproxen 85/500 mg vs placebo Patients had discontinued a short acting triptan in the past year because of poor response or intolerance.	2 DB, MC, PC, RCT, XO Patients 18 to 65 years of age with migraine with or without aura, up to eight migraine attacks during the three months preceding enrollment and <15 headache days monthly	N=283 Two migraine attacks	Primary: Sustained pain-free response Secondary: Proportion of patients with pain-free response at one-half, one, four and eight hours; proportion of patients with migraine-free response at	Primary: Combination therapy was “superior” to placebo for two to 24-hour sustained pain-free response (Trial 1: 26 vs 8%; OR, 4.50; 95% CI, 2.166 to 9.360; *P*<0.001, Trial 2: 31 vs 8%; OR, 5.63; 95% CI, 2.76 to 11.49; *P*<0.001). Secondary: Combination therapy was only “superior” to placebo for one (Trial 1: 19 vs 10%; OR, 2.20; 95% CI, 1.05 to 4.59; *P*<0.05, Trial 2: 25 vs 9%; OR, 3.19; 95% CI, 1.60 to 6.38; *P*≤0.001), two (Trial 1: 40 vs 17%; OR, 3.19; 95% CI, 1.80 to 5.65; *P*≤0.001, Trial 2: 44 vs 14%; OR, 4.69; 95% CI, 2.57 to 8.55; *P*≤0.001), four (Trial 1: 59 vs 23%; OR, 4.93; 95% CI, 2.85 to 8.54; *P*≤0.001, Trial 2: 62 vs 17%; OR, 8.12; 95% CI, 4.37 to 15.03; *P*≤0.001) and eight hour pain-free response (Trial 1: 65 vs 24%; OR, 5.81; 95% CI, 3.38 to 9.98; *P*≤0.001, Trial 2: 66 vs 24%; OR, 6.20; 95% CI, 3.58 to 10.76; *P*≤0.001). Combination therapy was “superior” to placebo for two (Trial 1: 35 vs 14%; OR,

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			two, four, eight and two to 24 hours; the proportion of patients with nausea, photophobia, phonophobia at two, four and eight hours and recurrence	3.18; 95% CI, 1.75 to 5.76; *P*≤0.001, Trial 2: 35 vs 11%; OR, 4.14; 95% CI, 2.20 to 7.80; *P*≤0.001), four (Trial 1: 53 vs 23%; OR, 3.88; 95% CI, 2.28 to 6.61; *P*≤0.001, Trial 2: 57 vs 15%; OR, 7.85; 95% CI, 4.17 to 14.77; *P*≤0.001) and eight hour migraine-free response (Trial 1: 59 vs 22%; OR, 5.14; 95% CI, 2.99 to 8.89, Trial 2: 63 vs 23%; OR, 5.97; 95% CI, 3.42 to 10.39; *P*≤0.001). Combination therapy was "superior" to placebo for two through 24-hour sustained response (Trial 1: 24 vs 8; OR, 3.43; 95% CI, 1.63 to 7.20; *P*≤0.001, Trial 2: 25 vs 6%; OR, 5.45; 95% CI, 2.52 to 11.80; *P*≤0.001). In both trials, combination therapy was "superior" to placebo in the absence of photophobia at two, four and eight hours (*P*≤0.001 for all). Similar results were seen for the incidence of phonophobia (*P*≤0.001 for all; except *P*<0.05 at eight hours in Trial 1). Significance between the two treatments for nausea occurred only at four (Trial 2; *P*<0.05) and eight hours (Trial 1: *P*<0.05, Trial 2: *P*<0.05). Fewer patients receiving combination therapy had recurrence at 24 (Trial 1: 20 vs 52%, Trial 2: 22 vs 26%) and 48 hours (Trial 1: 20 vs 57%, Trial 2: 22 vs 32%; *P* values not significant).
Brandes et al[88] Sumatriptan/naproxen 85/500 mg vs sumatriptan 85 mg vs naproxen 500 mg vs placebo All medications were	2 DB, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura six months and an average of two to six moderate or severe episodes monthly three months prior to trial onset	N=1,677 (Trial 1) N=1,736 (Trial 2) Single migraine attack	Primary: Headache relief at two hours; absence of photophobia, phonophobia and nausea at two hours; sustained pain-free response Secondary: Pain-free response at two hours; sustained headache relief; sustained	Primary: In Trial 1, sumatriptan/naproxen was significantly more effective than all other treatments for achieving relief at two hours (65 vs 55 [*P*=0.009], 44 [*P*<0.001] and 28% [*P*<0.001]). In Trial 2, the corresponding rates were 57 vs 50 (*P*=0.03), 43 (*P*<0.001) and 29% (*P*<0.001). In Trial 1, sumatriptan/naproxen was significantly more effective than placebo at achieving absence of photophobia (58 vs 36%), phonophobia (61 vs 38%) and nausea (71 vs 65%) (*P*<0.001 for all measures) at two hours. In Trial 2, the corresponding rates were (50 vs 32%, 56 vs 34% and 65 vs 64%) (*P*<0.001 for all measures). In Trial 1, sumatriptan/naproxen was significantly more effective than sumatriptan and naproxen for achieving a sustained pain-free response (25 vs 16 and 10%, respectively; *P*<0.01 for both]). In Trial 2, the corresponding rates were 23 vs 14 and 10%, respectively (*P*<0.001 for both). Secondary:

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
administered at the onset of a moderate to severe migraine attack.			absence of nausea, photophobia and phonophobia; use of rescue medications; headache recurrence and 24-hour incidence of vomiting	In Trial 1, combination therapy was significantly more effective for achieving freedom from pain at two hours compared to sumatriptan, naproxen and placebo (34 vs 25, 15 and 9%; *P*≤0.009 for all). The corresponding rates in Trial 2 were 30 vs 23, 16 and 10%, respectively (*P*≤0.009 for all). In Trial 1, combination therapy was significantly more effective compared to sumatriptan, naproxen and placebo, respectively, for achieving sustained headache relief (48 vs 35, 30 and 18%; *P*<0.001 for all). In Trial 2, the corresponding rates were 44 vs 33, 28 and 17%, respectively (*P*≤0.002 for all). In Trial 1, patients receiving combination therapy experienced sustained benefit of absence of nausea, photophobia and phonophobia compared to patients receiving placebo (*P*<0.001 for all measures) and sumatriptan (*P*=0.002, *P*=002, *P*<0.001). In Trial 2, combination therapy exhibited significant sustained benefit compared to placebo (*P*<0.001 for all), and compared to sumatriptan for only photophobia (*P*=0.05) and phonophobia (*P*=0.01). In Trial 1, patients receiving combination therapy used significantly less rescue medication compared to patients receiving sumatriptan (22 vs 32; *P*=0.004), naproxen (38; *P* value not reported) and placebo (53%; *P*<0.001]). In Trial 2, the corresponding rates were 23 vs 38 (*P*<0.001), 39 (*P* value not reported) and 58% (*P*<0.001), respectively. In Trial 1, the numbers of patients with headache recurrence were sumatriptan/naproxen, 30; sumatriptan, 47; naproxen, 25 and placebo, 26. In Trial 2, the corresponding numbers were 26, 34, 35 and 34 (*P* values not reported). In Trial 1, the 24-hour incidence of vomiting with combination treatment was no different than sumatriptan (4 vs 7%; *P*=0.14). Results were similar in Trial 2 (4 vs 9%; *P*=0.004).
Landy et al[89] Sumatriptan/naproxen 85/500 mg vs	2 DB, MC, PC, PG, RCT Men and women 18 to 65 years of age with a	N=1,468 (Trial 1) N=1,441 (Trial 2)	Primary: Ability to function, productivity assessed by 24-hour	Primary: In Trial 1, there was a significant difference in patients' ability to function between sumatriptan/naproxen vs naproxen and placebo during hour two through five (*P*<0.001). In Trial 2, there was a significant difference between combination therapy and naproxen (*P*<0.001), placebo (*P*<0.001) and sumatriptan (*P*<0.005).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
sumatriptan 85 mg vs naproxen 500 mg vs placebo All medications were administered at the onset of a moderate to severe migraine attack.	history of migraine attacks for at least six months, who had first migraine attack before age of 50 and experienced an average of two to six moderate to severe attacks in previous three months	Single migraine attack	postdose PAQ, patient satisfaction assessed by 24-hour postdose PPMQ Secondary: Not reported	In Trial 1, patients receiving sumatriptan/naproxen experienced significantly less total lost productivity compared to patients receiving naproxen (*P*=0.016) and placebo (*P*<0.001). In Trial 2, combination therapy was significantly more effective than naproxen (*P*=0.016), placebo (*P*<0.001) and sumatriptan (*P*=0.002). In Trial 1, overall satisfaction with sumatriptan/naproxen was 50% compared to 41, 35 and 21% with sumatriptan, naproxen and placebo (*P* values not reported). In Trial 2, the corresponding rates were 53 vs 42, 35 and 19% (*P* values not reported). Secondary: Not reported
Geraud et al[90] Zolmitriptan 5 mg vs sumatriptan 100 mg vs placebo Use of escape medication was permitted two hours post dose, if symptoms persisted.	DB, MC, PC, RCT Treatment naïve migraine patients 18 to 65 years of age with a history of migraine with or without aura for more than one year	N=1,058 24 hours	Primary: Complete headache response rates in acute treatment (defined as a reduction in headache pain from moderate to severe at baseline to mild or no pain two hours after taking study drug with no moderate or severe recurrences at 24 hours)	Primary: Complete headache response was 39, 38 and 32% with zolmitriptan, sumatriptan and placebo, respectively (*P* value not significant). In patients with moderate headache, response was significantly greater with zolmitriptan compared to placebo (48 vs 27%; *P*=0.01). In patients with a moderate headache, there was no difference in complete response with zolmitriptan and sumatriptan (48 vs 40%, respectively; *P* value not reported). In patients with a severe headache, there was no difference in complete response rates between placebo (44%) and zolmitriptan (27% and sumatriptan (35%; *P* values not reported). Secondary: Active treatment groups were significantly more effective than placebo for one, two and four hour headache responses (*P*<0.05).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Headache responses at one, two and four hours	
Dowson et al[91] Zolmitriptan 2.5 mg ODT vs sumatriptan 50 mg or rizatriptan 10 mg ODT or placebo	PC, RCT (vs placebo); OL, RCT, XO Patients with migraines	N=470 (vs placebo) N=168 (vs sumatriptan) N=171 (vs rizatriptan ODT) 12 weeks (vs sumatriptan)	Primary: Patient preference Secondary: Not reported	Primary: In the trial of zolmitriptan ODT vs placebo, 70% of patients preferred the ODT formation compared to conventional tablets (*P* value not reported). In terms of patient preference, a greater proportion of patients preferred zolmitriptan ODT compared to sumatriptan (60.1 vs 39.9%; *P*=0.013). Patients also found zolmitriptan ODT to be more efficacious compared to sumatriptan (76.7 vs 63.4%; *P*=0.006). Patient preference for zolmitriptan ODT was greater than that of rizatriptan ODT (70 vs 27%; *P*<0.001). Secondary: Not reported
Diener et al[92] Zolmitriptan 2.5 mg ODT A single dose was used to treat migraine headache. If headache returned, a second dose was allowed after an interval of at least two hours from initial	OS Patients nine to 95 years of age with migraines	N=14,543 2 years	Primary: Efficacy evaluation Secondary: Not reported	Primary: Headache pain improved in 96% of patients, and the mean time to headache improvement was 51±44 minutes (*P* value not reported). Physicians' assessment determined that 90% of patients had either 'good' or 'very good' efficacy with zolmitriptan ODT (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
dosing.				
Dowson et al[93] Zolmitriptan 0.5, 1, 2.5 or 5 mg IN (pre XO phase) vs zolmitriptan 5 mg IN (post XO phase)	DB, PG, RCT, XO Patients 18 to 65 years of age with migraine with or without aura, previous participation in a dose ranging trial, a one year history of migraine symptoms, with an age of onset of migraine <50 years and an average of one to six migraine attacks per month during the two months preceding the trial	N=1,093 (n=783 entered the post XO phase) 1 year	Primary: Tolerability Secondary: Headache response at two hours, pain-free response rate	Primary: Adverse events occurred in 22.1% of attacks treated with zolmitriptan 5 mg, and the majority were of short duration and mild or moderate intensity. Unusual taste and nasopharyngeal events were reported in 11.0 and 5.5% of attacks, respectively. Only 1.9% of patients withdrew from the one year trial due to adverse events. Serious adverse events occurred in 0.2% of attacks treated. There was no evidence of increased incidence of adverse events with increasing duration of treatment. Secondary: Efficacy was consistent over time with two-hour headache response rates of 73, 74, 75 and 74% during the four 90-day periods. Long-term usage of zolmitriptan 5 mg was associated with a consistently effective response, with 58% of patients experiencing a two-hour headache response in >75% of attacks. Pain-free response rates were also consistent over each four 90-day period (52 to 56%).
Loder et al[94] Zolmitriptan 2.5 mg ODT (Trials A and B) or zolmitriptan 5 mg ODT (Trial C) vs	3 DB, MC, PC, RCTs Patients with moderate to severe headaches (Trials A and C) Patients who had a migraine	N=470 (Trial A) N=565 (Trial B) N=670 (Trial C) 24 hours	Primary: Headache response (Trial A), pain-free rates at two hours (Trial B), migraine headache response at 30 minutes (Trial C)	Primary: In Trial A, headache response at two hours was significantly greater with zolmitriptan compared to placebo (63 vs 22%; *P*<0.0001). For Trial B, pain-free status at two hours was achieved in 40.1 and 19.8% of zolmitriptan- and placebo-treated patients (*P*<0.001). This was maintained at 24 hours (31.1 vs 14.6%; *P*<0.001). In Trial C, the proportions of zolmitriptan- and placebo-treated patients with reduced headache intensity at 30 minutes were 16 vs 13%, respectively (*P*<0.05).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
placebo	attack and who were instructed to treat it as soon as possible (Trial B)		Secondary: Headache response at 30 minutes (Trial A), reduction of headache intensity (Trials A and B), pain-free rates at two hours (Trials A and C), resumption of normal activities (Trials B and C)	Secondary: In Trial A, the proportions of zolmitriptan- and placebo-treated patients with reduced headache intensity at 30 minutes were 16 vs 10%, respectively (*P*=0.054). Pooled data from Trials A and B showed a significantly greater reduction of headache intensity (excluding mild intensity attacks) at 30 minutes with zolmitriptan compared to placebo (20.1 vs 12.7%; *P*<0.005). In Trial A, pain-free status at two hours was achieved in 27 and 7% of zolmitriptan- and placebo-treated patients (*P*<0.0001). In Trial C, pain-free status at two hours was achieved in 31 and 11% of zolmitriptan- and placebo-treated patients (*P*<0.0001). In trial B, 55.8 vs 34.0% of zolmitriptan- and placebo-treated patients were able to resume normal activities at two hours (*P*<0.001). In Trial C, there was a significantly greater proportion of patients that were able to resume normal activities at two hours with zolmitriptan compared to placebo (51.8 vs 25.7%; *P*<0.0001).
Spierings et al[95] Zolmitriptan 5 mg ODT vs placebo A single dose was used to treat migraine headache. If there was inadequate relief or if the headache returned, a second dose was allowed two	DB, MC, PC, PG, RCT Patients 18 to 65 years of age with at least two migraine headaches per month of moderate to severe intensity, in addition to <10 days of non migraine headaches per month for the three months	N=656 6 weeks	Primary: Migraine response at 30 minutes Secondary: Speed of onset of headache response, duration of response	Primary: Significantly more patients receiving zolmitriptan achieved migraine response at 30 minutes (16.5 vs 12.5%, respectively; *P*=0.048). Secondary: At one hour, the difference in the proportions of zolmitriptan- and placebo-treated patients with reduced migraine headache intensity was significant (41.1 vs 22.9%; *P*<0.0001). This difference was also consistent at two hours (59.0 vs 30.6%; *P*<0.0001). The proportions of patients that returned to normal activities at two hours was significantly greater with zolmitriptan (51.8 vs 25.7%, respectively; *P*<0.0001). A significantly greater proportion of patients receiving zolmitriptan achieved sustained headache response compared to placebo (42.5 vs 16.4%; *P*<0.0001).

Study and Drug Regimen	Study Design, and Demographics	Sample Size and Study Duration	End Points	Results
to 24 hours later.	prior to enrollment			
Charlesworth et al[96] Zolmitriptan 0.5 mg IN vs zolmitriptan 1 mg IN vs zolmitriptan 2.5 mg IN vs zolmitriptan 5 mg IN vs zolmitriptan 2.5 mg vs placebo	DB, DD, MC, PC, PG, RCT Patients 18 to 65 years of age with a history of migraine with or without aura for at least one year, with an age of onset of migraine <50 years and an average of one to six migraine attacks per month during the two months preceding the trial	N=1,547 Duration not specified	Primary: Headache response at two hours Secondary: Early headache response at 15, 30 and 45 minutes; headache response at one and four hours; pain-free rates at 15, 30 and 45 minutes and one, two and four hours	Primary: Headache response at two hours was reported to be the following: 31, 70 (P≤0.01), 59 (P≤0.01), 55 (P≤0.01) and 42% (P≤0.0008) with placebo and zolmitriptan 0.5, 1, 2.5 and 5 mg IN, respectively. Zolmitriptan 5 mg IN was significantly more effective than zolmitriptan 2.5 mg (P<0.05). Secondary: Zolmitriptan 2.5 and 5 mg IN showed a rapid onset of action, with a significant difference in headache response compared to placebo from 15 minutes through four hours after administration. At 15 minutes, early headache response was 5, 11 (P=0.0115) and 8% (P=0.0261) with placebo, zolmitriptan 5 mg IN and zolmitriptan 2.5 mg IN. Zolmitriptan 5 mg IN produced a significantly faster headache response than zolmitriptan 2.5 mg from 15 minutes through two hours (P value not reported). Zolmitriptan IN resulted in pain-free rates that were dose-dependent. While all doses ≥1 mg produced significant pain-free outcomes from 30 minutes compared to placebo, only the 5 mg dose produced pain-free rates significantly better than the 2.5 mg tablet (P values not reported).

*Strength not available in the United States.
Drug regimen abbreviations: IN=intranasal, ODT=orally disintegrating tablets, SC=subcutaneous
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, XO=crossover
Miscellaneous abbreviations: ALT=alanine transaminase, BUN=blood urea nitrogen, Migraine-ACT=Migraine assessment of current therapy, MIS=Migraine Intervention Scale, MqoLQ=Migraine Quality of Life Questionnaire, MSQ=Migraine-Specific Quality of Life Questionnaire, NSAID=non-steroidal anti-inflammatory drug, PAQ=Productivity Assessment Questionnaire, PPMQ=Patient Perception of Migraine Questionnaire, PPMQ-R= Revised Patient Perception of Migraine Questionnaire

Special Populations

Table 5. Special Populations[3-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Almotriptan	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <12 years of age have not been established.	Renal dosage adjustment required; for creatinine clearances ≤30 mL/minute, an initial dose of 6.25 mg and a maximum dose of 12.5 mg/day are recommended.	Hepatic dosage adjustment required; an initial dose of 6.25 mg and a maximum dose of 12.5 mg/day are recommended.	C	Unknown; use with caution.
Eletriptan	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction; use is contraindicated in severe hepatic dysfunction.	C	Unknown; use with caution.
Frovatriptan	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Use caution in severe hepatic dysfunction.	C	Unknown; use with caution.
Naratriptan	Not recommended for use in the elderly. Safety and efficacy in children <18	Renal dosage adjustment required; for mild to moderate renal dysfunction, an	Hepatic dosage adjustment required; for mild to moderate hepatic dysfunction, an	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	years of age have not been established.	initial dose of 1 mg and a maximum dose of 2.5 mg/day are recommended. Use is contraindicated in severe renal dysfunction (creatinine clearances <15 mL/minute).	initial dose of 1 mg and a maximum dose of 2.5 mg/day are recommended. Use is contraindicated in severe hepatic dysfunction (Child-Pugh C).		
Rizatriptan	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <6 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.
Sumatriptan	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <18 years of age have not been established.	Not studied in renal dysfunction.	No dosage adjustment required in mild to moderate hepatic impairment. Use is contraindicated in severe hepatic dysfunction (intranasal, oral and subcutaneous administration dosage forms).	C	Yes; use with caution.
Zolmitriptan	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <18	No dosage adjustment required.	Hepatic dose adjustment is required; the recommended daily dose is 1.25 mg in patients with moderate to severe hepatic impairment; the total daily dose should not exceed 5 mg in patients	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	years of age have not been established.		with severe hepatic impairment. The use of orally disintegrating tablets in patients with moderate to severe hepatic impairment is not recommended.		
Combination Products					
Sumatriptan/ naproxen	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Use is not recommended for creatinine clearances <30 mL/minute.	Use is contraindicated with hepatic dysfunction.	C	Yes/yes; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[3-12]

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Cardiovascular								
Acute coronary syndrome	-	-	-	-	-	-	-	≤1
Angina	-	<1	-	-	-	-	<1	-
Arrhythmia	-	<1	-	-	-	<1	<1	-
Atrial fibrillation	-	<1	-	<1	-	<1	-	-
Atrial flutter	-	-	-	<1	-	-	-	≤1
Atrial-ventricular block	-	<1	-	-	-	-	-	-
Bradycardia	-	<1	<1	-	<1	-	-	-
Chest tightness/pain	<1	1 to 4	2	-	<2 to 9	1 to 2[‡]/2 to 3[§]	2 to 4	3
Congestive heart failure	-	-	-	-	-	-	-	≤1
Coronary artery vasospasm	-	-	-	<1	-	-	<1	-
Cyanosis	-	<1	-	-	-	-	<1	-
Electrocardiogram changes	-	-	<1	-	-	<1	-	-
Flushing	-	-	4	-	✔	-	-	≤1
Heart block	-	-	-	-	-	<1	-	-
Hypertension	<1	<1	-	-	-	1[‡§]	<1	≤1
Hypertensive crisis	-	-	-	-	-	-	<1	-
Hypotension	-	<1	-	-	-	1[‡§]	-	-
Myocardial infarction	-	-	-	<1	-	-	<1	-
Myocardial ischemia	-	-	-	-	-	<1	<1	-
Myocarditis, viral	-	-	-	-	-	-	-	≤1
Palpitation	<1	✔	1	-	✔	-	≤2	>1
Peripheral vascular disease	-	<1	-	-	-	-	-	-
PR prolongation	-	-	-	<1	-	-	-	-
Premature ventricle contractions	-	-	-	<1	-	-	-	-
Prinzmetal angina	-	-	-	-	-	<1	-	-
Pulmonary embolism	-	-	-	-	-	<1	-	-
QTc prolongation	-	-	-	<1	-	-	<1	-
Tachycardia	<1	<1	<1	-	<1	-	-	≤1
Thrombophlebitis	-	-	-	-	-	<1	-	-
Thrombosis	-	-	-	-	-	<1	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Vasospasm	-	<1	-	-	-	-	-	-
Ventricular arrhythmia	-	<1	-	-	-	-	-	-
Ventricular extrasystoles	-	-	-	-	-	-	-	≤1
Ventricular failure, right	-	-	-	-	-	-	-	≤1
Ventricular fibrillation	-	-	-	<1	-	-	-	-
Ventricular tachycardia	-	-	-	<1	-	-	-	-
Central Nervous System								
Abnormal dreams	-	<1	-	-	-	-	-	-
Abnormal thinking	-	<1	-	-	-	-	-	-
Agitation	-	<1	<1	-	<1	<1	-	-
Amnesia	-	<1	<1	-	-	1§	-	-
Anxiety	<1	<1	1	-	-	1§	-	≤1
Apathy	-	<1	-	-	-	-	-	-
Aphasia	-	<1	-	-	-	-	-	≤1
Ataxia	-	<1	-	-	-	-	<1	-
Attention disturbances	-	-	-	-	<1†	-	-	≤1
Back pain	<1	✔	<1	-	-	-	-	-
Burning	-	-	-	-	-	1‡/7§	-	≤1
Catatonic reaction	-	<1	-	-	-	-	-	-
Central nervous system	<1	-	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	-	<1	<1	-
Cerebrovascular accident	-	-	-	-	-	<1	-	-
Cerebrovascular disorder	-	<1	-	-	-	-	-	-
Change in dreams	<1	-	-	-	-	-	-	-
Cold extremities	-	-	-	-	-	-	-	-
Cold sensation	-	-	-	-	-	1§	-	≤1
Confusion	-	<1	<1	-	<1	-	-	-
Convulsions	-	-	-	-	-	<1	-	-
Dementia	-	<1	-	-	-	-	-	-
Depersonalization	-	<1	<1	-	-	-	-	-
Depression	<1	<1	<1	-	-	-	-	≤1
Disorientation	-	-	-	-	-	-	-	≤1
Dizziness	3 to 4*	3 to 7	8	1 to 10	4 to 9	1 to 2‖/>1‡/	6 to 10	4

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
						12[§]		
Drowsiness	-	-	-	1 to 10	-	>1[‡]/3[§]	-	-
Dysesthesia	-	-	1	-	-	-	-	-
Emotional lability	-	<1	<1	-	-	-	-	-
Euphoria	<1	<1	<1	-	✔	-	-	-
Fatigue	<1	-	5	1 to 10	4 to 7, ✔[†]	2 to 3[‡]/1[§]	-	≥1
Feeling strange	-	-	-	-	-	2[§]	-	-
Hallucination	-	<1	-	<1	<1[†]	<1	<1	-
Headache	✔,1 to 2*	3 to 4	4	-	<2 to 2	<1[‖]/>1[‡]/2[§]	<1	-
Hearing loss	-	-	-	-	-	1[§]	-	-
Heaviness	-	-	-	-	-	7[§]	-	-
Hemiplegia	-	<1	-	-	-	-	-	-
Hot/cold sensation	-	-	3	-	-	-	-	-
Hyperacusis	<1	-	<1	-	-	-	-	-
Hyperalgesia	-	<1	-	-	-	-	-	-
Hyperesthesia	-	<1	<1	-	-	-	-	-
Hyperkinesia	-	<1	-	-	-	-	-	-
Hyperreflexia	<1	-	-	-	-	-	-	-
Hypertonia	<1	✔	<1	-	-	-	-	-
Hypoesthesia	<1	✔	1	-	✔	-	1 to 2	-
Hypokinesia	-	<1	-	-	-	-	-	-
Hypotonia	-	-	<1	-	-	-	-	-
Hysteria	-	<1	-	-	-	-	-	-
Impaired concentration	<1	-	<1	-	-	-	-	-
Incoordination	<1	<1	-	-	<1[†]	-	-	-
Insomnia	<1	<1	1	-	<1	-	-	≤1
Intracranial pressure increased	-	-	-	-	-	<1	-	-
Manic reaction	-	<1	-	-	-	-	-	-
Memory impairment	-	-	-	-	<1	-	-	-
Mental impairment	-	-	-	-	-	-	-	≤1
Migraine	-	<1	-	-	-	-	-	-
Nervousness	<1	<1	<1	-	-	-	-	≤1
Neuropathy	<1	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Neurosis	-	<1	-	-	-	-	-	-
Nightmares	<1	-	-	-	-	-	-	-
Nystagmus	<1	-	-	-	-	-	-	-
Oculogyric crisis	-	<1	-	-	-	-	-	-
Optic neuropathy	-	-	-	-	-	<1	-	-
Pain	-	✔	1	-	-	1 to 2[§]	2 to 3	-
Paralysis	-	<1	-	-	-	-	-	-
Paresthesia	1, <1 to 1	3 to 4	4	1 to 10	3 to 4	<1[‖]/3 to 5[‡]/14[§]	5 to 9	2
Personality disorder	-	-	<1	-	-	-	-	-
Psychomotor disorders	-	-	-	-	-	<1	-	≤1
Psychotic depression	-	<1	-	-	-	-	-	-
Restlessness	<1	-	-	-	-	-	-	-
Shakiness	<1	-	-	-	-	-	-	-
Sleep disorder	-	<1	-	-	-	-	-	-
Somnolence	<1 to 5*	3 to 7	-	-	4 to 8	-	5 to 8	3
Stupor	-	<1	-	-	-	-	-	-
Subarachnoid hemorrhage	-	-	-	-	-	<1	-	-
Twitching	-	<1	-	-	-	-	-	-
Vertigo	<1	✔	<1	-	<1	<1 to 2[‡]	≤2	≤1
Warm/cold sensation	-	-	-	-	-	2 to 3[‡]	5 to 7	-
Warm/hot sensation	-	-	-	-	✔	11[§]	-	>1
Weakness	-	-	-	-	-	5[§]	3 to 9	≥1
Dermatological								
Alopecia	-	<1	-	-	-	-	-	-
Bullous eruption	-	-	<1	-	-	-	-	-
Cheilitis	-	-	<1	-	-	-	-	-
Dermatitis	<1	<1	-	-	-	-	-	-
Dry skin	-	<1	-	-	-	-	-	-
Eczema	-	<1	-	-	-	-	-	-
Erythema	<1	-	-	-	<1	-	-	-
Flushing	-	2	-	-	-	<1[‡‖]/7[§]	-	-
Itching	-	-	<1	-	-	<1	-	-
Photosensitivity	<1	-	-	-	-	<1	<1	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Pruritus	<1	<1	-	-	<1	-	-	≤1
Psoriasis	-	<1	-	-	-	-	-	-
Rash	<1	<1	-	-	<1	<1	<1	≤1
Skin discoloration	-	<1	-	-	-	-	-	-
Skin hypertrophy	-	<1	-	-	-	-	-	-
Sweating	<1	✔	1	-	<1	2[§]	<3	-
Urticaria	-	<1	-	-	<1	-	<1	≤1
Vasculitis	-	-	-	-	-	<1	-	-
Endocrine and Metabolic								
Alkaline phosphatase increased	-	<1	-	-	-	-	-	-
Bilirubin	-	<1	-	-	-	-	-	-
Diabetes mellitus	-	-	-	-	-	-	-	≤1
Edema	-	<1	-	-	<1	<1	-	-
Goiter	-	<1	-	-	-	-	-	≤1
Growth hormone increase (mild)	-	-	-	-	1 to 10	-	-	-
Hot flashes	-	-	<1	-	<1	-	-	-
Hypercholesterolemia	<1	-	-	-	-	-	-	-
Hyperglycemia	<1	<1	-	-	-	-	-	-
Hypocalcemia	-	-	<1	-	-	-	-	-
Hypoglycemia	-	-	<1	-	-	-	-	≤1
Hypothyroidism	-	-	-	-	-	-	-	≤1
Increased gamma glutamyl transpeptidase	<1	-	-	-	-	-	-	-
Liver function tests abnormal or elevated	-	<1	-	-	-	<1	-	-
Menstrual irregularity	<1	<1	-	-	-	<1	-	-
Thyroid adenoma	-	<1	-	-	-	-	-	-
Thyroiditis	-	<1	-	-	-	-	-	-
Thyrotropin stimulating hormone levels increased	-	-	-	-	-	<1	-	-
Weight gain	-	<1	-	-	-	-	-	-
Weight loss	-	<1	-	-	-	-	-	-
Gastrointestinal								
Abdominal aortic aneurysm	-	-	-	-	-	<1	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Abdominal distension	-	<1	-	-	<1, ✔[†]	-	-	≤1
Abdominal cramp or pain	<1	1 to 2	1	-	-	<1[‡‖]/1[§]	-	≥1
Anorexia	-	<1	-	-	-	-	-	-
Bad taste	-	-	-	-	-	13 to 24[‖]	-	-
Biliary colic	-	-	-	-	-	-	-	≤1
Colitis	<1	-	-	-	-	<1	<1	≤1
Constipation	-	<1	<1	-	-	-	-	≤1
Diarrhea	<1	<1	1	-	✔	<1[§‖]/1[‡]	-	≤1
Diverticulitis	-	-	-	-	-	-	-	≤1
Dysgeusia	-	-	-	-	-	-	-	≤1
Dyspepsia	<1	1 to 2	2	-	<1	<1	1 to 3	2
Dysphagia	-	1 to 2	<1	-	-	<1[‡‖]/1[§]	<2	≤1
Eructation	-	<1	<1	-	-	-	-	-
Esophagitis	-	<1	-	-	-	-	-	-
Flatulence	-	<1	-	-	-	-	-	≤1
Gastric ulcer	-	-	-	-	-	-	-	≤1
Gastritis	<1	<1	-	-	-	-	-	≤1
Gastroenteritis	<1	-	-	-	-	-	-	-
Gastroesophageal reflux	<1	-	<1	-	-	-	-	≤1
Gastrointestinal disorder	-	<1	-	-	-	-	-	-
Gastrointestinal pain	-	-	-	-	-	<1	-	-
Glossitis	-	<1	-	-	-	-	-	-
Hematemesis	-	<1	-	-	-	-	<1	-
Hiccup	-	-	<1	-	-	-	-	-
Hypersalivation	<1	<1	<1	-	-	-	-	-
Hyposalivation	-	-	3	-	-	>1[‡]	-	-
Intestinal obstruction	-	-	-	-	-	<1	-	-
Irritable bowel syndrome	-	-	-	-	-	-	-	≤1
Melena	-	-	-	-	-	-	<1	-
Nausea	1 to 2, 1 to 3*	4 to 8	-	1 to 10	4 to 6	11 to 13[‖]/>1[‡]	4 to 9	3
Pancreatitis	-	-	-	-	-	-	<1	-
Peptic ulcer disease	-	-	<1	-	-	-	<1	-
Rectal disorder	-	<1	-	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Splenic infarction	-	-	-	-	-	-	<1	-
Swallowing disorders	-	-	-	-	-	<1	-	-
Taste alteration	<1	<1	<1	-	-	-	-	-
Vomiting	<1, 2*	-	1	1 to 10	✔	11 to 13[‖]/>1[‡]	-	≤1
Genitourinary								
Acute renal failure	-	-	-	-	-	<1	-	-
Dysuria	-	-	<1	-	-	-	-	-
Hematuria	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Impotence	-	<1	-	-	-	-	-	-
Kidney pain	-	<1	-	-	-	-	-	-
Leukorrhea	-	<1	-	-	-	-	-	-
Menorrhagia	-	<1	-	-	-	-	-	-
Micturition	-	-	<1	-	-	-	-	-
Nephrolithiasis	-	-	-	-	-	-	-	≤1
Nocturia	-	-	<1	-	-	-	-	-
Polyuria	-	<1	<1	-	-	-	-	-
Renal insufficiency	-	-	-	-	-	-	-	≤1
Urinary tract disorder	-	<1	-	-	-	-	-	-
Vaginitis	-	<1	-	-	-	-	-	-
Hematologic								
Anemia	-	<1	-	-	-	-	-	≤1
Eosinophilia	-	-	-	-	-	-	<1	-
Hemolytic anemia	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Monocytosis	-	<1	-	-	-	-	-	-
Pancytopenia	-	-	-	-	-	<1	-	-
Purpura	-	<1	<1	-	-	-	-	-
Thrombocytopenia	-	-	-	-	-	<1	<1	-
Musculoskeletal								
Abnormal gait	-	<1	<1	-	<1	-	-	≤1
Abnormal reflexes	-	-	<1	-	-	-	-	-
Arthralgia	<1	<1	<1	-	-	-	-	≤1
Arthritis	<1	<1	-	-	-	-	-	-
Arthrosis	-	<1	<1	-	-	-	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Asthenia	<1	4 to 10	<1	-	-	-	-	-
Ataxia	-	-	<1	-	-	-	-	-
Back pain	-	-	-	-	-	-	-	≤1
Bone neoplasm	-	<1	-	-	-	-	-	-
Bone pain	-	<1	-	-	-	-	-	-
Creatinine phosphokinase increase	<1	<1	<1	-	-	-	-	-
Dystonias	-	<1	-	-	-	<1	-	-
Facial palsy	-	-	-	-	-	-	-	≤1
Involuntary muscle contractions	-	-	<1	-	-	-	-	-
Joint ache	-	-	-	-	-	<1	-	-
Joint disorder	-	<1	-	-	-	-	-	-
Muscle cramps	-	-	<1	-	<1	1[§]	-	-
Muscle tightness	-	-	-	-	-	-	-	>1
Muscle stiffness	-	-	-	-	<1	<1	-	-
Muscle weakness	<1	-	<1	-	<1	1[§]	-	≥1
Myalgia	<1	<1	<1	-	<1	1[‡]/2[§]	1 to 2	≤1
Myasthenia	-	<1	-	-	-	-	<2	-
Myopathy	<1	<1	-	-	-	-	-	-
Numbness	-	-	-	-	-	1[‡]/5[§]	-	-
Rigid neck	<1	-	-	-	-	-	-	-
Rigors	-	-	<1	-	-	-	-	-
Skeletal pain	-	-	3	-	-	-	-	-
Tenosynovitis	-	<1	-	-	-	-	-	-
Tetany	-	-	-	-	-	-	<1	-
Tremor	<1	<1	<1	-	✔	-	-	≤1
Respiratory								
Asthma	-	<1	-	-	-	-	-	≤1
Bronchitis	<1	<1	-	-	-	-	-	-
Bronchospasm	-	-	-	-	-	<1	<1	-
Choking sensation	-	<1	-	-	-	-	-	-
Dyspnea	<1	<1	<1	-	✔	1[§]	-	≤1
Esophagitis	-	<1	-	-	-	-	<1	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Hyperventilation	<1	<1	<1	-	-	-	-	-
Laryngitis	<1	<1	<1	-	-	-	-	-
Nasal disorder/discomfort	-	-	-	-	-	2 to 4[‖]/2[§]	-	-
Nose/throat hemorrhage	-	-	-	-	-	<1[§‖]/1[‡]	-	-
Pharyngeal edema	-	-	-	-	<1	-	-	-
Pharyngitis	<1	✔	<1	-	-	-	-	-
Pleurisy	-	-	-	-	-	-	-	≤1
Respiratory disorder	-	<1	-	-	-	-	-	-
Respiratory tract infection	-	<1	-	-	-	-	-	-
Rhinitis	<1	<1	1	-	-	1[‡]	-	-
Sinusitis	<1	<1	1	-	-	1[‡]	-	-
Sneezing	<1	-	-	-	-	-	-	-
Sputum	-	<1	-	-	-	-	-	-
Throat discomfort	-	-	-	-	-	1 to 2[‖]/3[§]	-	-
Throat or neck pain/pressure	<1	-	-	1 to 10	-	-	-	-
Upper respiratory inflammation	-	-	-	-	-	1[‡]	-	-
Voice alteration	-	<1	-	-	-	-	-	-
Other								
Abscess	-	<1	-	-	-	-	-	-
Accidental injury	-	<1	-	-	-	-	-	-
Accommodation disorders	-	-	-	-	-	<1	-	-
Allergic reaction	-	<1	-	<1	-	<1[§‖], 1[‡]	1	-
Anaphylactoid reaction	-	-	-	-	-	<1	<1	-
Anaphylaxis	-	-	-	-	-	<1	<1	-
Angioneurotic edema	-	-	-	-	-	<1	-	-
Breast pain	-	<1	-	-	-	-	-	-
Bruising	-	-	-	-	-	-	-	≤1
Cataract	-	-	-	-	-	-	-	≤1
Chills	<1	✔	-	-	-	-	-	-
Conjunctival hemorrhage	-	-	-	-	-	-	-	≤1
Conjunctivitis	<1	<1	<1	-	-	-	-	≤1
Cough	-	<1	-	-	-	-	-	≤1
Deafness	-	-	-	-	-	<1	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Death	-	-	-	-	-	<1	-	-
Decreased appetite	-	-	-	-	-	<1	-	-
Dental pain	-	-	-	-	-	<1	-	-
Dry eyes	<1	<1	-	-	-	-	-	-
Diplopia	<1	<1	-	-	-	-	-	-
Dry mouth	1	2 to 4	-	-	3	-	-	-
Earache	<1	<1	<1	-	-	-	-	≤1
Ear hemorrhage	-	<1	-	-	-	-	-	-
Epistaxis	<1	<1	<1	-	-	-	-	≤1
Eye irritation	<1	-	-	-	-	-	-	-
Eye pain	<1	<1	<1	-	-	-	-	-
Eye swelling	-	-	-	-	<1	-	-	-
Facial edema	-	-	-	-	<1	-	-	≤1
Fever	<1	<1	<1	-	-	-	-	≤1
Flu syndrome	-	<1	-	-	-	-	-	-
Gingivitis	-	<1	-	-	-	-	-	-
Halitosis	-	<1	-	-	-	-	-	-
Heaviness sensation	-	-	-	-	-	-	-	≤1
Hernia	-	<1	-	-	-	-	-	-
Hiccups	-	<1	-	-	-	<1	-	-
Hyperhidrosis	-	-	-	-	-	-	-	≤1
Hypoacusis	-	-	-	-	<1†	-	-	-
Hypothermia	-	<1	-	-	-	-	-	-
Increased appetite	-	<1	-	-	-	-	-	-
Infection (various)	-	-	-	-	-	-	-	≤1
Irritability	-	-	-	-	-	-	-	≤1
Jittery	-	-	-	-	-	-	-	≤1
Lab test abnormal	-	<1	-	-	-	-	-	-
Lacrimation disorder	-	<1	<1	-	-	-	-	-
Lethargy	-	-	-	-	-	-	-	≤1
Leukopenia	-	<1	-	-	-	-	-	≤1
Lymphadenopathy	-	<1	-	-	-	-	-	≤1
Malaise	-	<1	-	-	-	-	-	≤1

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Miscarriage	-	-	-	-	-	-	<1	-
Moniliasis	-	<1	-	-	-	-	-	-
Motion sickness	-	-	-	-	-	-	-	≤1
Mouth/tongue discomfort	-	-	-	-	-	5[§]	-	-
Neck/throat/jaw pain/ tightness/Pressure	-	-	-	-	<2 to 2	2 to 5[§]/2 to 3[‡]	4 to 10	3
Numbness of tongue	-	-	-	-	-	<1	-	-
Optic neuropathy (ischemic)	-	-	-	-	-	<1	-	-
Oral mucosal blistering	-	-	-	-	-	-	-	≤1
Oropharyngeal edema	-	-	-	-	-	-	-	≤1
Otitis media	<1	<1	-	-	-	-	-	-
Pain at injection site	-	-	-	-	-	59[§]	-	-
Parosmia	<1	<1	-	-	-	-	-	-
Peripheral edema	-	<1	-	-	-	-	-	≤1
Photophobia	-	<1	-	-	-	-	-	-
Pressure sensation	-	-	-	-	-	7[§]/1 to 3[‡]	-	-
Presyncope	-	-	-	-	<1†	-	-	-
Ptosis	-	<1	-	-	-	-	-	-
Raynaud's syndrome	-	-	-	-	-	<1	-	-
Rheumatoid arthritis	-	<1	-	-	-	-	-	-
Scotoma	<1	-	-	-	-	-	-	-
Sedation	-	-	-	-	-	-	-	≤1
Seizure	-	-	-	<1	-	-	-	-
Shock	-	<1	-	-	-	<1	-	-
Speech disorder	-	<1	<1	-	-	-	-	-
Stomatitis	-	<1	<1	-	-	-	-	-
Stroke	-	-	-	-	-	-	-	-
Syncope	<1	<1	<1	-	<1	<1[§‖]/1[‡]	<1	-
Systemic lupus erythematosus	-	-	-	-	-	-	-	≤1
Temperature intolerance	-	-	-	-	-	-	-	≤1
Thirst	<1	<1	<1	-	-	-	-	≤1
Thrombophlebitis	-	<1	-	-	-	-	-	-
Tightness feeling	-	-	-	-	-	5[§]	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Tinnitus	<1	<1	1	-	<1	1‡	<1	≤1
Tooth disorder	-	<1	-	-	-	-	-	-
Tongue edema	-	<1	-	-	<1	-	-	≤1
Vision abnormalities	-	<1	1	-	-	1§	-	≤1
Vision loss	-	-	-	-	<1	<1	-	-
Xerostomia	-	-	-	-	-	<1	3 to 5	2

* Rate of adverse event in adolescents 12 to 17 years of age.
† Rate of adverse event in pediatric and adolescent patients six to 17 years of age.
‡By mouth.
§Subcutaneous.
‖Intranasal.
-Event not reported.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[3-12]

Contraindication	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Allergy to naproxen; asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs	-	-	-	-	-	-	-	✔
Cerebrovascular syndromes	✔	✔	✔	-	-	-	✔‡	-
Concurrent administration or recent discontinuation (i.e., within two weeks) of a monoamine oxidase A inhibitor	-	-	-	-	✔	✔*	✔	✔
Concomitant use with 5-hydroxytryptamine-1agonists (within 24 hours of each other)	✔	✔	✔	✔	✔	✔	✔	✔
Hemiplegic or basilar migraine	✔	✔	✔	✔	✔	✔	✔	✔
Hepatic impairment	-	-	-	-	-	-	-	✔
History of coronary artery bypass graft surgery	-	-	-	-	-	-	-	✔

Contraindication	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
History of stroke or transient ischemic attack	-	-	-	-	✔	-	-	-
History, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes or with significant underlying cardiovascular disease	-	-	-	✔	-	✔	-	✔
Hypersensitivity to the agent or any of its inactive ingredients	✔	✔	✔	✔	✔	✔	✔	✔
Intravenous administration may cause coronary vasospasm	-	-	-	-	-	✔ †	-	-
Ischemic bowel disease	-	-	-	-	✔	-	-	-
Ischemic heart disease or symptoms, or findings, consistent with ischemic heart disease, coronary artery vasospasm, including Prinzmetal's variant angina, or other significant underlying cardiovascular disease	-	✔	✔	-	-	-	-	-
Ischemic or vasospastic coronary artery disease, or other significant underlying cardiovascular disease	✔	-	-	-	✔	-	✔	-
Peripheral vascular disease	✔	✔	✔	-	✔	-	✔ ‡	-
Severe hepatic impairment	-	✔	-	✔	-	✔	-	-
Severe renal impairment	-	-	-	✔	-	-	-	-
Uncontrolled hypertension	✔	✔	✔	✔	✔	✔	✔	✔
Use within 24 hours of using an ergotamine-containing or ergot-derived medication like dihydroergotamine, ergotamine tartrate, or methysergide	✔	✔	✔	✔	✔	✔	✔	✔

Black Box Warning for Treximet® (sumatriptan/naproxen)[12]

Warning
Cardiovascular risk: Sumatriptan/naproxen may cause an increased risk of serious cardiovascular thrombotic reactions, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Gastrointestinal risk: Sumatriptan/naproxen contains a nonsteroidal anti-inflammatory drug (NSAID). NSAID-containing products cause an increased risk of serious gastrointestinal adverse reactions, including bleeding, ulceration and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal reactions.

Warnings and Precautions

Table 8. Warnings and Precautions[3-12]

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Advanced renal disease; use is not recommended, if therapy must be initiated, close monitoring of renal function is advised	-	-	-	-	-	-	-	✔*
Anaphylactic/anaphylactoid reactions; do not administer to patients with aspirin triad	-	-	-	-	-	-	-	✔
Anemia may be seen with NSAIDs; patients on long-term treatment with NSAIDs should have hemoglobin or hematocrit checked if signs or symptoms of anemia occur	-	-	-	-	-	-	-	✔
Arrhythmias, including life-threatening disturbances of cardiac rhythm, ventricular tachycardia and ventricular fibrillation leading to death, have been reported; if these events occur, discontinue use	-	-	-	-	✔	-	-	-
Binding to melanin-containing tissues	✔	✔	✔		-	✔*	✔	✔
Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been	✔	✔	✔	✔	-	✔	✔	✔

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
reported and some events have resulted in fatalities								
Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported and some events have resulted in fatalities; do not administer to patients with a history of stroke or transient ischemic attack	-	-	-	-	✔	-	-	-
Concomitant monoamine oxidase A inhibitor use; coadministration is not recommended but if coadministration is clinically warranted, suitable dose adjustment and appropriate patient observation is advised	-	-	-	-	-	✔	-	-
Corneal opacities	✔	✔	-	-	-	✔ †	-	✔
Cytochrome P450 3A4 inhibitors; do not administer within at least 72 hours of treatment with drugs with potent cytochrome P450 3A4 inhibition	-	✔	-	-	-	-	-	-
Development of potentially life-threatening serotonin syndrome may occur, particularly during combined use with selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitors; if concomitant treatment with a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor is clinically warranted, careful observation of the patient is advised	✔	✔	✔	-	-	✔ †	✔	✔
Elevated blood pressure, including hypertensive crisis, has been reported in patients with and without a history of	-	✔	-	-	✔	-	-	-

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
hypertension; use in patients with uncontrolled hypertension is contraindicated								
Fluid retention and edema have been observed; use consideration in patients that require severely restricted overall sodium intake	-	-	-	-	-	-	-	✔
Gastrointestinal adverse events may occur, including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which may be fatal; use with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding	-	-	-	-	-	-	-	✔
Hepatic impairment; should not be used in patients with severe hepatic impairment	-	✔	-	-	-	-	-	-
Hepatic impairment; use is contraindicated	-	-	-	-	-	-	-	✔
Hypersensitivity; anaphylaxis and anaphylactoid reactions may occur and can be life threatening or fatal	-	-	-	✔	-	✔	-	-
Hypersensitivity to sulfonamides	✔	-	-	-	-	-	-	-
Impaired hepatic or renal function; use with caution	✔	-	-	✔	-	-	-	-
Impaired renal function, preexisting kidney disease or dehydration; use with caution	-	-	-	-	-	-	-	✔
Increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal; to minimize the potential risk in patients treated with an NSAID,	-	-	-	-	-	-	-	✔

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
the lowest effective dose should be used for the shortest duration possible								
Increases in blood pressure; use in patients with uncontrolled hypertension is contraindicated	✔	-	✔	✔	-	✔	✔	-
Local irritation: burning, numbness, paresthesia, discharge, and pain or soreness have been reported	-	-	-	-	-	✔ ‡	-	-
May cause coronary vasospasm; do not administer to patients with documented ischemic or vasospastic coronary artery disease	✔	✔	✔	✔	-	✔ † ‡	✔	✔
Myocardial ischemia, myocardial infarction, and Prinzmetal's angina; do not administer to patients with ischemic or vasospastic coronary artery disease	-	-	-	-	✔	-	-	-
Naproxen containing products; avoid concomitant use	-	-	-	-	-	-	-	✔
Onset of new hypertension or worsening of preexisting hypertension, which may contribute to the increased incidence of cardiovascular events; monitor blood pressure closely during initiation of NSAID treatment and throughout course of therapy	-	-	-	-	-	-	-	✔ *
Other vasospasm-related events, including peripheral vascular ischemia and colonic ischemia; if experienced, the patient should be further evaluated	✔	-	-	-	-	-	-	-
Overuse of acute migraine drugs may lead to exacerbation of headache or medication overuse headache	-	-	-	✔	✔	✔ ‡ §	✔	✔
Patients with preexisting asthma may	-	-	-	-	-	-	-	✔

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
have aspirin-sensitive asthma; use with caution								
Patients with risk factors for coronary artery disease; use is not recommended in patients in whom unrecognized coronary artery disease is predicted by the presence of risk factors unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease	✔	✔	✔	✔	-	✔	✔	✔
Patients with risk factors predictive of coronary artery disease and with a satisfactory cardiovascular evaluation; recommended that the first dose take place in the setting of a physician's office or similar medically staffed and equipped facility	✔	✔	✔	✔	-	✔	✔	✔
Phenylketonurics; contains phenylalanine	-	-	-	-	-	-	✔ #	-
Pregnancy; should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus	-	-	-	-	-	✔ ‖	-	✔
Pregnancy; should not be used in late pregnancy	-	-	-	-	-	-	-	✔
Renal papillary necrosis and other renal injury; discontinuation of NSAID therapy is usually followed by recovery to pretreatment state	-	-	-	-	-	-	-	✔
Risk of myocardial ischemia and infarction and other adverse cardiac events	✔	✔	✔	✔	-	✔	✔	✔

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
Seizures have been reported; use with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold	-	-	-	-	-	✔ ‖¶	-	✔
Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw have been reported; patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of coronary artery disease or a predisposition to Prinzmetal's variant angina before receiving additional doses and should be monitored	✔	✔	✔	✔	✔	✔	✔	✔
Serious adverse cardiac events, including acute myocardial infarction, life-threatening cardiac rhythms and death have been reported	✔	✔	✔	✔	-	✔	✔	✔
Serious adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal, may occur; discontinue treatment at the first appearance of skin rash or any other sign of hypersensitivity	-	-	-	-	-	-	-	✔
Serotonin syndrome may occur, particularly during combined use with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors; discontinue use of 5-hydroxytryptamine-1 receptor agonist if serotonin syndrome is suspected	-	-	-	✔	✔	✔ ‡ §	✔	-
Significant elevation in blood pressure, including hypertensive crisis has been	-	-	-	-	-	✔	-	✔

Warnings/Precautions	Single-Entity Agents							Combination Products
	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Sumatriptan/ Naproxen
reported; use is contraindicated in patients with uncontrolled hypertension; administer with caution to patients with controlled hypertension								
Transient and permanent blindness and significant partial vision loss have been reported	✔	-	-	-	✔	✔	✔ ‡	✔
Triptan-naïve patients who have multiple cardiovascular risk factors should have a cardiovascular evaluation prior to initiation; if there is evidence of coronary artery disease or coronary artery vasospasm, do not administer	-	-	-	-	✔	-	-	-
Ulcerative colitis and Crohn's disease; use caution as NSAID may exacerbate conditions	-	-	-	-	-	-	-	✔
Use only where a clear diagnosis of migraine has been established	-	-	-	✔	-	✔ *‡§	✔ #	✔
Vasospastic reactions other than coronary artery vasospasm have been reported	-	✔	✔	✔	✔	✔	✔	✔
Wolff-Parkinson-White syndrome; do not use	-	-	-	-	-	-	✔ ‡	-

NSAIDS=nonsteroidal antiinflamatory
* Imitrex® (sumatriptan) injection.
† All injectable sumatriptan formulations.
‡ Nasal spray.
§ Sumatriptan tablets.
‖ Alsuma® (sumatriptan) injection.
¶ Sumavel® (sumatriptan) injection.
# Oral formulations.

Drug Interactions

Table 9. Drug Interactions[3-12]

Generic Name	Interacting Medication or Disease	Potential Result
5-HT1 receptor agonists (all)	Linezolid	Concurrent use may result in serotonin syndrome in some patients.
5-HT1 receptor agonists (all)	Serotonin reuptake inhibitors	Concurrent use may result in serotonin syndrome in some patients.
5-HT1 receptor agonists (eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)	Erogt derivatives	Concurrent use may increase the risk of vasospastic reactions.
5-HT1 receptor agonists (rizatriptan, sumatriptan, zolmitriptan)	Monoamine oxidase inhibitors	Serum concentrations of 5-HT1 receptor agonists may be elevated, increasing the risk of cardiac toxicity.
5-HT1 receptor agonists (almotriptan, eletriptan)	Azole antifungals	Plasma concentrations of 5-HT1 receptor agonists may be elevated, increasing the pharmacological effects and adverse reactions.
Naproxen	Aminoglycosides	Plasma aminoglycoside concentrations may be elevated.
Naproxen	Anticoagulants	Concurrent use may result in increased anticoagulant activity and risk of bleeding.
Naproxen	Azole antifungals	Plasma concentrations of naproxen may be elevated, increasing the pharmacological effects and adverse reactions.
Naproxen	β-blockers	Concurrent use may result in impaired antihypertensive effects of β-blockers.
Naproxen	Heparin	Concurrent use may increase the risk of hemorrhagic adverse reactions.
Naproxen	Lithium	Plasma lithium concentrations may be elevated, increasing the pharmacological effects and adverse reactions.
Naproxen	Methotrexate	Concurrent use may increase the risk of methotrexate toxicity.
Naproxen	Probenecid	Concurrent use may increase the toxicity of naproxen.
Naproxen	Salicylates	Concurrent use may reduce the cardioprotective effect of low dose, uncoated aspirin. These agents are also gastric irritants.
Naproxen	Selective serotonin reuptake inhibitors	Concurrent use may increase the risk of gastrointestinal bleeding.

5-HT=serotonin.

Dosage and Administration

Table 10. Dosing and Administration[3-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Almotriptan	Acute treatment of migraine attacks in	Acute treatment of migraine	Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	adults with a history of migraine with or without aura: Tablet: initial, 6.25 or 12.5 dose, may repeat after two hours if headache returns; maximum, 25 mg/day	headache pain in children 12 to 17 years of age with a history of migraine attacks with or without aura, and who have migraine attacks usually lasting four hours or more : Tablet: initial, 6.25 or 12.5 mg, may repeat after two hours if headache returns; maximum, 25 mg/day	6.25 mg 12.5 mg
Eletriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 20 or 40 mg, may repeat after two hours if headache returns; maximum, 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg
Frovatriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 2.5 mg, may repeat after two hours if headache returns; maximum, 7.5 mg/day	Safety and efficacy in children have not been established.	Tablet: 2.5 mg
Naratriptan	Acute treatment of migraine attacks with or without aura: Tablet: initial, 1 or 2.5 mg, may repeat after four hours if headache returns; maximum, 5 mg/day	Safety and efficacy in children <18 years of age have not been established.	Tablet: 1 mg 2.5 mg
Rizatriptan	Acute treatment of migraine attacks with or without aura: Orally disintegrating tablet, tablet: 5 or 10 mg, may repeat after two hours if headache returns; maximum, 30 mg/day	Acute treatment of migraine with or without aura in pediatric patients six to 17 years of age: Orally disintegrating tablet: 5 mg for patients <40 kg, 10 mg for patients ≥40 kg Tablet: 5 to 10 mg	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg
Sumatriptan	Acute treatment of migraine attacks with or without aura: Nasal spray: initial, 5, 10 or 20 mg, may repeat after two hours if headache returns; maximum, 40 mg/day Subcutaneous injection: initial, 6 mg, may repeat after one hour if headache returns; maximum, 12 mg/day Tablet: initial, 25, 50 or 100 mg, may repeat after two hours if headache returns; maximum, 200 mg/day Acute treatment of cluster headache episodes: Subcutaneous injection: initial, 6 mg,	Safety and efficacy in children <18 years of age have not been established.	Nasal spray: 5 mg 20 mg Subcutaneous injection: 4 mg/0.5 mL 6 mg/0.5 mL Tablet: 25 mg 50 mg 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	may repeat after one hour if headache returns; maximum, 12 mg/day		
Zolmitriptan	Acute treatment of migraine attacks with or without aura: Orally disintegrating tablet: initial, 2.5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day Nasal spray: initial, 5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day Tablet: initial, 1, 2.5 or 5 mg, may repeat after two hours if headache returns; maximum, 10 mg/day	Safety and efficacy in children <18 years of age have not been established.	Nasal spray: 5 mg Orally disintegrating tablet: 2.5 mg 5 mg Tablet: 2.5 mg 5 mg
Combination Products			
Sumatriptan/ naproxen	Acute treatment of migraine attacks with or without aura: Tablet: initial, 85/500 mg, may repeat after two hours if headache returns; maximum, 170/1,000 mg/day	Safety and efficacy in children have not been established.	Tablet: 85/500 mg

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that due to the Food and Drug Administration approved indications of the serotonin (5-HT) 1 receptor agonists, or triptans, only recommendations addressing the acute treatment of migraine attacks are outlined. The acute treatment of migraine attacks are presented globally, addressing the role of various medication classes in the treatment of this disorder.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Neurology: **Practice Parameter: Evidence-Based Guidelines for Migraine Headache (2000)**[13]	Acute migraine attacks, mild to moderate • First-line therapy consists of oral nonsteroidal anti-inflammatory drugs (NSAIDs). Acute migraine attacks, moderate to severe • Triptans (i.e., naratriptan, rizatriptan, sumatriptan and zolmitriptan) are effective and relatively safe for the acute treatment of migraine headaches, and are an appropriate initial treatment choice in patients with moderate to severe migraine and no contraindications for their use. • Initial treatment with any triptan is a reasonable choice for moderate to severe headaches or in migraine, regardless of severity, that has not resulted in adequate relief from the administration of nonspecific medication (e.g., NSAIDs, non opiates and combination analgesics). • Experts recommend limiting acute therapy to two headache days per week on a regular basis. • Opiate analgesics, particularly butorphanol nasal spray or oral combinations such as acetaminophen with codeine should only be used on a limited basis as rescue therapy. • For treatment of status migrainosus, the therapy of choice in the emergency department should be intravenous dihydroergotamine plus antiemetics. Intramuscular or intravenous prochlorperazine as

Clinical Guideline	Recommendation(s)
	needed should be chosen as the first-line antiemetic in the emergency department.
American Academy of Neurology/Child Neurology Society: **Practice Parameter: Pharmacological Treatment of Migraine Headache in Children and Adolescents (2004)**[14]	• Ibuprofen should be considered first-line therapy. Acetaminophen may also be used as an alternative option. • Sumatriptan nasal spray may also be used when the above analgesics fail; there is no data to support or contest the use of oral triptans in this population and inadequate data to draw conclusions on the efficacy of subcutaneous sumatriptan.
American Academy of Family Physicians/ American College of Physicians-American Society of Internal Medicine: **Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headaches (2002)**[15]	• NSAIDs are considered first-line therapy. • In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents include dihydroergotamine nasal spray, naratriptan, rizatriptan, subcutaneous or oral sumatriptan and zolmitriptan. • Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea with an antiemetic. • Acute therapies should be limited to no more than two times per week to guard against medication overuse headache, or drug-induced headache, per expert opinion.
European Federation of Neurological Societies: **European Federation of Neurological Societies Guideline on the Drug Treatment of Migraine-Revised Report of an European Federation of Neurological Societies Task Force (2009)**[16]	Acute treatment • Drugs of first choice for mild or moderate migraine attacks are analgesics. In order to prevent drug overuse headache, the intake of simple analgesics should be restricted to 15 days per month and the intake of combined analgesic to 10 days per month. • The use of antiemetics in acute migraine attacks is recommended to treat nausea and potential emesis and because it is assumed that these drugs improve the resorption of analgesics. Of note, there is no evidence to support this. Metoclopramide is recommended for adults and adolescents, and domperidone for children. • There are very few randomized, placebo-controlled trials on the efficacy of ergot alkaloids in acute migraine treatment. The advantage of these agents is a lower recurrence rate in some patients. The ergot alkaloids should be restricted to patients with very long migraine attacks or with regular recurrence. Use must be limited to 10 days per month. • Triptans are migraine medications and should not be applied in other headache disorders except cluster headache. The efficacy of all available triptans has been proven in large, placebo-controlled trials. Evidence suggests that the earlier the triptans are taken the better their efficacy; however, there is evidence to support that triptans can be effective at any time during a migraine attack. The use of triptans is restricted to maximum nine days per month by the International Headache Society criteria. A second dose of the triptan is effective in most cases; if the first dose of a triptan is not effective, the second dose is useless. Combining an NSAID with a triptan reduces headache recurrence. • A triptan can be efficacious even if another triptan was not. Subcutaneous sumatriptan has the fastest onset of efficacy (10 minutes). There is no evidence that different oral formulations, such as rapidly dissolving tablets, wafer forms or rapid release forms act earlier than others.

Clinical Guideline	Recommendation(s)
	• The highest recurrence rate is observed after subcutaneous sumatriptan. Naratriptan and frovatriptan show the lowest recurrence rates but have poor initial response rates. • There is weak evidence to suggest that intravenous valproic acid or flunarizine are efficacious in acute migraine attacks. Tramadol plus paracetamol has also shown efficacy in acute migraine attacks. • Opioids offer minor efficacy, and these agents, along with tranquilizers, should not be used in the acute treatment of migraine. Specific situations • First-line treatment of a severe migraine attack in an emergency situation consists of intravenous aspirin, with or without metoclopramide. Subcutaneous sumatriptan can be administered as an alternative. • Steroids are recommended for the treatment of status migrainosus. • Dihydroergotamine nasal spray may also be used for the treatment of severe migraine attacks. • Triptans, naproxen and oestrogen therapy have all been evaluated for the treatment of menstrual migraines. • There are no specific clinical trials evaluating drug treatment of migraine during pregnancy. Most of the drugs are contraindicated in pregnancy. If migraine occurs, only paracetamol is allowed during the whole period, while NSAIDs can be administered during the second trimester. • The only analgesics with evidence of efficacy for the acute migraine treatment in childhood and adolescents are ibuprofen and paracetamol. There is evidence supporting the use of triptans. Ergotamine should not be used.
American Academy of Neurology: **Acute and Preventative Pharmacologic Treatment of Cluster Headache (2010)**[17]	Acute treatment • Subcutaneous sumatriptan, zolmitriptan nasal spray and oxygen should be offered. • Sumatriptan nasal spray and zolmitriptan should be considered. • Cocaine/lidocaine and octreotide may be considered. • There is insufficient evidence to advise on the use of dihydroergotamine nasal spray, somatostatin and prednisone.

Conclusions

According to the International Headache Society, the two major subtypes of migraine include migraine without aura and migraine with aura. Migraine without aura is described as a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the focal neurological symptoms that usually precede or sometimes accompany the headache.[1] The serotonin (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.[21-96] These agents work via the release of vasoactive peptides, promotion of vasoconstriction 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.[2] While there is data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent "superiority" of one triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist.[21-26,35,36,45,47,53,56,57,69] Guidelines do not generally distinguish among the available triptans. Current guidelines recommend the use of triptans as initial therapy in the acute treatment of migraine attacks of moderate to severe severity, especially if "nonspecific" therapies have not provided adequate relief.[13-16] All available triptans are Food and Drug Administration (FDA)-approved for the acute treatment of migraine with or without aura.[3-12] Of note,

almotriptan is approved for use in children 12 years of age and older while rizatriptan is approved for use in children as young as six years of age.[3,7] The subcutaneous sumatriptan injection is also FDA-approved for the acute treatment of cluster headache episodes.[8] Current guidelines, recognize subcutaneous sumatriptan injection, as well as zolmitriptan nasal spray, as potential treatment options for the acute management of cluster headaches.[17]

Currently there are seven single-entity triptans (Axert® [almotriptan], Relpax® [eletriptan], Frova® [frovatriptan], Amerge® [naratriptan], Maxalt® and Maxalt MLT® [rizatriptan], Imitrex® [sumatriptan] and Zomig® and Zomig ZMT® [zolmitriptan]) and one fixed-dose triptan/nonsteroidal anti-inflammatory combination product (Treximet® (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of dosage formulations. Specifically, sumatriptan (nasal spray, 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.[16] Naratriptan, rizatriptan and sumatriptan are available generically in at least one dosage form or strength.[18]

References

1. International Headache Society (IHS). The international classification of headache disorders 2nd edition [monograph on the Internet]. Oxford (UK): IHS. 2004 [cited 2013 Apr 3]. Available from: http://ihs-classification.org/en/0_downloads/.
2. Bajwa ZH, Sabahat AS. Acute treatment of migraine in adults. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Apr 3]. Available from: http://www.utdol.com/utd/index.do.
3. Axert® [package insert]. Titusveille (NJ): Janssen Pharmaceuticals, Inc.; 2011 Sept.
4. Replax® [package insert]. New York (NY): Roerig; 2012 Jan.
5. Frova® [package insert]. Malvern (PA): Endo Pharmaceuticals Inc.; 2012 Dec.
6. Amerge® [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Mar.
7. Maxalt®, Maxalt-MLT® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2013 Jan.
8. Imitrex® injection [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
9. Imitrex® spray [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
10. Imitrex® tablets [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2012 Oct.
11. Zomig®, Zomig-ZMT® [package insert]. Wilmington (DE): AstraZeneca Pharmaceuticals LP; 2012 Sept.
12. Treximet® [package insert]. Research Triangle Park (NC): GlaxoSmithKline LLC; 2011 Apr.
13. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62.
14. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63:2215-24.
15. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002 Nov 19;137(10):840-9.
16. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81.
17. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventative pharmacologic treatment of cluster headache. Neurology. 2010;75:463-73.
18. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2013 [cited 2013 Apr 3]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
19. Gobel H, Linder V, Heinze A, Ribbat M, Deushl G. Acute therapy for cluster headache with sumatriptan: Findings of a one-year long-term study. Neurology. 1998;51(3):908-11.
20. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. Acta Neurol Scand. 1993;88(1):63-9.
21. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalagia. 2002;22:633-58.
22. Adelman JU, Lipton RB, Ferrari MD, Diener HC, McCarrol KA, Vandormael K, et al. Comparison of rizatriptan and other triptans on stringent measures of efficacy. Neurology. 2001;57:1377-83.
23. Colman SS, Brod MI, Krishnamurthy A, Rowland CR, Jirgens KJ, Gomez-Mancilla B. Treatment satisfaction, functional status, and health related quality of life of migrating patients treated with almotriptan or sumatriptan. Clin Ther. 2001;23(1):127-45.
24. Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, et al. Oral almotriptan vs oral sumatriptan in the abortive treatment of migraine: a double-blind, randomized, parallel-group, optimum-dose comparison. Arch Neurol. 2001;58(6):944-50.
25. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan is an effective and well-tolerated treatment for migraine pain: results of a randomized, double-blind, placebo-controlled clinical trial. Cephalagia. 2002;22(6):453-61.

26. Allais G, Acuto G, Cabarrocas X, Esbri R, Benedetto G, Bussone G. Efficacy and tolerability of almotriptan vs zolmitriptan for the acute treatment of menstrual migraine. Neurol Sci. 2006;27:S193-7.
27. Berenson F, Vasconcellos E, Pakalnis A, Mao L, Biondi M, Armstrong RB. Long-term, open-label safety study of oral almotriptan 12.5 mg for acute treatment of migraine in adolescents. Headache. 2010;50:795-807.
28. Cabarrocas X, Esbri R, Peris F, Ferrer P. Long-term efficacy and safety of oral almotriptan: interim analysis of a one-year open study. Headache. 2001;41:57-62.
29. Lanteri-Minet M, Diaz-Insa S, Leone M, Vila C, Clissold SP. Efficacy of almotriptan in early intervention for treatment of acute migraine in a primary care setting: the START*study. Int J Clin Pract. 2010;64(7):936-43.
30. Pascual J, Falk R, Docekal R, Prusinski A, Jelencsik J, Cabarrocas X, et al. Tolerability and efficacy of almotriptan in the long-term treatment of migraine. Eur Neurol. 2001;45:206-13.
31. Diener HC, Gendolla A. Part IV: effects of zolmitriptan orally disintegrating tablet on migraine symptoms and ability to perform normal activities: a post-marketing surveillance study in Germany. Curr Med Res Opin. 2005;21(Suppl 3):S18-24.
32. Dahlof CG, Tfelt-Hansen P, Massiou H, Fazekas A. Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. Neurology. 2001;57(10):1811-7.
33. Dahlof C, Pascual J, Dodick DW, Dowson AJ. Efficacy, speed of action and tolerability of almotriptan in the acute treatment of migraine: pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. Cephalagia. 2006;26:400-8.
34. Garcia-Ramos G, MacGregor EA, Hilliard B, Bordini CA, Leston J, Hettiarachchi J. Comparative efficacy of eletriptan vs naratriptan in the acute treatment of migraine. Cephalalgia. 2003;23:869-76.
35. Schoenen J, Pascual J, Rasmussen S, Sun W, Sikes C, Hettiarachchi J. Patient preference for eletriptan 80 mg vs subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. Eur J Neurol. 2005;25:108-17.
36. Sandrini G, Farkkila M, Burgess G, Forster E, Haughie S. Eletriptan vs sumatriptan a double-blind, placebo-controlled, multiple migraine attack study. Neurol. 2002;59:1210-7.
37. Mathew NT, Schoenen J, Winner P, Muirhead N, Sikes CR. Comparative efficacy of eletriptan 40 mg vs sumatriptan 100 mg. Headache. 2003;43:214-22.
38. Goadsby PJ, Ferrari MD, Olesen J, Stovner LJ, Senard JM, Jackson JC, et al. Eletriptan in acute migraine: a double blind, placebo-controlled comparison to sumatriptan. Neurology. 2000;54(1):156-61.
39. Mandema JW, Cox E, Alderman J. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain-results of a model-based meta-analysis that accounts for encapsulation. Cephalalgia. 2005;25:715-25.
40. Steiner TJ, Diener HC, MacGregor EA, Schoenen J, Muirhead N, Sikes CR. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. Cephalalgia. 2003;23:942-52.
41. Olesen J, Diener HC, Schoenen J, Hettiarachchi J. No effect of eletriptan administration during the aura phase of migraine. Eur J Neurol. 2004;11:671-7.
42. Farkkila M, Olesen J, Daholf C, Stovner LJ, Bruggen JP, Rasmussen S, et al. Eletriptan for the treatment of migraine in patients with previous poor response or tolerance to sumatriptan. Cephalagia. 2003;23:463-71.
43. Sheftell F, Ryan R, Pitman V. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. Headache. 2003;43:202-13.
44. Diener HC, Jansen JP, Reches A, Pascual J, Pitei D, Steiner TJ. Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot®) in the treatment of migraine: A multicentre, randomized, double-blind, placebo-controlled comparison. Eur Neurol. 2002;47:99-107.
45. Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, et al. A double-blind, randomized, multicenter, Italian study of frovatriptan vs almotriptan for the acute treatment of migraine. J Headache Pain. 2011;12:361-8.
46. Bartolini M. Giamberardino MA. Lisotto C. Martelletti P. Moscato D. Panascia B, et al. Frovatriptan vs almotriptan for acute treatment of menstrual migraine: analysis of a double-blind, randomized, cross-over, multicenter, Italian, comparative study. J Headache Pain. 2012 Jul;13(5):401-6.

47. Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, et al. Frovatriptan vs zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci. 2010;31(Suppl1):S51-4.
48. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled comparison of early use of frovatriptan in a migraine attack vs dosing after the headache has become moderate or severe. Curr Med Res Opin. 2004;20:1465-72.
49. Ryan R, Geraud G, Goldstein J, Cady R, Keywood C. Clinical efficacy of frovatriptan: placebo-controlled studies. Headache. 2002;(42 Suppl 2):S84-92.
50. Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology. 2004;63:261-9.
51. Gobel H, Heinze A. The Migraine Intervention Score – a tool to improve efficacy of triptans in acute migraine therapy: the ALADIN study. Int J Clin Pract. 2011 Aug;65(8):879-86.
52. Stark S, Spierings EL, McNeal S, Putnam GP, Bolden-Watson CP, O'Quinn S. Naratriptan efficacy in migraineurs who respond poorly to oral sumatriptan. Headache. 2000;40:513-20.
53. Gobel H, Winter P, Boswell D, Crisp A, Becker W, Hauge T, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. Clin Ther. 2000 Aug;22(8):981-9.
54. Ashcroft DM, Millson D. Naratriptan for the treatment of acute migraine: meta-analysis of randomized controlled trials. Pharmacoepidemiol Drug Saf. 2004;13(2):73-82.
55. Klassen A, Elkind A, Asgharnejad M, Webster C, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine: results of a double-blind, placebo-controlled, parallel-group study. Headache. 1997;37:640-5.
56. Ng-Mak DS, Hu XH, Bigal M. Migraine treatment with rizatriptan and almotriptan: a crossover study. Headache. 2009;49:655-62.
57. Láinez MJA, Evers S, Kinge E, Allais G, Allen C, Rao NA, et al. Preference for rizatriptan 10-mg wafer vs eletriptan 40-mg tablet for acute treatment of migraine. Cephalalgia. 2006;26:246-56.
58. Bomhof M, Paz J, Legg N, Allen C, Vandermael K, Patel K; Rizatriptan-Naratriptan Study Group. Comparison of rizatriptan 10 mg vs naratriptan 2.5 in migraine. Euro Neurol. 1999;42:173-9.
59. Kolodny A, Polis A, Battisti WP, Johnson-Pratt L, Skobieranda F. Comparison of rizatriptan 5 and 10 mg tablets and sumatriptan 25 and 50 mg tablets. Cephalagia. 2004;24:540-6.
60. Lipton RB, Pascual J, Goadsby PJ, Massiou H, McCarroll KA, Vandormael K, et al. Effect of rizatriptan and other triptans on the nausea symptom of migraine: a post hoc analysis. Headache. 2001;41(8):754-63.
61. Seeburger JL, Cady RK, Winner P, MacGregor A, Valade D, Zhang Y, et al. Rizatriptan for treatment of acute migraine in patients taking topiramate for migraine prophylaxis. Headache. 2012;52:57-67.
62. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. Headache. 2004;44:669-73.
63. Cady RK, Martin VT, Geraud G, Rodgers A, Zhang Y, Ho AP, et al. Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response. Headache. 2009 May;49(5):687-96.
64. Ferrari MD, Loder E, McCarroll KA, Lines CR. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. Cephalalgia. 2001;21:129-36.
65. Oldman AD, Smith LA, McQuay HJ, Moore RA, Derry S. Rizatriptan for acute migraine. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.:CD003221. DOI:10.1002/14651858.CD003221.pub2.
66. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD008615.
67. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD009665.
68. Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD009663.
69. Loder E, Brandes JL, Silberstein S, Skobieranda F, Bohidar N, Wang L, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. Headache. 2001 Sept;41(8):745-53.

70. Gershovich OE, Billups SJ, Delate T, Hoffman CK, Carroll N. Assessment of clinical, service, and cost outcomes of a conversion program of sumatriptan to rizatriptan ODT in primary care patients with migraine headaches. J Manag Care Pharm. 2006 Apr;12:246-53.
71. Cutler N, Mushet GR, Davis R, Clements B, Whitcher L. Oral sumatriptan for the acute treatment of migraine: evaluation of three dosage strengths. Neurology.1995;45(Suppl 7):S5-9.
72. Winner P, Landy S, Richardson M, Ames M. Early intervention in migraine with sumatriptan tablets 50 vs 100 mg: a pooled analysis of data from six clinical trials. Clin Ther. 2005;27:1785-94.
73. Cady RK, Sheftell F, Lipton RB, Quinn S, Jones M, Putnam G, et al. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. Clin Ther. 2000;22:1035-48.
74. Djupesland PG, Docekal P. Intranasal sumatriptan powder delivered by a novel breath-actuated bi-directional device for the acute treatment of migraine: a randomized, placebo-controlled study. Cephalagia. 2010;30(8):933-42.
75. Salonen R, Ashford E, Dahlöf C, Dawson R, Gilhus NE, Luben V, et al. Intranasal sumatriptan for the acute treatment of migraine. J Neurol. 1994;241:463-9.
76. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. JAMA. 1991;265(21):2831-5.
77. No authors listed. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. Sumatriptan Auto-Injector Study Group. Eur Neurol. 1991;31:323-31.
78. Cady RK, Aurora SK, Brandes JL, Rothrock JF, Myers JA, Fox AW, et al. Satisfaction with and confidence in needle-fee subcutaneous sumatriptan in patients currently treated with triptans. Headache. 2011;51:1202-11.
79. Rothrock JF, Cady RK, Aurora SK, Brandes JL, Myers JA, Fox AW, et al. Needle-free subcutaneous sumatriptan for triptan users requiring a change in migraine therapy: efficacy and impact on patient-rated functionality, satisfaction, and confidence. Curr Med Res Opin. 2011 Nov;27(11):2185-91.
80. Boureau F, Kappos L, Schoenen J, Esperanca P, Ashford E. A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine (abstract). Int J Clin Pract. 2000 Jun;54(5):281-6.
81. Touchan J, Bertin L, Pilgrim AJ, Ashford E, Bes A. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. Neurology. 1996;47:361-5.
82. Smith T, Blumenthal H, Diamond M, Mauskop A, Ames M, McDonald S, et al. Sumatriptan/naproxen sodium for migraine: efficacy, health related quality of life, and satisfaction outcomes. Headache. 2007;47:683-92.
83. Winner P, Cady R, Ruoff G, Frishberg B, Alexander WJ, Zhang Y, et al. Twelve-month tolerability and safety of sumatriptan-naproxen sodium for the treatment of acute migraine. Mayo Clin Proc. 2007 Jan;82(1):61-8.
84. Landy S, Hoagland R, Hoagland NA. Sumatriptan-naproxen migraine efficacy in allodynic patients: early intervention. Headache. 2012;52:133-9.
85. Silberstein S, Mannix L, Goldstein J, Couch J, Byrd SC, Ames MH, et al. Multi mechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. Neurology. 2008;71:114-21.
86. Lipton RB, Dodick DW, Adelman JU, Kaniecki RG, Lener SE, White JD, et al. Consistency of response to sumatriptan/naproxen sodium in a placebo-controlled, crossover study. Cephalagia. 2009;29:826-36.
87. Mathew NT, Landy S, Stark S, Tietjen GE, Derosier FJ, White J. Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life. Headache. 2009;49:971-82.
88. Brandes J, Kudrow D, Stark S, O'Carroll C, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007 April;297:1443-54.
89. Landy S, DeRossett S, Rapoport A, Rothrock J, Ames MH, McDonald SA, et al. Two double-blind, multicenter, randomized, placebo-controlled, single-dose studies of sumatriptan/naproxen sodium in the acute treatment of migraine: function, productivity, and satisfaction outcomes. MedGenMed. 2007 Jun;9(2):53.
90. Geraud G, Olsen J, Pfaffenrath V, Tfelt-Hansen P, Zupping R, Diener HC, Sweet R. Comparison of the efficacy of zolmitriptan and sumatriptan: issues in migraine trial design. Cephalagia. 2000;20:30-8.

91. Dowson AJ, Almqvist P. Part III: The convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. Curr Med Res Opin. 2005;21(Suppl 3):S13-7.
92. Diener HC, Gendolla A, Gerbert I, Beneke M. Almotriptan in migraine patients who respond poorly to oral sumatriptan: a double-blind, randomized trial. Headache. 2005;45:874-82.
93. Dowson AJ, Charlesworth BR, Prudy A, Becker WJ, Boes-Hansen S, Farkkila M. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. CNS Drugs. 2003;17:839-51.
94. Loder EW, Dowson AJ, Spierings ELH. Part II: Clinical efficacy and tolerability of zolmitriptan orally disintegrating tablet in the acute treatment of migraine. Curr Med Res Opin. 2005;21(Suppl 3):S8-12.
95. Spierings ELH, Rapoport AM, Dodick DW, Charlesworth B. Acute treatment of migraine with zolmitriptan 5 mg orally disintegrating tablet. CNS Drugs. 2004;18:1133-41.
96. Charlesworth BR, Dowson AJ, Purdy A, Becker WJ, Boes-Hansen S, Farkkila M. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomized, double-blind, placebo-controlled, dose-ranging study vs zolmitriptan tablet. CNS Drugs. 2003;17:653-67.