Rizatriptan Benzoate *(BANM, USAN, pINNM)*

Benzoato de rizatriptán; MK-0462; MK-462; Rizatriptan, Benzoate de; Rizatriptani Benzoas. 3-[2-(Dimethylamino)ethyl]-5-(1*H*-1,2,4-triazol-1-ylmethyl)indole monobenzoate; Dimethyl{2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)indol-3-yl]ethyl}amine monobenzoate.

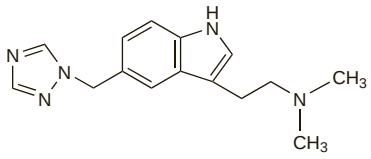
Ризатриптана Бензоат

$C_{15}H_{19}N_5,C_7H_6O_2$ = 391.5.

CAS — 144034-80-0 (rizatriptan); 145202-66-0 (rizatriptan benzoate).

ATC — N02CC04.

ATC Vet — QN02CC04.



(rizatriptan)

Adverse Effects and Precautions

As for Sumatriptan, p.625. Toxic epidermal necrolysis has also been reported with rizatriptan.

Rizatriptan should not be used in patients with severe hepatic or renal impairment and should be given with caution to patients with mild or moderate hepatic or renal impairment.

Interactions

As for Sumatriptan, p.626.

Propranolol increases plasma-rizatriptan concentrations and it is recommended that lower doses of rizatriptan should be used in patients receiving both drugs (see Uses and Administration, below).

Pharmacokinetics

After oral doses, peak plasma-rizatriptan concentrations are obtained in about 1 to 1.5 hours or 1.6 to 2.5 hours depending on the formulation. Bioavailability is about 40 to 45%. Food may delay the time to peak plasma concentrations of the tablet formulation by about 1 hour. Plasma protein binding is low (14%).

Rizatriptan is metabolised primarily by monoamine oxidase type A to the inactive indole acetic acid derivative. The active metabolite *N*-monodesmethyl-rizatriptan is formed to a minor degree; other minor metabolites are also produced. About 14% of an oral dose is excreted in the urine as unchanged rizatriptan, 51% as the indole acetic acid metabolite, and 1% as *N*-monodesmethyl-rizatriptan. The plasma half-life is about 2 to 3 hours.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Lee Y, *et al.* Pharmacokinetics and tolerability of oral rizatriptan in healthy male and female volunteers. *Br J Clin Pharmacol* 1999; **47:** 373–8.
2. Goldberg MR, *et al.* Rizatriptan, a novel 5-HT agonist for migraine: single- and multiple-dose tolerability and pharmacokinetics in healthy subjects. *J Clin Pharmacol* 2000; **40:** 74–83.
3. Vyas KP, *et al.* Disposition and pharmacokinetics of the antimigraine drug, rizatriptan, in humans. *Drug Metab Dispos* 2000; **28:** 89–95.
4. Swan SK, *et al.* Pharmacokinetic profile of rizatriptan 10-mg tablet and 10-mg orally disintegrating tablet administered with or without water in healthy subjects: an open-label, randomized, single-dose, 3-period crossover study. *J Clin Pharmacol* 2006; **46:** 172–8.

Uses and Administration

Rizatriptan is a selective serotonin (5-HT_1) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of the headache phase of migraine attacks. It should not be used for prophylaxis. Rizatriptan is given as the benzoate, and doses are expressed in terms of the base; rizatriptan benzoate 14.53 mg is equivalent to about 10 mg of rizatriptan.

The usual dose in the UK of rizatriptan is 10 mg orally. If this is ineffective, a second dose should not be taken for the same attack. If symptoms recur after an initial response, a further dose of 10 mg may be taken after an interval of at least 2 hours. In the USA a dose of 5 or 10 mg is used. The recommended maximum dose in 24 hours is 20 mg in the UK and 30 mg in the USA. A reduced dose of 5 mg is recommended in patients also receiving propranolol, with the maximum dose in 24 hours reduced to 10 mg in the UK and 15 mg in the USA. It is also recommended that doses of the 2 drugs should be separated by at least 2 hours. For doses in hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. In patients with mild to moderate hepatic or renal impairment, the dose of rizatriptan should be reduced to 5 mg. If the headache recurs following an initial response, a further dose of 5 mg may be taken after an interval of at least 2 hours. The recommended maximum dose in 24 hours in these patients is 10 mg in the UK. Rizatriptan should not be used in patients with severe hepatic or renal impairment.

Migraine. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Dooley M, Faulds D. Rizatriptan: a review of its efficacy in the management of migraine. *Drugs* 1999; **58:** 699–723. Correction. *ibid.* 2000; **59:** 179.
2. Wellington K, Plosker GL. Rizatriptan: an update of its use in the management of migraine. *Drugs* 2002; **62:** 1539–74.
3. Pascual J. A review of rizatriptan, a quick and consistent 5-HT1B/1D agonist for the acute treatment of migraine. *Expert Opin Pharmacother* 2004; **5:** 669–77.
4. Ahonen K, *et al.* A randomized trial of rizatriptan in migraine attacks in children. *Neurology* 2006; **67:** 1135–40.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Maxalt†; ***Austria:*** Maxalt; Rizalief; ***Belg.:*** Maxalt; ***Braz.:*** Maxalt; ***Canad.:*** Maxalt; ***Chile:*** Maxalt; ***Cz.:*** Maxalt†; ***Denm.:*** Maxalt; ***Fin.:*** Maxalt; ***Ger.:*** Maxalt; ***Gr.:*** Maxalt; Modinol†; ***Hung.:*** Maxalt†; ***India:*** Rizact; ***Israel:*** Rizalt; ***Ital.:*** Maxalt; Rizaliv; ***Mex.:*** Maxalt; ***Neth.:*** Maxalt; Rizatan; ***Norw.:*** Maxalt; ***NZ:*** Maxalt; ***Pol.:*** Maxalt; ***Port.:*** Maxalt; Migrof; ***S.Afr.:*** Maxalt; ***Spain:*** Maxalt; ***Swed.:*** Maxalt; ***Switz.:*** Maxalt; ***UK:*** Maxalt; ***USA:*** Maxalt; ***Venez.:*** Maxalt.

Sumatriptan *(BAN, rINN)*

GR-43175X; Sumatriptaani; Sumatriptán; Sumatriptanum. 3-(2-Dimethylaminoethyl)indol-5-yl-*N*-methylmethanesulfonamide.

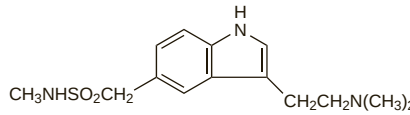
Суматриптан

$C_{14}H_{21}N_3O_2S$ = 295.4.

CAS — 103628-46-2.

ATC — N02CC01.

ATC Vet — QN02CC01.



Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Protect from light.

USP 31 (Sumatriptan). A white to pale yellow powder. Very slightly soluble in water. Store in airtight containers at below 30°. Do not allow to freeze. Protect from light.

Sumatriptan Succinate *(BANM, USAN, rINNM)*

GR-43175C; Succinato de sumatriptán; Sumatriptaanisuksinaatti; Sumatriptan, succinate de; Sumatriptani Succcinas; Sumatriptani succinas; Sumatriptano sukcinatas; Sumatriptansuccinat; Sumatriptan-sukcinát; Sumatriptanum Succinas; Sumatryptanu bursztynian; Szumatriptánszukcinát.

Суматриптана Суксинат

$C_{14}H_{21}N_3O_2S,C_4H_6O_4$ = 413.5.

CAS — 103628-47-3 (sumatriptan hemisuccinate); 103628-48-4 (sumatriptan succinate).

ATC — N02CC01.

ATC Vet — QN02CC01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 5.3. Protect from light.

USP 31 (Sumatriptan Succinate). A white or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers at a temperature not exceeding 30°. Do not allow to freeze. Protect from light.

Stability. Oral liquid preparations of sumatriptan 5 mg/mL prepared from crushed sumatriptan succinate tablets in 3 different syrups were stable for at least 21 days when stored at 4° and protected from light.[1]

1. Fish DN, *et al.* Stability of sumatriptan succinate in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 1619–22.

Adverse Effects

The most commonly reported adverse effects of serotonin (5-HT_1) agonists such as sumatriptan include dizziness, flushing, weakness, drowsiness, and fatigue. Nausea and vomiting may occur. Dyspnoea and sensory disturbance including paraesthesia and hypoaesthesia have been reported. Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. Transient increases in blood pressure may occur soon after treatment. Hypotension, bradycardia or tachycardia, palpitations, Raynaud's syndrome, and ischaemic colitis have been reported. Visual disturbances have also occurred.

Medication-overuse headache has been reported with sumatriptan and may necessitate withdrawal of the drug. Sumatriptan has occasionally been associated with minor disturbances in liver function. There have also been rare reports of seizures with sumatriptan. Hypersensitivity reactions ranging from skin rashes to, more rarely, anaphylaxis have occurred.

Transient pain at the injection site is common after subcutaneous sumatriptan injections; stinging, burning, erythema, bruising, and bleeding have also been reported. Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use.

Incidence of adverse effects. In a Dutch postmarketing survey[1] completed by 1187 patients the most common adverse reactions attributed to sumatriptan were paraesthesia (reported by 11.7% of patients), dizziness (8.1%), feeling of heaviness (8.0%), chest pain (7.9%), nausea and/or vomiting (7.3%), drowsiness/sedation (7.0%), flushing (5.1%), fatigue (4.6%), pressure in throat (3.3%), headache (3.1%), injection site reaction (3.0%), palpitations (2.8%), abdominal pain (2.6%), muscle pain (2.4%), and dyspnoea (2.2%).

The safety and tolerability of the triptans have been reviewed.[2]

1. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47:** 305–9.
2. Nappi G, *et al.* Tolerability of the triptans: clinical implications. *Drug Safety* 2003; **26:** 93–107.

Effects on the cardiovascular system. About 10 months after sumatriptan injection had been made available commercially, the UK CSM noted that it had received 34 reports of pain or tightness in the chest and 2 reports of myocardial ischaemia.[1] The Netherlands Centre for Monitoring of Adverse Reactions to Drugs declared about the same time that it had received 12 reports of chest or anginal pain mostly associated with oral sumatriptan.[2] A later postmarketing survey based on data from Dutch general practitioners identified chest pain in 1.3% of 1727 patients,[3] a figure considered to be lower than that seen in earlier studies, but in a subsequent questionnaire completed by 1187 of these patients 7.9% reported chest pain.[4] The Australian Adverse Drug Reactions Advisory Committee (ADRAC)[5] stated in December 1994 that it had received 114 reports of chest pain since sumatriptan had been marketed in mid 1992. Most patients had recovered quickly but 2 had died. The first developed a fatal myocardial infarction after coronary artery dissection but the causal relation with sumatriptan was unclear. The second patient who had hypertrophic obstructive cardiomyopathy developed ventricular fibrillation a few hours after the onset of chest pain and this led to fatal cardiac arrest.

One group of workers[6] who studied the effect of sumatriptan 16 mg given subcutaneously suggested that the symptoms of chest pain might be due to an effect of sumatriptan on oesophageal function, but others have argued against this suggestion.[7] ADRAC[5] considered that the reaction in the 28 reports of throat tightness they had received by December 1994 was a different reaction to that of chest pain, and probably resulted from changes in oesophageal motility.

Several reports have provided details of individual cases of the adverse cardiovascular effects of sumatriptan including arrhythmias (ventricular tachycardia,[8] ventricular fibrillation,[8,9] or atrial fibrillation[10]), acute myocardial infarction,[11-15] and unstable an-

gina.[16] Most of these reports concerned subcutaneous sumatriptan, but myocardial infarction occurred in 1 case,[13] and fatal cardiac arrhythmia in another,[9] after oral use. Acute myocardial infarction[11] and cardiac arrhythmias[9] have been reported in patients with no predisposing factors.

A review[17] of published reports on chest pain as well as relevant data held by the UK manufacturer considered that the risk of myocardial ischaemia following vasoconstriction induced by sumatriptan was small. However, the contra-indications and cautions given under Precautions, below, should be observed. A recent study[18] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of cardiovascular death in those patients treated with serotonin agonists.

1. CSM. Sumatriptan (Imigran) and chest pain. *Current Problems 34* 1992. Also available at: http:// www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 22/08/08)
2. Stricker BHC. Coronary vasospasm and sumatriptan. *BMJ* 1992; **305:** 118.
3. Ottervanger JP, *et al.* Postmarketing study of cardiovascular adverse reactions associated with sumatriptan. *BMJ* 1993; **307:** 1185.
4. Ottervanger JP, *et al.* Adverse reactions attributed to sumatriptan: a postmarketing study in general practice. *Eur J Clin Pharmacol* 1994; **47:** 305–9.
5. Boyd IW, Rohan AP. Sumatriptan-induced chest pain. *Lancet* 1994; **344:** 1704–5.
6. Houghton LA, *et al.* Is chest pain after sumatriptan oesophageal in origin? *Lancet* 1994; **344:** 985–6.
7. Hood S, *et al.* Sumatriptan-induced chest pain. *Lancet* 1994; **344:** 1500–1.
8. Curtin T, *et al.* Cardiorespiratory distress after sumatriptan given by injection. *BMJ* 1992; **305:** 713–14.
9. Laine K, *et al.* Fatal cardiac arrhythmia after oral sumatriptan. *Headache* 1999; **39:** 511–12.
10. Morgan DR, *et al.* Atrial fibrillation associated with sumatriptan. *BMJ* 2000; **321:** 275.
11. Ottervanger JP, *et al.* Transmural myocardial infarction with sumatriptan. *Lancet* 1993; **341:** 861–2.
12. Kelly KM. Cardiac arrest following use of sumatriptan. *Neurology* 1995; **45:** 1211–13.
13. O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. *Neurology* 1995; **45:** 2274–6.
14. Mueller L, *et al.* Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996; **36:** 329–31.
15. Main ML, *et al.* Cardiac arrest and myocardial infarction immediately after sumatriptan injection. *Ann Intern Med* 1998; **128:** 874.
16. Walton-Shirley M, *et al.* Unstable angina pectoris associated with Imitrex therapy. *Cathet Cardiovasc Diagn* 1995; **34:** 188.
17. Hillis WS, MacIntyre PD. Drug reactions: sumatriptan and chest pain. *Lancet* 1993; **341:** 1564–5. Correction. *ibid.*; **342:** 1310.
18. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the cerebrovascular system. Adverse cerebrovascular effects have been reported after the use of subcutaneous sumatriptan including hemiparesis,[1] stroke,[2,3] and intracerebral haemorrhage.[4] Cerebral vasospasm has also been reported[5] with the use of oral sumatriptan. However, a study[6] of over 63 500 migraine patients in the UK General Practice Research Database failed to find an increased risk of stroke in those patients treated with serotonin agonists.

1. Luman W, Gray RS. Adverse reactions associated with sumatriptan. *Lancet* 1993; **341:** 1091–2.
2. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.
3. Meschia JF, *et al.* Reversible segmental cerebral arterial vasospasm and cerebral infarction: possible association with excessive use of sumatriptan and Midrin. *Arch Neurol* 1998; **55:** 712–14.
4. Edwards KR, *et al.* Intracerebral hemorrhage associated with sumatriptan. *Headache* 1995; **35:** 309.
5. Dash S, *et al.* Cerebral vasospasm from sumatriptan. *Neurology* 2004; **63:** 2128.
6. Hall GC, *et al.* Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; **62:** 563–8.

Effects on the gastrointestinal tract. Ischaemic colitis and mesenteric ischaemia have been reported in a few patients receiving sumatriptan,[1-3] including repeated episodes in 2 patients,[2] each within hours of a dose; some of these episodes were associated with doses above the recommended daily maximum.[2]

Oesophageal constriction or throat tightness has been reported in some patients taking sumatriptan and may be due to a direct effect on the oesophagus (see Effects on the Cardiovascular System, above).

1. Knudsen JF, *et al.* Ischemic colitis and sumatriptan use. *Arch Intern Med* 1998; **158:** 1946–8.
2. Liu JJ, Ardolf JC. Sumatriptan-associated mesenteric ischemia. *Ann Intern Med* 2000; **132:** 597.
3. Naik M, *et al.* Sumatriptan-associated ischemic colitis. *Dig Dis Sci* 2002; **47:** 2015–16.

Effects on the respiratory system. See Asthma under Precautions, below.

Hypersensitivity. Reactions to sumatriptan such as skin rashes and, more rarely, anaphylaxis have been noted by the manufacturer. Published reports include angioedema occurring in a patient 5 minutes after subcutaneous sumatriptan,[1] and urticaria occurring 20 to 24 hours after oral or subcutaneous sumatriptan in another patient.[2]

1. Dachs R, Vitillo J. Angioedema associated with sumatriptan administration. *Am J Med* 1995; **99:** 684–5.
2. Pradalier A, *et al.* Delayed urticaria with sumatriptan. *Cephalalgia* 1996; **16:** 280–1.

Medication-overuse headache. Sumatriptan may have a similar risk of misuse to that associated with analgesics and ergotamine compounds in patients with medication-overuse headache (p.616). There have been reports[1-3] of patients using one or more daily doses of sumatriptan to control migraine. Many of the patients had a history of abuse of other antimigraine drugs and were using sumatriptan to prevent recurrence of headache. Whether misuse of sumatriptan was due to addiction or rebound headache as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache.[4] One study[5] and an anecdotal report[6] suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation.

The development of medication-overuse headache has also been reported with naratriptan and zolmitriptan.[7]

1. Osborne MJ, *et al.* Is there a problem with long term use of sumatriptan in acute migraine? *BMJ* 1994; **308:** 113.
2. Kaube H, *et al.* Sumatriptan. *BMJ* 1994; **308:** 1573–4.
3. Gaist D, *et al.* Misuse of sumatriptan. *Lancet* 1994; **344:** 1090.
4. Ottervanger JP, *et al.* Pattern of sumatriptan use and overuse in general practice. *Eur J Clin Pharmacol* 1996; **50:** 353–5.
5. Sullivan JT, *et al.* Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992; **52:** 635–42.
6. Bakshi R, Yan-Go FL. Prolonged marijuana-like dysphoria after subcutaneous sumatriptan. *Ann Pharmacother* 1996; **30:** 683.
7. Limmroth V, *et al.* Headache after frequent use of serotonin agonists zolmitriptan and naratriptan. *Lancet* 1999; **353:** 378.

Precautions

Sumatriptan and other serotonin (5-HT_1) agonists should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine.

Serotonin (5-HT_1) agonists are contra-indicated in patients with uncontrolled hypertension, ischaemic heart disease (coronary artery disease), a history of myocardial infarction, coronary vasospasm (Prinzmetal's angina), peripheral vascular disease, or a previous cerebrovascular accident or transient ischaemic attack. Unrecognised cardiovascular disease should be excluded before the use of serotonin (5-HT_1) agonists in postmenopausal women, men over 40 years of age, and those with risk factors for ischaemic heart disease. If chest pain and tightness occur during use, appropriate investigations should be performed. Sumatriptan should not be used intravenously because of the increased risk of producing coronary vasospasm.

Drowsiness may occur after treatment with serotonin (5-HT_1) agonists and patients thus affected should not drive or operate machinery.

Sumatriptan should be used with caution in patients with hepatic or renal impairment, and should generally be avoided if impairment is severe.

There have been rare reports of seizures after use of sumatriptan and it should therefore be used with caution in patients with a history of epilepsy or other conditions predisposing to seizures. Patients with hypersensitivity to sulfonamides may exhibit a similar reaction to sumatriptan.

Asthma. The manufacturers reviewed data from more than 75 clinical studies of sumatriptan involving 12 701 patients and reported[1] that the incidence of adverse events related to asthma did not differ between patients with or without the condition. Earlier there had been concern over the safety of sumatriptan in patients with asthma after 2 reports of bronchospasm and a report of a patient with asthma who died during a study of sumatriptan although the patient had not received sumatriptan in the month before her death.

1. Lloyd DK, Pilgrim AJ. The safety of sumatriptan in asthmatic migraineurs. *Cephalalgia* 1993; **13:** 201–4.

Breast feeding. No adverse effects have been observed in breast-feeding infants whose mothers were receiving sumatriptan, and the American Academy of Pediatrics considers that it is therefore usually compatible with breast feeding.[1] However, the manufacturers have suggested that infant exposure can be minimised by avoiding breast feeding for 12 hours after treatment.

The distribution of sumatriptan into breast milk after a 6-mg subcutaneous dose has been studied in 5 lactating mothers.[2] The mean total recovery of sumatriptan in breast milk was estimated to be 14.4 micrograms or 0.24% of the dose. It was calculated that on a weight-adjusted basis an infant could receive a maximum of 3.5% of the maternal dose.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/06/04)
2. Wojnar-Horton RE, *et al.* Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; **41:** 217–21.

Cerebrovascular disorders. A patient with a superior sagittal sinus thrombosis who presented with headache and was misdiagnosed as having migraine variant developed a cortical stroke within minutes of a second 6-mg subcutaneous injection of sumatriptan.[1] The importance of establishing a diagnosis of typical migraine or cluster headache before using sumatriptan was emphasised and caution given against its use in any patient who may have unstable cerebrovascular disease or raised intracranial pressure. Additionally, there was no clinical evidence that a second injection would relieve a headache when the initial injection had been ineffective.

1. Cavazos J, *et al.* Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994; **343:** 1105–6.

Pregnancy. Sumatriptan crosses the placenta; however, only a very small quantity reaches the fetus. A literature review concluded that exposure to sumatriptan in pregnancy posed no additional risk of birth defects compared with that in the general population,[1] but as for other drugs sumatriptan should only be used in pregnancy when the benefit justifies the potential risk to the fetus.

1. Hilaire ML, *et al.* Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004; **38:** 1726–30.

Interactions

Sumatriptan and other serotonin (5-HT_1) agonists should not be given with ergotamine or related compounds (including methysergide) since there is an increased risk of vasospastic reactions. In addition, a delay is advised before starting a serotonin (5-HT_1) agonist in patients who have been receiving ergotamine or related compounds: sumatriptan, almotriptan, eletriptan, frovatriptan, rizatriptan, or zolmitriptan should not be given until at least 24 hours after stopping the use of preparations containing ergotamine. Conversely, ergotamine should not be given until 6 hours after stopping these drugs or at least 24 hours in the case of eletriptan and frovatriptan. Serotonin (5-HT_1) agonists should not be given together.

Sumatriptan or rizatriptan should not be used with, and for 2 weeks after stopping, an MAOI. Use with the selective monoamine oxidase type B inhibitor selegiline is thought unlikely to provoke an interaction, but see p.817. Opinion varies on the concomitant use of zolmitriptan and inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A whereas in the USA it contra-indicates such combinations. There have been rare reports of serotonin syndrome associated with the use of triptan serotonin (5-HT_1) agonists with SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), but see also under Antidepressants, below.

◊ Oral sumatriptan appeared to delay gastric emptying and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients.[1]

1. Rani PU, *et al.* Sumatriptan delays paracetamol absorption in migraine patients. *Clin Drug Invest* 1996; **11:** 300–304.

Antidepressants. Sumatriptan and rizatriptan are metabolised mainly by monoamine oxidase type A and licensed product information advises that patients taking *MAOIs*, including reversible selective type A inhibitors such as moclobemide, should not be given triptan serotonin (5-HT_1) agonists. Clearance of zolmitriptan was decreased after moclobemide and in the UK a reduced dose of zolmitriptan is advised if the drug is used with an inhibitor of monoamine oxidase type A; in the USA, the use of these drugs together is contra-indicated. *SSRIs* such as fluoxetine may also interact with serotonin (5-HT_1) agonists with an increased risk of serotonin syndrome (p.416), and it has been suggested that *lithium* and sumatriptan may interact similarly. However, a review of the use of sumatriptan with MAOIs, SSRIs, or lithium found little evidence of an increased risk of serotonin

syndrome.[1] It was concluded that most patients tolerate the combination of sumatriptan and an SSRI or lithium without incident. However, it was suggested that the use of sumatriptan with an MAOI should continue to be avoided until further data supporting safety becomes available. As there have since been rare reports of serotonin syndrome associated with the use of triptans with SSRIs or *serotonin and noradrenaline reuptake inhibitors (SNRIs)*, licensed product information for the triptans states that when such use is clinically warranted, appropriate observation of the patient is advised, particularly when starting treatment, with dose increases, or with addition of another serotonergic drug. Product information for zolmitriptan also advises a reduction in dosage if it is given with fluvoxamine as the latter may inhibit zolmitriptan metabolism through its effects on the cytochrome P450 isoenzyme CYP1A2.

Increased serotonergic effects with increased incidence of adverse effects have been reported following the use of *St John's wort* with triptans.[2] Patients should be advised to stop taking St John's wort if treatment with a serotonin (5-HT_1) agonist is necessary.

1. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. *Ann Pharmacother* 1998; **32:** 33–8.
2. CSM/MCA. Reminder: St John's wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Antimigraine drugs. Although the efficacy and tolerability of subcutaneous sumatriptan in the acute treatment of migraine did not appear to be affected in patients already taking *dihydroergotamine* orally for migraine prophylaxis,[1] the bioavailability of oral dihydroergotamine is low and it could not be assumed that it was safe to use parenteral dihydroergotamine with sumatriptan.[2] Licensed product information for sumatriptan contra-indicates its use with *ergotamine* or other related compounds and also recommend that it should not be given until at least 24 hours after stopping ergotamine or related compounds (see Interactions, above).

Acute myocardial infarction has been reported[3] in a premenopausal woman with controlled hypertension and no known coronary artery disease after subcutaneous use of sumatriptan within a few hours of taking *methysergide* by mouth.

1. Henry P, *et al.* Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. *Headache* 1993; **33:** 432–5.
2. Campbell JK. [Editor's comment]. *Headache* 1993; **33:** 435.
3. Liston H, *et al.* The association of the combination of sumatriptan and methysergide in myocardial infarction in a premenopausal woman. *Arch Intern Med* 1999; **159:** 511–13.

Antipsychotics. For reference to a potential interaction between sumatriptan and *loxapine*, see Chlorpromazine, p.974.

Pharmacokinetics

Sumatriptan is rapidly but incompletely absorbed when given orally and undergoes first-pass metabolism, resulting in a low absolute bioavailability of about 14%. Peak plasma concentrations after oral doses are achieved in about 2 hours. Bioavailability is much higher (96%) after subcutaneous doses with peak concentrations occurring within 25 minutes. Bioavailability after intranasal doses is 16% of that achieved subcutaneously, with peak concentrations occurring in about 1.5 hours. Plasma protein binding is low at about 14 to 21%.

The elimination half-life of sumatriptan is about 2 hours. Sumatriptan is extensively metabolised in the liver predominantly by monoamine oxidase type A and is excreted mainly in the urine as the inactive indole acetic acid derivative and its glucuronide. Sumatriptan and its metabolites also appear in the faeces. Small amounts of sumatriptan are distributed into breast milk (see Breast Feeding, above).

◊ Reviews.

1. Scott AK. Sumatriptan clinical pharmacokinetics. *Clin Pharmacokinet* 1994; **27:** 337–44.
2. Lacey LF, *et al.* Single dose pharmacokinetics of sumatriptan in healthy volunteers. *Eur J Clin Pharmacol* 1995; **47:** 543–8.
3. Fuseau E, *et al.* Clinical pharmacokinetics of intranasal sumatriptan. *Clin Pharmacokinet* 2002; **41:** 801–11.
4. Moen MD, Keating GM. Sumatriptan fast-disintegrating/rapid-release tablets. *Drugs* 2006; **66:** 883–90.

Uses and Administration

Sumatriptan is a selective serotonin agonist that acts at 5-HT_1 receptors and produces vasoconstriction of cranial arteries. Drugs like sumatriptan, which are commonly known as triptans, are believed to act mainly at 5-HT_{1B} and 5-HT_{1D} subtype receptors and are therefore sometimes referred to as $5HT_{1B/1D}$-receptor agonists.

Sumatriptan is used for the acute treatment of migraine attacks and of cluster headache. It should not be used for prophylaxis. It may be given orally or subcutaneously as the succinate and intranasally as the base. Doses are expressed in terms of the base; sumatriptan succinate 70 mg is equivalent to about 50 mg of sumatriptan.

For the acute treatment of **migraine** sumatriptan should be used as soon as possible after the onset of the headache phase, but efficacy is independent of the duration of the attack before starting treatment. If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

- It is given *orally* to adults aged 18 years and over; the recommended dose in the UK is 50 mg, although some patients may require 100 mg. A clinical response can be expected after about 30 minutes. If symptoms recur after an initial response, further doses may be given provided that there is a minimum interval of 2 hours between doses and that not more than 300 mg is taken in any 24-hour period. In the USA a lower dose of 25 mg may be used, although some patients require 50 or 100 mg. This may be followed by a second dose of up to 100 mg if the headache returns or the patient has a partial response provided that the total daily dose does not exceed the recommended maximum of 200 mg. A minimum interval of 2 hours is recommended between doses. For oral doses in children and hepatic impairment, see below.
- When used *intranasally* a clinical response can be expected in 15 minutes. In the UK, patients aged 18 years and over may be given a single dose of 20 mg into one nostril, although 10 mg may be effective in some patients. In the USA, a dose of 5, 10, or 20 mg may be used. If symptoms recur, a second dose may be given at least 2 hours after the first dose. Not more than 40 mg should be used in a 24-hour period. For intranasal doses in adolescents, see below.
- In patients aged 18 years and over sumatriptan may be self-administered by *subcutaneous injection* in a single dose of 6 mg; a clinical response may be expected after 10 to 15 minutes. If symptoms recur, a second dose of 6 mg may be injected at least one hour after the first dose; not more than 12 mg should be given in a 24-hour period. In the USA, it may also be used in single doses of 4 mg if adverse effects are dose-limiting.

For the acute treatment of **cluster headache,** sumatriptan succinate is given by subcutaneous injection in similar doses to those used for migraine.

Administration in children. Sumatriptan may be given for the treatment of acute migraine in children and adolescents. Although not licensed for oral paediatric use in the UK, the *BNFC* suggests that a single *oral* dose of 25 mg may be given to children aged 6 to 10 years and 50 mg to those aged 10 to 12 years, repeated once after at least 2 hours if symptoms recur after an initial response; older children may be given the usual adult dose (see above).

In the UK, *intranasal* sumatriptan is licensed for use in adolescents aged 12 to 17 years in a dose of 10 mg into one nostril; the dose may be repeated after at least 2 hours if symptoms recur within 24 hours although not more than 20 mg should be used within a 24-hour period. The *BNFC* suggests that either this dose or an unlicensed dose equivalent to the usual adult dose (see above) may be used in those aged 12 years and over.

If no response is obtained with the initial dose by any route, a second dose should not be given for the same attack.

Administration in hepatic impairment. Sumatriptan should be used with caution in patients with hepatic impairment. A dose of up to 50 mg by mouth is considered suitable. It should not be given to patients with severe impairment.

High-altitude disorders. Sumatriptan has been tried with some success in a small study[1] for the prevention of symptoms of acute mountain sickness (p.1168).

1. Jafarian S, *et al.* Sumatriptan for prevention of acute mountain sickness: randomized clinical trial. *Ann Neurol* 2007; **62:** 273–7.

Migraine and cluster headache. The use of sumatriptan and other triptans in the treatment of cluster headache (p.616) and migraine (p.616) has been reviewed.[1-8]

In **migraine** serotonin (5-HT_1) agonists are preferred to ergotamine for the treatment of acute attacks unresponsive to non-opioid analgesics.

There are several *different triptans* clinically available. In a meta-analysis of 53 trials (involving 24 089 patients) and a separate analysis of all direct comparative trials of 5 of the triptans and sumatriptan, all were found to be more effective than placebo.[5] At the marketed doses, all oral triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) were effective and well tolerated. Almotriptan, eletriptan, or rizatriptan were considered to provide the highest likelihood of consistent success. A review of the efficacy of the 5 triptans available in the USA also showed pain relief at 2 hours was comparable for all.[6] Almotriptan 12.5 mg offered high tolerability and good efficacy; eletriptan 80 mg provided high efficacy and low recurrence; and rizatriptan 10 mg was associated with consistent and rapid freedom from pain.[5] Frovatriptan was not included in the analyses, but publicly available data suggested lower efficacy. Only sumatriptan, though, has parenteral formulations and the 6-mg subcutaneous formulation is still the fastest and most effective acute treatment.[5]

About 21 to 57% of patients who initially respond to sumatriptan have a *recurrence* of their headache within 24 to 48 hours; this may be related in part to its short half-life. Such recurrences usually respond to a second dose[9,10] but if a first dose is ineffective subsequent doses for the same attack are of no benefit and should not be given. Sumatriptan is considered[11] to be effective when given at any time once the headache phase of migraine has started but giving it during migraine aura appears to be of little benefit since it does not affect the aura or prevent or delay the development of headache.[12] Repeated or long-term use does not appear to be associated with reduced efficacy.[13,14] For reports of an association between sumatriptan and medication-overuse headache, see under Adverse Effects, above.

Sumatriptan's effectiveness appears to be maintained in *menstrual migraine*, a condition which is considered to be less responsive to treatment than nonmenstrual migraine.[15] Frovatriptan,[16] rizatriptan,[17] and zolmitriptan[18] have also been found to be effective in menstrual migraine.

Experience of subcutaneous use in *children* has been reported.[19] Results of a randomised, placebo-controlled study[20] of intranasal sumatriptan in adolescents aged 12 to 17 years showed evidence of efficacy, tolerability, and safety in this age group; it was felt that the nasal spray might be particularly well suited for adolescent use. Intranasal sumatriptan has also been tried in younger children (aged 8 years and over) with some success.[21]

Subcutaneous sumatriptan has also been shown to be effective in relieving acute attacks of headache in patients with **cluster headache**. In studies about 75% of patients have obtained relief within 15 minutes of a 6-mg subcutaneous injection;[22,23] the use of higher doses was found to be of no advantage. Long term efficacy appears to be maintained[24] but the significance of the transient increase in the frequency of attacks seen in some patients remains to be determined.[25] It does not appear to be effective for the prevention of headache during cluster periods.[26] Another triptan found to be effective in the treatment of episodic cluster headache is zolmitriptan.[27]

1. Fullerton T, Gengo FM. Sumatriptan: a selective 5-hydroxytryptamine receptor agonist for the acute treatment of migraine. *Ann Pharmacother* 1992; **26:** 800–8.
2. Hsu VD. Sumatriptan: a new drug for vascular headache. *Clin Pharm* 1992; **11:** 919–29.
3. Bateman DN. Sumatriptan. *Lancet* 1993; **341:** 221–4.
4. Perry CM, Markham A. Sumatriptan: an updated review of its use in migraine. *Drugs* 1998; **55:** 889–922.
5. Ferrari MD, *et al.* Oral triptans (serotonin 5-HT agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001; **358:** 1668–75.
6. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med* 2002; **112:** 135–40.
7. Rapoport AM, Tepper SJ. Triptans are all different. *Arch Neurol* 2001; **58:** 1479–80.
8. McCrory DC, Gray RN. Oral sumatriptan for acute migraine. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 27/04/05).
9. Ferrari MD, *et al.* Oral sumatriptan: effect of a second dose, and incidence and treatment of headache recurrences. *Cephalalgia* 1994; **14:** 330–8.
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11. Ferrari MD. Sumatriptan in the treatment of migraine. *Neurology* 1993; **43** (suppl 3): S43–S47.
12. Bates D, *et al.* Sumatriptan Aura Study Group. Subcutaneous sumatriptan during the migraine aura. *Neurology* 1994; **44:** 1587–92.
13. Cady RK, *et al.* Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. *Neurology* 1993; **43:** 1363–8.
14. Tansey MJB, *et al.* Long-term experience with sumatriptan in treatment of migraine. *Eur Neurol* 1993; **33:** 310–15.
15. Solbach MP, Waymer RS. Treatment of menstruation-associated migraine headache with subcutaneous sumatriptan. *Obstet Gynecol* 1993; **82:** 769–72.
16. Silberstein SD, *et al.* A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 2004; **27:** 261–9.
17. Silberstein SD, *et al.* Rizatriptan in the treatment of menstrual migraine. *Obstet Gynecol* 2000; **96:** 237–42.
18. Loder E, *et al.* Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 2004; **44:**120–30.
19. Linder SL. Subcutaneous sumatriptan in the clinical setting: the first 50 consecutive patients with acute migraine in a pediatric neurology office practice. *Headache* 1996; **36:** 419–22.

20. Winner P, *et al.* A randomized, double-blind, placebo-controlled study of sumatriptan nasal spray in the treatment of acute migraine in adolescents. *Pediatrics* 2000; **106:** 989–997.
21. Åhonen K, *et al.* Nasal sumatriptan is effective in treatment of migraine attacks in children: a randomized trial. *Neurology* 2004; **62:** 883–7.
22. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med* 1991; **325:** 322–6.
23. Ekbom K, *et al.* Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. *Acta Neurol Scand* 1993; **88:** 63–9.
24. Ekbom K, *et al.* Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6 mg). *Cephalalgia* 1995; **15:** 230–6.
25. Hardebo JE. Subcutaneous sumatriptan in cluster headache: a time study of the effect on pain and autonomic symptoms. *Headache* 1993; **33:** 18–21.
26. Monstad I, *et al.* Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995; **35:** 607–13.
27. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–39.

Preparations

BP 2008: Sumatriptan Injection; Sumatriptan Nasal Spray; Sumatriptan Tablets;
USP 31: Sumatriptan Nasal Spray; Sumatriptan Succinate Oral Suspension.

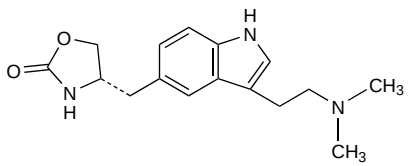
Proprietary Preparations (details are given in Part 3)
Arg.: Imigran; Imitrex†; Micranil; Migraneitor; ***Austral.:*** Imigran; Sumatab; Suvalan; ***Austria:*** Glaxotriptan; Imigran; ***Belg.:*** Imitrex; ***Braz.:*** Imigran; Sumax; ***Canad.:*** Imitrex; ***Chile:*** Imigran; Liotrex†; Somatran; ***Cz.:*** Cinie; Dolorstad; Imigran; Rosemig; Sumamigren; Sumigra; ***Denm.:*** Imigran; ***Fin.:*** Imigran; ***Fr.:*** Imigrane; Imiject; ***Ger.:*** Imigran; ***Gr.:*** Imigran; Sutriptan; ***Hong Kong:*** Imigran; ***Hung.:*** Cinie; Illument; Imigran; ***India:*** Suminat; ***Indon.:*** Cetatrex; Imitrex; Triptagic; ***Irl.:*** Imigran; ***Israel:*** Imitrex; ***Ital.:*** Imigran; Sumigrene†; ***Malaysia:*** Imigran; ***Mex.:*** Imigran; Sumitrex; Tebegran; ***Neth.:*** Imigran; ***Norw.:*** Imigran; ***NZ:*** Imigran; Sumagran; ***Philipp.:*** Imigran; ***Pol.:*** Cinie; Imigran; Sumamigren; Sumigra; ***Port.:*** Diletan†; Imigran; ***Rus.:*** Amigrenin (Амигренин); Imigran (Имигран); ***S.Afr.:*** Imigran; ***Singapore:*** Imigran; ***Spain:*** Arcoiran; Dolmigral†; Imigran; ***Swed.:*** Imigran; ***Switz.:*** Imigran; ***Thai.:*** Imigran; ***Turk.:*** Imigran; Sumatran; ***UK:*** Imigran; ***USA:*** Imitrex; ***Venez.:*** Imigran; Migraval.

Zolmitriptan *(BAN, USAN, rINN)*

311C90; Tsolmitriptaani; Zolmitriptán; Zolmitriptanum. (*S*)-4-{3-[2-(Dimethylamino)ethyl]indol-5-ylmethyl}-1,3-oxazolidin-2-one.

Золмитриптан

$C_{16}H_{21}N_3O_2$ = 287.4.
CAS — 139264-17-8.
ATC — N02CC03.
ATC Vet — QN02CC03.



Adverse Effects and Precautions

As for Sumatriptan, p.625.

Zolmitriptan should also be avoided in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways. It should be given with caution in patients with moderate to severe hepatic impairment.

Ischaemia. A spinal cord lesion related to the use of zolmitriptan has been reported in a 50-year-old woman;[1] clinical features suggested that the lesion was an ischaemic infarct.

1. Vijayan N, Peacock JH. Spinal cord infarction during use of zolmitriptan: a case report. *Headache* 2000; **40:** 57–60.

Medication-overuse headache. For a report of an association between zolmitriptan and medication-overuse headache, see under Adverse Effects of Sumatriptan, p.626.

Interactions

As for Sumatriptan, p.626.

It is recommended that the maximum dose of zolmitriptan in 24 hours should be reduced in patients receiving cimetidine (see Uses and Administration, below). A similar reduction in zolmitriptan dosage is anticipated if it is given with drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2. Opinion varies on the use of zolmitriptan with inhibitors of monoamine oxidase type A such as moclobemide. In the UK licensed product information recommends that the maximum dose of zolmitriptan should be reduced when used with inhibitors of monoamine oxidase type A (see Uses and Administration, below), whereas in the USA such combinations are contra-indicated.

◊ References.

1. Dixon R, *et al.* The metabolism of zolmitriptan: effects of an inducer and an inhibitor of cytochrome P450 on its pharmacokinetics in healthy volunteers. *Clin Drug Invest* 1998; **15:** 515–22.

Beta blockers. *Propranolol* increased plasma-zolmitriptan concentrations in a study in 12 healthy subjects, but the changes were not thought to be clinically important enough to warrant dosage adjustment during concomitant use.[1]

1. Peck RW, *et al.* The interaction between propranolol and the novel antimigraine agent zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **44:** 595–9.

Pharmacokinetics

The absolute bioavailability of zolmitriptan after oral and intranasal doses is about 40%, and peak plasma concentrations are achieved in about 1.5 to 3 hours after oral doses, depending on the formulation, and in about 3 hours with the intranasal spray. Plasma protein binding is about 25%. Zolmitriptan undergoes hepatic metabolism, principally to the indole acetic acid, and also the *N*-oxide and *N*-desmethyl analogues. The *N*-desmethyl metabolite (183C91) was more active than the parent compound in *animal* studies, and would be expected to contribute to the therapeutic effect of zolmitriptan. The primary metabolism of zolmitriptan is mediated mainly by the cytochrome P450 isoenzyme CYP1A2 while monoamine oxidase type A is responsible for further metabolism of the *N*-desmethyl metabolite. Over 60% of a dose is excreted in the urine, mainly as the indole acetic acid, and about 30% appears in the faeces, mainly as unchanged drug. The elimination half-life is 2.5 to 3 hours, and is prolonged in patients with liver disease.

Distribution into milk has been found in studies in *rats*.

◊ References.

1. Dixon R, *et al.* The pharmacokinetics and effects on blood pressure of multiple doses of the novel anti-migraine drug zolmitriptan (311C90) in healthy volunteers. *Br J Clin Pharmacol* 1997; **43:** 273–81.
2. Seaber E, *et al.* The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol* 1997; **43:** 579–87.
3. Peck RW, *et al.* The pharmacodynamics and pharmacokinetics of the 5HT -agonist zolmitriptan in healthy young and elderly men and women. *Clin Pharmacol Ther* 1998; **63:** 342–53.
4. Dixon R, *et al.* A comparison of the pharmacokinetics and tolerability of the novel antimigraine compound zolmitriptan in adolescents and adults. *J Child Adolesc Psychopharmacol* 1999; **9:** 35–42.
5. Yates R, *et al.* Pharmacokinetics, dose proportionality, and tolerability of single and repeat doses of a nasal spray formulation of zolmitriptan in healthy volunteers. *J Clin Pharmacol* 2002; **42:** 1244–50.

Uses and Administration

Zolmitriptan is a selective serotonin ($5\text{-}HT_1$) agonist with actions and uses similar to those of sumatriptan (p.627). It is used for the acute treatment of migraine attacks. Zolmitriptan should not be used for prophylaxis.

The recommended dose in the UK is 2.5 mg orally. A clinical response can be expected within 1 hour. If symptoms persist or return within 24 hours, a second dose may be taken not less than 2 hours after the first dose. If a patient does not achieve satisfactory relief with a dose of 2.5 mg, subsequent attacks may be treated with doses of 5 mg. The maximum dose of zolmitriptan in 24 hours is 10 mg. Recommended doses in the USA are somewhat lower; the dose is 1.25 or 2.5 mg with a maximum dose of 10 mg in 24 hours.

When used intranasally a clinical response can be expected in 15 minutes. The usual dose is 5 mg as a single dose into one nostril. If symptoms persist or return within 24 hours, a second dose may be given after at least 2 hours, up to a maximum of 10 mg daily.

Dose reductions are recommended in patients taking certain other drugs. The maximum dose of zolmitriptan in 24 hours should be 5 mg in those receiving cimetidine or an inhibitor of monoamine oxidase type A (although use with inhibitors of monoamine oxidase type A is contra-indicated in the USA). A similar reduction is also recommended in those taking drugs, such as fluvoxamine and ciprofloxacin, that inhibit the cytochrome P450 isoenzyme CYP1A2.

For dosage in hepatic or renal impairment see below.

Administration in hepatic impairment. A study[1] has indicated that while there is no need to reduce the size of the initial dose of zolmitriptan in patients with moderate or severe hepatic impairment, accumulation may occur with repeated doses in patients with severe impairment and their total daily dosage should be reduced.

A maximum oral dose of 5 mg in 24 hours is recommended by licensed product information in the UK in patients with moderate to severe impairment. A dose of less than 2.5 mg is recommended in the USA.

1. Dixon R, *et al.* Effect of hepatic impairment on the pharmacokinetics of zolmitriptan. *J Clin Pharmacol* 1998; **38:** 694–701.

Administration in renal impairment. Although renal clearance of zolmitriptan and its metabolites was reduced in patients with moderate to severe impairment,[1] the resulting effect was unlikely to be of clinical importance and adjustment of zolmitriptan dosage in patients with renal impairment was considered unnecessary.

1. Gillotin C, *et al.* No need to adjust the dose of 311C90 (zolmitriptan), a novel anti-migraine treatment in patients with renal failure not requiring dialysis. *Int J Clin Pharmacol Ther* 1997; **35:** 522–6.

Migraine and cluster headache. For comparison of the relative benefits of different triptans in migraine, see under Sumatriptan, p.627.

Further references.

1. Spencer CM, *et al.* Zolmitriptan: a review of its use in migraine. *Drugs* 1999; **58:** 347–74.
2. Bahra A, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000; **54:** 1832–9.
3. Dowson AJ, Charlesworth B. Review of zolmitriptan and its clinical applications in migraine. *Expert Opin Pharmacother* 2002; **3:** 993–1005.
4. Charlesworth BR, *et al.* Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomised, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs* 2003; **17:** 653–67.
5. Dowson AJ, *et al.* Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *CNS Drugs* 2003; **17:** 839–51.
6. Lewis DW, *et al.* Adolescent Migraine Steering Committee. Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; **120:** 390–6.
7. Rapoport AM, *et al.* Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007; **69:** 821–6. Correction. *ibid.*; 2029.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zomigon; ***Austral.:*** Zomig; ***Austria:*** Zomig; ***Belg.:*** Zomig; ***Braz.:*** Zomig†; ***Canad.:*** Zomig; ***Cz.:*** Zomig; ***Denm.:*** Zomig; ***Fin.:*** Zomig; ***Fr.:*** Zomig; Zomigoro; ***Ger.:*** AscoTop; ***Gr.:*** Zomigon; ***Hong Kong:*** Zomig; ***Hung.:*** Zomig; ***Irl.:*** Zomig; ***Israel:*** Zomig; ***Ital.:*** Zomig; ***Mex.:*** Zomig; ***Neth.:*** Zomig; ***Norw.:*** Zomig; ***Philipp.:*** Zomig; ***Pol.:*** Zomig; ***Port.:*** Zomig; ***Rus.:*** Zomig (Зомиг); ***S.Afr.:*** Zomig; ***Singapore:*** Zomig; ***Spain:*** Flezol†; Zomig; ***Swed.:*** Zomig; ***Switz.:*** Zomig; ***Thai.:*** Zomig; ***Turk.:*** Zomig; ***UK:*** Zomig; ***USA:*** Zomig; ***Venez.:*** Zomig.