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.

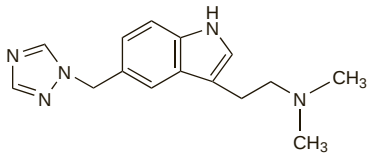
Ризатриптана Бензоат

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

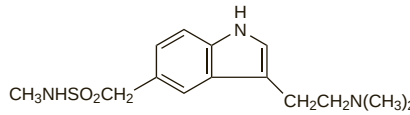
Суматриптан

$C_{14}H_{21}N_3O_2S$ = 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-