

Arrow - Sumatriptan

Sumatriptan Tablets 50mg and 100mg

Presentation

Arrow - Sumatriptan 50 mg Tablets: White to off white, round, biconvex tablet, embossed with 'SA' over '50' on one side and 'S' on the other side.

Arrow - Sumatriptan 100 mg Tablets: White to off-white, round, biconvex tablet, embossed with "SA' over '100'; on one side and 'S' on the other side.

Uses

Actions

Pharmacodynamics

Sumatriptan has been demonstrated to be a specific vascular 5-hydroxytryptamine-1 (5HT₁) receptor agonist with no effect at other 5HT receptor (5HT₂ to 5HT₇) subtypes. The vascular 5HT₁ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction.

In animals, sumatriptan selectively constricts the carotid arterial circulation, but does not alter cerebral blood flow. The carotid arterial circulation supplies blood to the extracranial and intracranial tissues such as the meninges. Dilatation and/or oedema formation in these vessels is thought to be the underlying mechanism of migraine in humans. In addition, experimental evidence suggests that sumatriptan inhibits trigeminal nerve activity. Both these actions may contribute to the anti-migraine action of sumatriptan in humans.

Clinical response begins in 30 minutes following a 100 mg oral dose of sumatriptan.

Although the recommended dose of sumatriptan is 50 mg, migraine attacks vary in severity both within and between patients. Doses of 25 to 100 mg have shown greater efficacy than placebo in clinical trials, but 25 mg is statistically significantly less effective than 50 and 100 mg.

Pharmacokinetics

After oral administration, sumatriptan is rapidly absorbed with 70% of maximum concentration occurring at 45 minutes. After a 100 mg dose, mean maximum plasma concentration is 54 ng/mL. Mean absolute oral bioavailability is 14%, partly due to pre-systemic metabolism and partly due to incomplete absorption. Oral absorption of sumatriptan is not significantly affected by food.

Plasma protein binding is low (14 to 21%); the mean volume of distribution is 170 L.

The major metabolite, the indole acetic acid analogue of sumatriptan, is mainly excreted in urine, where it is present as a free acid and the glucuronide conjugate. It has no known 5HT₁ or 5HT₂ activity. Minor metabolites have not been identified.

Sumatriptan is eliminated primarily by oxidative metabolism mediated by monoamine oxidase A. The mean total plasma clearance is approximately 1160 mL/minute and the mean renal plasma clearance is approximately 260 mL/minute. Non-renal clearance accounts for about 80% of the total clearance. The elimination half-life is approximately two hours.

The pharmacokinetics of oral sumatriptan does not appear to be significantly affected by migraine attacks.

In a pilot study, no significant differences were found in the pharmacokinetic parameters between elderly and young healthy volunteers.

In patients with hepatic impairment, pre-systemic clearance of sumatriptan is reduced, resulting in increased plasma levels of sumatriptan.

Preclinical safety data

Sumatriptan was devoid of genotoxic and carcinogenic activity *in vitro* and in animal studies.

In a rat fertility study, oral doses of sumatriptan, which resulted in plasma levels approximately 200 times those seen in man after a 100 mg oral dose, were associated with a reduction in the success of insemination.

This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 150 times those in man by the oral route.

Indications

Sumatriptan is indicated for acute relief of migraine attacks with or without aura.

There is no information available on the use of sumatriptan in the treatment of basilar or hemiplegic migraine.

Dosage and Administration

Sumatriptan should not be used prophylactically.

It is recommended to start the treatment at the first sign of a migraine headache or associated symptoms such as nausea, vomiting or photophobia. It is equally effective at whatever stage of the attack it is administered.

Administration during a migraine aura prior to other symptoms occurring may not prevent the development of a headache.

The initial recommended adult dose of sumatriptan is 50 mg. Some patients may require 100 mg.

If a patient does not respond to the first dose of sumatriptan, a second dose should not be taken for the same attack. Sumatriptan may be taken for subsequent attacks.

If the patient has responded to the first dose but the symptoms recur, further doses may be given in the next 24 hours, provided that not more than 300 mg are taken in any 24 hour period.

The tablet should be swallowed whole with water.

Use in children and adolescents

A myocardial infarct has been reported in a 14-year old male following the use of oral sumatriptan; with clinical signs occurred within one day of drug administration. Since the safety and efficacy of oral sumatriptan have not been demonstrated in the paediatric population, sumatriptan is not recommended for use in patients under the age of 18.

Use in the elderly

Experience of the use of sumatriptan in patients aged over 65 is limited. However, the pharmacokinetic data do not differ significantly from a younger population. Until further clinical data are available, the use of sumatriptan in patients aged over 65 is not recommended.

Contraindications

Sumatriptan is contraindicated in patients who have:

- hypersensitivity to any component of the preparation (see Further Information)
- a history of myocardial infarction
- ischaemic heart disease (IHD), symptoms or signs consistent with IHD
- Prinzmetal's angina or coronary vasospasm
- peripheral vascular disease
- a history of previous cerebrovascular accident or transient ischaemic attack
- uncontrolled hypertension
- severe hepatic impairment.

Sumatriptan must not be used within 24 hours of treatment with an ergotamine or ergot-type medication such as dihydroergotamine or methysergide (see Interactions).

Sumatriptan must not be given to patients receiving monoamine oxidase inhibitors (MAOIs). It must not be used within two weeks of discontinuation of MAOI therapy.

Sumatriptan should not be administered to patients with hemiplegic, basilar or ophthalmoplegic migraine.

Warnings and Precautions

Sumatriptan should only be used where there is a clear diagnosis of migraine. However, if a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given. The recommended doses of sumatriptan should not be exceeded.

Cerebrovascular

Cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with oral sumatriptan and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Thus, sumatriptan should not be administered if the headache being experienced is atypical of the patient.

It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischaemic attack). Before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.

Sumatriptan should be used with caution in patients with a history of epilepsy or other risk factors that lower their convulsion threshold.

There is no experience in patients with recent cerebrovascular accidents. Until further information is available, the use of sumatriptan is not recommended in these patients (see Contraindications).

Cardiovascular

Sumatriptan should not be given to patients in whom risk factors indicate a possibility of unrecognised coronary artery disease (CAD), unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischaemic myocardial disease or other significant underlying cardiovascular disease. The risk factors include hypertension, hypercholesterolaemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best and, in extremely rare cases (less than 1 in 10,000), serious cardiac events have occurred in patients

without underlying cardiovascular disease. During the cardiovascular evaluation, if the patient's medical history of electrocardiographic investigations reveals findings indicative of or consistent with coronary artery vasospasm or myocardial ischaemia, sumatriptan should not be administered (see Contraindications).

Serious cardiac events, including those that have been fatal, have occurred within a few hours following the use of sumatriptan tablets. These events are extremely rare (less than 1 in 10,000) and the majority of these case reports were confounded by patients having pre-existing heart disease or risk factors for ischaemic heart disease, and may reflect underlying disease and spontaneous events. Under these circumstances, the specific contribution of sumatriptan cannot be determined. Events reported have included coronary artery vasospasm, transient myocardial ischaemia, myocardial infarction, and cardiac arrhythmias including ventricular tachycardia and ventricular fibrillation. Thus, sumatriptan should not be given to patients in whom unrecognised cardiac disease is likely without a prior evaluation for underlying cardiovascular disease.

Significant cardiovascular sequelae have been reported in patients in whom risk factors were not readily identifiable. There is no experience in patients with recent cardiac arrhythmias (especially tachycardia). Until further information is available, the use of sumatriptan is not recommended in these patients.

Sumatriptan may cause transient elevation of blood pressure and peripheral vascular resistance in a small proportion of patients. It should therefore be administered with caution to patients with controlled hypertension.

Following administration, sumatriptan can be associated with transient symptoms, including chest pain and tightness, which may be intense and involve the throat (see Adverse Effects). If symptoms consistent with IHD occur, appropriate investigations should be carried out and further doses should not be given until the results of these investigations are known. Patients should be advised to contact their doctor immediately if they experience symptoms consistent with IHD (see Contraindications).

Renal or hepatic impairment

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism and/or excretion of the drug, such as hepatic or renal impairment. Studies have shown reduced sumatriptan clearance in patients with reduced hepatic function. Lower doses should be considered in these patients. If appropriate, the first dose should be given under supervision to these patients.

Hypersensitivity

Patients with known hypersensitivity to sulfonamides may exhibit an allergic reaction following administration of sumatriptan. Reactions may range from cutaneous hypersensitivity to anaphylaxis. Evidence of cross sensitivity is

limited, however, caution should be exercised before using sumatriptan in these patients.

Other vasospastic events

Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischaemia and colonic ischaemia with abdominal pain and bloody diarrhoea have been reported.

Ophthalmic

Intermittent transient changes on the surface of the cornea have been observed in toxicology studies in dogs. No causative mechanism has been established for these changes but there is no evidence to suggest that this is relevant to clinical exposure.

Use in Pregnancy (Category B3)

Administration of this drug should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Post-marketing data from multiple prospective pregnancy registers have documented the pregnancy outcomes in over 1,000 women exposed to sumatriptan. While there is insufficient data to draw definite conclusions, the findings have not detected an increase in the frequency of birth defects, nor a consistent pattern of birth defects, amongst women exposed to sumatriptan compared with the general population.

No teratogenic effects have been seen in rats or rabbits and sumatriptan had no effect on the post-natal development of rats.

Reproduction studies in rats have not revealed any clear evidence of impaired fertility or of impaired postnatal pup development. When administered to pregnant rabbits throughout the period of organogenesis, sumatriptan has caused embryoletality at doses that were sufficiently high to produce maternal toxicity. Term foetuses from Dutch Stride rabbits treated during the period of organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular defects and skeletal abnormalities.

Use in Lactation

It has been demonstrated that following subcutaneous administration sumatriptan is excreted into breast milk. Infant exposure can be minimised by avoiding breastfeeding for 24 hours after treatment. Caution should therefore be exercised when considering the administration of sumatriptan to a breastfeeding woman.

Effects on ability to drive or operate machinery

Drowsiness may occur as a result of migraine or its treatment with sumatriptan. Caution is recommended in patients performing skilled tasks, e.g. driving or operating machinery.

Adverse Effects

The most common side effects associated with treatment with sumatriptan are as follows:

- pain, sensations of tingling, heat, heaviness, pressure or tightness - usually transient, and may be intense and can affect any part of the body including the chest and throat
- flushing, dizziness and feelings of weakness - transient, mostly mild to moderate in intensity
- fatigue and drowsiness
- nausea and vomiting (in some patients), but the relationship to sumatriptan is not clear
- transient increases in blood pressure soon after treatment.

Serious coronary events have been reported (see Warnings and Precautions). Other cardiovascular adverse reactions include hypotension, bradycardia, tachycardia and palpitations.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1000, < 1/100), rare (> 1/10,000, < 1/1000) and very rare (< 1/10,000) including isolated reports. The data from clinical trials are estimates. It should be noted that the background rate in comparator groups was not taken into account. Post-marketing data refer to reporting rate rather than true frequency.

Clinical Trial Data

Nervous system disorders

Common: tingling, dizziness, drowsiness.

Vascular disorders

Common: transient increases in blood pressure arising soon after treatment; flushing.

Gastrointestinal disorders

Common: nausea and vomiting occurred in some patients but the relationship to sumatriptan is not clear.

Musculoskeletal and connective tissue disorders

Common: sensations of heaviness (usually transient, but may be intense and can affect any part of the body including the chest and throat).

General disorders

Common: pain, sensations of heat, pressure or tightness (usually transient, but may be intense and can affect any part of the body including the chest and throat).

Common: feelings of weakness, fatigue (mostly mild to moderate in intensity and transient).

Laboratory tests

Very rare: minor disturbances in liver function tests.

Post-Marketing Data

Immune system disorders

Very rare: hypersensitivity reactions, ranging from cutaneous hypersensitivity (e.g. rash, urticaria, pruritus or erythema) to rare cases of anaphylaxis.

Nervous system disorders

Very rare: seizures, although some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures there are also reports in patients where no such predisposing factors are apparent.

Musculoskeletal and connective tissue disorders

Very rare: tremor, dystonia.

Eye disorders

Very rare: flickering, diplopia, reduced vision, loss of vision (usually transient), nystagmus, scotoma. However, visual disorders may also occur during a migraine attack itself.

Cardiac disorders

Very rare: bradycardia, tachycardia, palpitations, cardiac arrhythmias, transient ischaemic ECG changes, coronary artery vasospasm, myocardial infarction (see Contraindications, Warnings and Precautions).

Vascular disorders

Very rare: hypotension, Raynaud's phenomenon.

Gastrointestinal

Very rare: ischaemic colitis.

Interactions

Pharmacodynamic

Prolonged vasospastic reactions have been reported with ergotamine. As these effects may be additive, concomitant use of ergotamine or ergotamine derivatives and sumatriptan should be avoided. Twenty-four hours should elapse before sumatriptan is taken following any ergotamine containing preparation. Conversely, ergotamine containing preparations should not be taken until six hours have elapsed following sumatriptan administration (see Contraindications).

Co-administration of sumatriptan within 24 hours of other 5HT₁ agonists (e.g. naratriptan, zolmitriptan) is not recommended due to the potential for vasoconstrictive effects.

Pharmacokinetic

An interaction may occur between sumatriptan and MAOIs, and concomitant administration is contraindicated (see Contraindications). Rarely, an interaction may occur between sumatriptan and selective serotonin reuptake inhibitors (SSRI). There have been rare post-marketing reports describing patients with weakness, hyper reflexia and in-coordination following the use of an SSRI. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Interactions with other drugs

There is no evidence of interactions with propranolol, flunarizine, pizotifen or alcohol.

Although there is no clear evidence, it is possible that an interaction may occur between serotonin 5HT₁ agonists and the herbal remedy St John's wort (*Hypericum perforatum*), which may result in an increase in side effects.

Overdosage

Single doses of sumatriptan up to 400 mg orally have not been associated with side effects other than those mentioned. There is no experience of doses greater than these.

If overdosage with sumatriptan occurs, the patient should be monitored for at least ten hours and standard supportive treatment applied as required.

It is unknown what effect haemodialysis or peritoneal dialysis has on the plasma concentrations of sumatriptan.

Pharmaceutical Precautions

Shelf Life

Arrow - Sumatriptan 50: 48 months

Arrow - Sumatriptan 100: 48 months

Storage

Store in a cool, dry place where it stays below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Arrow - Sumatriptan 50: Blister packs of 2 and 4 tablets. Bottles of 100 tablets.

Arrow - Sumatriptan 100: Blister packs of 2 tablets. Bottles of 100 tablets.

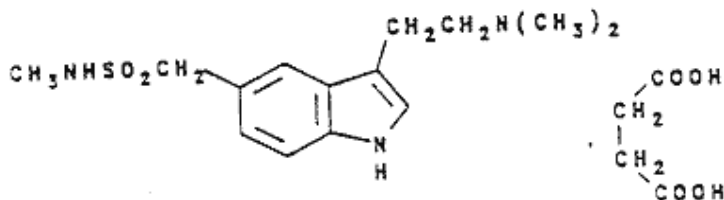
Not all pack sizes or pack types may be marketed.

Further Information

Arrow - Sumatriptan is the succinate salt of sumatriptan.

The chemical name of sumatriptan is 3-[2-(dimethylamino)ethyl]-N-methyl-1*H*-indole-5-methane sulphonamide. Its empirical formula is $C_{14}H_{21}N_3O_2S$ and the molecular weight is 295.4 g/mol. It takes the form of a white to pale yellow powder.

The chemical name for sumatriptan succinate is 3-[2-(dimethylamino) ethyl]-N-methyl-1*H*-indole-5-methane sulfonamide, butane-1,4-dioate (1:1). It is a white to off-white powder. Its structural formula is:



$C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$ Molecular weight: 413.5 g/mol CAS: 103628-46-2

Arrow - Sumatriptan Tablets contain microcrystalline cellulose, croscarmellose sodium, magnesium stearate and anhydrous lactose. The tablets are gluten free.

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