New Zealand Data Sheet

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 '  ' 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 '  ' on the other side.

Uses

Actions

Pharmacodynamics

Sumatriptan has been demonstrated to be a specific vascular 5-hydroxytryptamine-1 (5HT₁D) receptor agonist with no effect at other 5HT receptor (5HT₂ to 5HT₇) subtypes. The vascular 5HT₁D 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.
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 5HT$_1$ or 5HT$_2$ 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 patients with hepatic impairment, pre-systemic clearance of sumatriptan is reduced following oral administration, 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.

**Dosage and Administration**

Sumatriptan should not be used prophylactically.

It is advisable that sumatriptan be given as early as possible after the onset of a migraine headache. It is equally effective at whatever stage of the attack it is administered.

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 (under 12 years of age)**
Sumatriptan tablets have not been studied in children.

**Adolescents (12 to 17 years of age)**
The efficacy of sumatriptan tablets in this population has not been demonstrated.

**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.

Sumatriptan is not indicated for use in the management of hemiplegic, basilar or ophthalmoplegic migraine.

As with other acute migraine therapies, 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. It should be noted that migraineurs may be at increased risk of certain cerebrovascular events (e.g. cerebrovascular accident, transient ischaemic attack).

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). Where such symptoms are thought to indicate ischaemic heart disease appropriate evaluation should be carried out.

Sumatriptan should not be given to patients in whom unrecognised cardiac disease is likely without prior evaluation for underlying cardiovascular disease. Such patients include postmenopausal women, males over 40 and patients with risk factors for coronary artery disease. However, these evaluations may not identify every patient who has cardiac disease and, in very rare cases, serious cardiac events have occurred in patients without underlying cardiovascular disease.

Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental alert status, automatic instability, neuromuscular abnormalities) following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. Serotonin syndrome has been reported following concomitant treatment with triptans and serotonin noradrenaline reuptake inhibitors (SNRIs)

If concomitant treatment with sumatriptan and an SSRI/SNRI is clinically warranted, appropriate observation of the patient is advised (see Interactions).

The concomitant administration of any triptan/5HT\textsubscript{1} agonists with sumatriptan is not recommended.

Sumatriptan should be administered with caution to patients with conditions which may affect significantly the absorption, metabolism or excretion of the drug, such as hepatic or renal impairment.
Sumatriptan should be used with caution in patients with a history of seizures or other risk factors which lower the seizure threshold.

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as selective serotonin reuptake inhibitors or triptans.

Patients with known hypersensitivity to sulphonamides 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.

Overuse of acute migraine treatments has been associated with exacerbation of headache (medication overuse headache, MOH) in susceptible patients. Withdrawal of the treatment may be necessary.

The recommended dose of sumatriptan should not be exceeded.

**Use in Pregnancy (Category B3)**
Caution should be exercised by considering the expected benefit to the mother against 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.

When administered to pregnant rabbits throughout the period of organogenesis sumatriptan has occasionally caused embryo lethality at doses which were sufficiently high to produce maternal toxicity.

**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 12 hours after treatment.

**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

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, sensory disturbance including paraesthesia and hypoaesthesia.

Vascular disorders

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

Respiratory, Thoracic and Mediastinal Disorders

Common: Dyspnoea

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).

Investigations

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 disorders**

Very rare: ischaemic colitis.

**Interactions**

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

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.

An interaction may occur between sumatriptan and MAOIs, and concomitant administration is contraindicated (see Contraindications).

Rarely an interaction may occur between sumatriptan and SSRIs (see Warnings and Precautions).

There have been rare post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular abnormalities) following the use of an SSRI and sumatriptan.

Serotonin syndrome has also been reported following concomitant treatment with triptans and SNRIs (see Warnings and Precautions).

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-1H-indole-5-methane sulphonamide. Its empirical formula is C_{14}H_{21}N_{3}O_{2}S 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-1H-indole-5-methane sulfonamide, butane-1,4-dioate (1:1). It is a white to off-white powder. Its structural formula is:

\[\text{C}_{14}\text{H}_{21}\text{N}_{3}\text{O}_{2}\text{S} \cdot \text{C}_{4}\text{H}_{6}\text{O}_{3}\text{ Molecular weight: 413.5 g/mol CAS: 103628-46-2}\]

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

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